

Method Development, Validation and Forced Degradation Study of a UV-Spectrophotometric Method for the Estimation of Venlafaxine Hydrochloride by Analytical Quality by Design (AQbD) Approach

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Abstract—The present study focused on the development and validation of a simple, rapid, accurate, sensitive, and economical UV spectrophotometric method for the estimation of Venlafaxine Hydrochloride in bulk drug and pharmaceutical dosage forms using an Analytical Quality by Design (AQbD) approach. Methanol and distilled water (80:20) were used as the solvent system, and the drug showed maximum absorbance at 225 nm. A 3² full factorial design was applied to optimize critical analytical parameters, including methanol composition and sonication time. The method demonstrated good linearity within the concentration range of 5–25 µg/ml and complied with Beer-Lambert's law. Validation was performed according to ICH Q2 (R1) guidelines for linearity, accuracy, precision, robustness, ruggedness, LOD, and LOQ. The results confirmed that the method was accurate, precise, reproducible, and reliable. Forced degradation studies under acidic, alkaline, oxidative, thermal, and photolytic conditions demonstrated noticeable drug degradation, confirming the method's stability-indicating capability. Overall, the developed UV spectrophotometric method was found to be simple, cost-effective, reliable, and suitable for routine quality control analysis of Venlafaxine Hydrochloride in bulk and pharmaceutical dosage forms.

Index Terms—Venlafaxine HCl, AQbD, ICH guidelines, Factorial design, UV-Visible Spectroscopy

I. INTRODUCTION

Venlafaxine hydrochloride (VENLA) is a synthetic antidepressant derived from ethyl cyclohexanol and is

extensively metabolized to its pharmacologically active metabolite, O-desmethylvenlafaxine. It belongs to the serotonin-norepinephrine reuptake inhibitor (SNRI) class and produces its therapeutic effect by inhibiting the reuptake of serotonin (5-HT) and norepinephrine (NA), thereby increasing their availability at synaptic sites in the central nervous system. In comparison with conventional tricyclic antidepressants (TCAs), VENLA has low affinity for cholinergic, adrenergic, and histaminergic receptors, which contributes to a comparatively lower sedative effect. It is primarily used in the treatment of depressive disorders and helps improve mood, energy, and interest in routine activities. The therapeutic action of VENLA is mainly associated with its combined inhibition of serotonin and norepinephrine reuptake. The drug is highly soluble in methanol but shows relatively poor solubility in aqueous media.

Major depressive disorder (MDD) is a common psychiatric disorder characterized by persistent depressed mood, reduced interest or pleasure in daily activities, and impaired cognitive and emotional functions. Its development is associated with disturbances in several neurotransmitter systems, particularly serotonin, norepinephrine, and dopamine. Serotonin plays an important role in the regulation of mood, sleep, aggression, and other behavioural functions. Reduced serotonergic activity in the central nervous system is considered one of the important

neurochemical factors associated with depressive symptoms.

Venlafaxine hydrochloride is a modern antidepressant belonging to the phenylethylamine class. Its pharmacological activity is primarily mediated through inhibition of serotonin and norepinephrine reuptake, resulting in increased synaptic concentrations of these neurotransmitters and subsequent improvement in depressive symptoms.

Quality by Design (QbD) is a systematic and scientific approach that incorporates quality into the development of a product or process from its initial stages. In analytical method development, QbD involves understanding the factors that influence method performance and controlling them to achieve consistent and reliable analytical results. In contrast to conventional trial-and-error methods, QbD employs statistical techniques such as Design of Experiments (DoE) to identify critical method parameters and their interactions. This approach facilitates method optimization while improving robustness, reproducibility, and overall performance.

Various analytical techniques, including UV spectrophotometry, reverse-phase high-performance liquid chromatography (RP-HPLC), ultra-performance liquid chromatography (UPLC), and high-performance thin-layer chromatography (HPTLC), have been reported for the estimation of venlafaxine hydrochloride. However, the development of a simple, economical, specific, and QbD-based UV-Visible Spectrophotometric method including combination of solvents specifically optimized for pharmaceutical dosage forms remains limited. Therefore, there is a need for a statistically optimized, accurate, precise, and robust analytical method. Accordingly, the present study is focused on the development and optimization of a simple, efficient, and reliable UV-Visible Spectrophotometric method for the estimation of venlafaxine hydrochloride in bulk

drug and pharmaceutical formulations using a 3^2 factorial design.^[1]

1.1. Aim:

To develop and validate simple, rapid, sensitive & novel UV-Visible Spectrophotometric method for estimation of API in bulk and formulations using a 3^2 factorial design. In addition, to perform forced degradation studies of selected API to establish degradation pathways of drug substances & drug products.

1.2. Objectives:

To develop a UV spectrophotometric analytical method for the selected drug using the Analytical Quality by Design (AQbD). To identify and optimize critical method parameters for reliable analysis. To identify degradation mechanism such as hydrolysis, oxidation, thermolysis or photolysis in drug substances and drug products following ICH conditions. To evaluate the inherent stability of a drug substance when incorporated into a formulation. To assist in early identification and resolution of potential stability concerns during the drug development process using the AQbD approach. To evaluate the stability indicating capability of the developed UV-Spectrophotometric method.

1.3. Drug Profile:

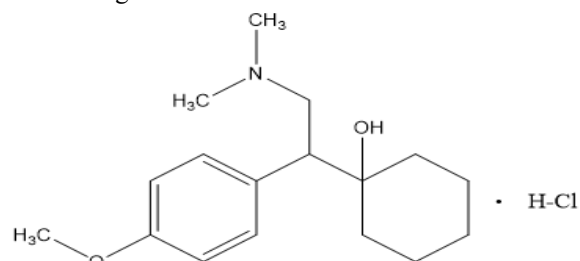


Fig. No. 1: Chemical structure of Venlafaxine hydrochloride

Table No. 1: Drug profile of Venlafaxine HCl

IUPAC name	1-(2-(dimethylamino)-1-(4-methoxyphenyl) ethyl) cyclohexan-1-ol monohydrochloride
Molecular Formula	C ₁₇ H ₂₈ ClNO ₂
Molecular Weight	313.87 g/mol
Description	Venlafaxine is in a class of medications called selective serotonin and norepinephrine reuptake inhibitors (SNRIs). It works by increasing the amounts of serotonin and norepinephrine, natural substances in the brain that help maintain mental balance.

Solubility	Soluble in distilled water, methanol, ethanol, acetonitrile, etc.
Therapeutic category	Anti-depressant
Storage	Store at room temperature, store in a well-ventilated place. Keep cool.
Melting point	217 °C
Mechanism of action	Venlafaxine increases serotonin and norepinephrine levels in the central nervous system by blocking transport proteins and inhibiting their reuptake at the presynaptic terminal. This leads to a greater availability of neurotransmitters at the synapse, ultimately enhancing the activation of postsynaptic receptors.
Uses	Major depressive disorder (unipolar), social anxiety disorder, panic disorder.

II. METHODOLOGY

2.1. Materials:

a) Instruments:

Digital weighing balance, Sonicator, Hot air oven, Double beam UV/Visible Spectrophotometer.

b) Reagents and chemicals:

Venlafaxine HCl powder was gifted by the Alembic Pharmaceuticals Ltd Vadodara, India. All other chemicals and reagents used were of analytical grade.

2.2. Methods:

a) Selection of solvents:

Selection of a suitable solvent is influenced by the wavelength expected to be studied.

b) Preparation of stock and standard solutions:

10 mg of drug was weighed & 10 ml of mixture of solvent were used to dissolve 10 mg of drug. To reach a concentration of 100 µg/ml, a 1 ml solution was taken out of 1st stock solution and then diluted using 10 ml mixture of solvent. Then 10 ml volumetric

flasks were filled with the standard solution, increasing in size from 0.5 ml to 2.5 ml. Then, using mixture of solvent, the volume in each flask was adjusted to 10 ml to produce a concentration range of 5 – 25 µg/ml. After measuring the solutions, absorbance at 225 nm with respect to the blank, a calibration curve for Venlafaxine HCl was plotted.

c) Development of UV- Visible spectroscopy method^[2,3]

A 3² full factorial design was created using Stat-Ease360® Design Expert software (version 13) to study the effect of independent variables methanol composition and sonication time on key responses: absorbance (R1) and wavelength (R2) Each variable was tested at three levels (low, medium, and high). The statistical significance of the model was assessed using ANOVA and model fitting parameters. Method optimization was carried out using response surface methodology.

Table No. 2: Independent variables and their levels

Variables	Name	Unit	Type	Coded value			Actual value		
				Low	Mid	High	Low	Mid	High
A	Methanol composition	ml	Numeric	-1	0	+1	75	80	85
B	Sonication time	min	Numeric	-1	0	+1	10	15	20

d) Validation of developed analytical method by using UV spectrophotometry^[4-6]

The UV method developed for was validated in terms of parameters. The validation was carried out according to ICH guideline Q2 (R1). Validation was conducted using predefined calibration standards to ensure the method's reliability and reproducibility across different condition.

1. Linearity

To reach concentration of 5, 10, 15, 20, and 25 µg/ml, aliquots of the standard solution were precisely transferred into several flasks and diluted to volume with distilled water. The linearity of the process was assessed.

2. System precision

Absorbance was measured at a concentration of 15 µg/ml using six replications of the sample solution on the same day.

3. Method Precision

Through intra-day and inter-day precision experiments, the method's precision was established. Three identical solutions were made and examined at three separate times in a single day for the intra-day precision investigation. In the meanwhile, identical solutions were prepared and analyzed for three days in order to assess the inter-day precision. In addition, the RSD was computed.

4. Robustness

The method's robustness was assessed by varying the wavelength of Venlafaxine HCl by ± 2 nm, from 223 nm and 227 nm.

5. Ruggedness

The method's robustness was assessed for a Venlafaxine HCl concentration of 15 $\mu\text{g/ml}$ & by two analysts evaluate aliquots from a homogeneous slot under identical operational and environmental circumstances.

6. Accuracy

The study was carried out at three distinct percentage: 80%, 100%, and 120%. The percent recovery and RSD were calculated.

7. Limit of Detection (LOD) & Limit of Quantification (LOQ)

The LOD and the LOQ were determined utilizing the SD of the intercept and the slope of the curve.

e) Forced degradation studies (FDS) of API by UV Spectrophotometry^[7-9]

i) Acid Degradation

Sample was treated with 10 ml of 0.1 M HCl & placed at room temperature for 90 mins. Then neutralize with 0.1 M NaOH solution and scanned in UV region at 225 nm. The same solution was scanned on 3th & 5th day to check the Inter-day effects.

ii) Alkali Degradation

Sample was treated with 10 ml of 0.1 M NaOH & placed at room temperature for 90 mins. Then neutralize with 0.1 M HCl solution and scanned in UV region at 225 nm. The same solution was scanned on 3rd & 5th day to check the Inter-day effects.

iii) Oxidative Degradation

Sample was treated with 5% H₂O₂ & placed at room temperature for 90 mins. Scanned in UV region at 225 nm. The same solution was scanned on 3rd & 5th day to check the Inter-day effects.

iv) Thermal Degradation

Sample was kept in oven at 50 °C for about 24 hours. Sample was dissolved in methanol & scanned in UV region at 225 nm.

v) Photolytic Degradation

Sample was exposed to sunlight. On next day sample was dissolved in methanol & scanned in UV region at 225 nm.

III. RESULTS AND DISCUSSION

3.1 λ max determination:

A 10 $\mu\text{g/ml}$ solution was analyzed by UV spectroscopy in the 200–400 nm range, showing a maximum absorbance at 225 nm using mixture of solvent as the reference.^[10]

3.2 Analytical method development, validation & forced degradation study by using UV Spectrophotometry.

(a) Analytical method development by using UV spectrophotometry

• Selection of solvent

Selection of a suitable solvent is influenced by the wavelength expected to be studied. The solvent thus used for present study was in proportion of an 80:20, 80ml of methanol and 20ml of distilled water.

• Selection of wavelength

The final solution of 10 $\mu\text{g/ml}$ was scanned in the UV region of 200-400 nm with the highest absorbance at 225 nm against mixture of solvent as a blank.

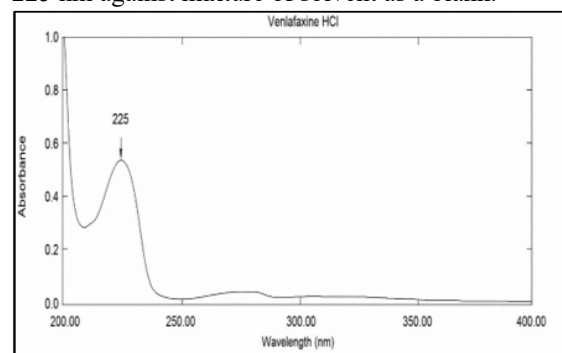


Fig. No. 2: UV spectrum of Venlafaxine HCl

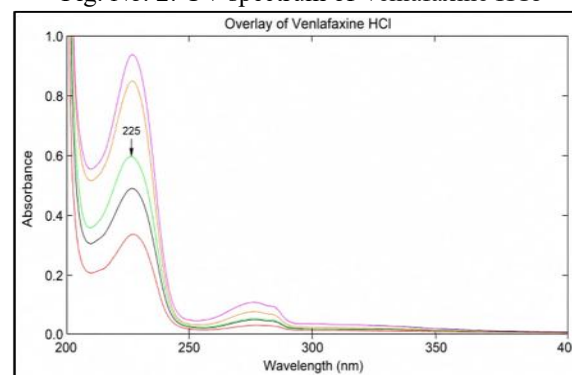


Fig. No. 3: Overlay spectrum of Venlafaxine HCl

(b) Factorial design:

Analysis of responses:

A 3² full factorial design was employed to perform nine experimental runs aimed at evaluating the influence of two independent variables, methanol composition (A) and sonication time (B) on two responses: absorbance and wavelength (λ max) The

experimental design and data analysis were conducted using Design Expert® software (version 13). two responses exhibited a quadratic relationship with the selected method parameters, indicating that both the methanol composition and sonication time significantly affected.

Table No. 3: Full factorial design (3²) for the development of UV-Visible spectroscopy method

Run	Factor 1 A: Methanol composition (ml)	Factor 2 B: Sonication time (min)	Response 1 Absorbance	Response 2 Wavelength (nm)
1	80	20	0.689	228
2	85	20	0.721	237
3	75	15	0.627	210
4	80	10	0.683	224
5	85	15	0.719	233
6	75	20	0.623	214
7	75	10	0.621	208
8	85	10	0.712	231
9	80	15	0.698	226

Table No. 4: Fit Summary Response 1: Absorbance

Source	Sequential p-value	Adjusted R ²	Predicted R ²	
Linear	0.0003	0.9159	0.8756	
2FI	0.8022	0.9004	0.7508	
Quadratic	0.0071	0.9939	0.9822	Suggested
Cubic	0.9660	0.9828	0.6089	

Table No. 5: Sequential Model Sum of Squares [Type I] Response 1: Absorbance

Source	Sum of Square	df	Mean Square	F-value	P-value	
Mean vs Total		1	4.12			
Linear vs Mean	0.0132	2	0.0066	44.54	0.0003	
2FI vs Linear	0.0000	1	0.0000	0.0698	0.8022	
Quadratic vs 2FI	0.0008	2	0.0004	39.10	0.0071	Suggested
Cubic vs Quadratic	2.167E-06	2	1.083E-06	0.0358	0.9660	
Residual	0.0000	1	0.0000			

Table No. 6: Model Summary Statistics

Source	Std. Dev	R ²	Adjusted R ²	Predicted R ²	PRESS	
Linear	0.0122	0.9369	0.9159	0.8756	0.0018	
2FI	0.0132	0.9378	0.9004	0.7508	0.0035	
Quadratic	0.0033	0.9977	0.9939	0.9822	0.0003	Suggested
Cubic	0.0055	0.9979	0.9828	0.6089	0.0055	

Table No. 7: ANOVA for Quadratic model Response 1: Absorbance

Source	Sum of Square	df	Mean Square	F-value	P-value	
Model	0.0141	5	0.0028	260.34	0.0004	significant
A-Methanol composition	0.0132	1	0.0132	1217.91	< 0.0001	
B-Sonication time	0.0000	1	0.0000	4.46	0.1252	
AB	0.0000	1	0.0000	1.13	0.3651	
A ²	0.0008	1	0.0008	70.38	0.0036	
B ²	0.0001	1	0.0001	7.82	0.0681	
Residual	0.0000	3	0.0000			

The Model F-value of 260.34 implies the model is significant. There is only a 0.04% chance that an F-value this large could occur due to noise.

P-values less than 0.0500 indicate model terms are significant. In this case A, A² are significant model terms. Values greater than 0.1000 indicate the model terms are not significant. If there are many insignificant model terms (not counting those required to support hierarchy), model reduction may improve your model

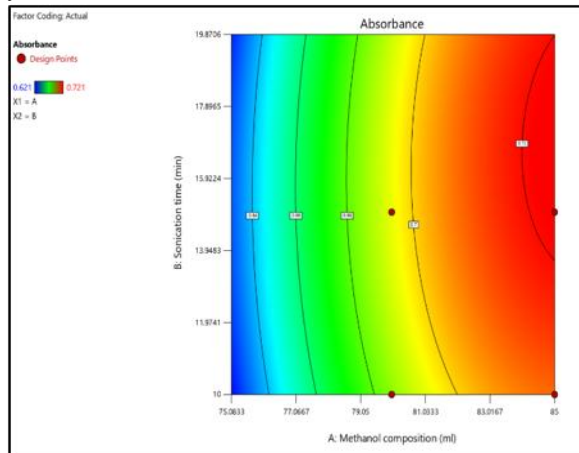


Fig No. 4: Effect of Methanol composition and sonication time on absorbance presented by contour plot

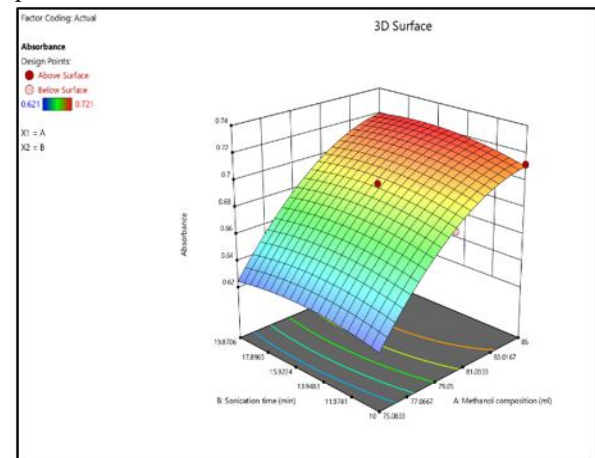


Fig No. 5: Effect of Methanol composition and sonication time on absorbance presented by response surface plot

Table No. 8: Fit Summary Response 2: Wavelength

Source	Sequential p-value	Adjusted R ²	Predicted R ²	
Linear	< 0.0001	0.9508	0.9280	
2FI	1.0000			
Quadratic	0.0131	0.9945	0.9775	Suggested
Cubic	0.5000	0.9959	0.9067	

Table No. 9: Sequential Model Sum of Squares [Type I] Response 2: Wavelength

Source	Sum of Square	df	Mean Square	F-value	P-value	Source
Mean vs Total	4.493E+05	1	4.493E+05			
Linear vs Mean	836.17	2	418.08	78.25	< 0.0001	
2FI vs Linear	0.0000	1	0.0000	0.0000	1.0000	

Quadratic vs 2FI	30.28	2	15.14	25.55	0.0131	Suggested
Cubic vs Quadratic	1.33	2	0.6667	1.50	0.5000	

Table No. 10: Model Summary Statistics

Source	Std. Dev	R ²	Adjusted R ²	Predicted R ²	PRESS	
Linear	2.31	0.9631	0.9508	0.9280	62.51	
2FI	2.53	0.9631	0.9409	0.8935	92.48	
Quadratic	0.7698	0.9980	0.9945	0.9775	19.56	Suggested
Cubic	0.6667	0.9995	0.9959	0.9067	81.00	

Table No. 11: ANOVA for Quadratic model Response 2: Wavelength

Source	Sum of Square	df	Mean Square	F-value	P-value	
Model	866.44	5	173.29	292.42	0.0003	Significant
A-Methanol composition	793.50	1	793.50	1339.03	< 0.0001	
B-Sonication time	42.67	1	42.67	72.00	0.0034	
AB	0.0000	1	0.0000	0.0000	1.0000	
A ²	29.39	1	29.39	49.59	0.0059	
B ²	0.8889	1	0.8889	1.50	0.3081	
Residual	1.78	3	0.5926			

The Model F-value of 292.42 implies the model is significant. There is only a 0.03% chance that an F-value this large could occur due to noise.

p- values less than 0.0500 indicate model terms are significant. In this case A, B, A² are significant model terms. Values greater than 0.1000 indicate the model terms are not significant. If there are many insignificant model terms (not counting those required to support hierarchy), model reduction may improve your model.

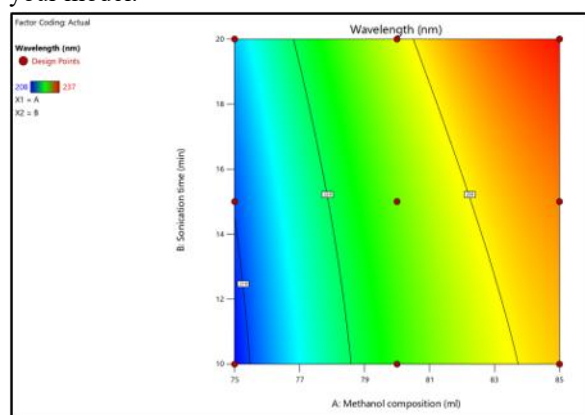


Fig No. 6: Effect of Methanol composition and sonication time on wavelength presented by contour plot

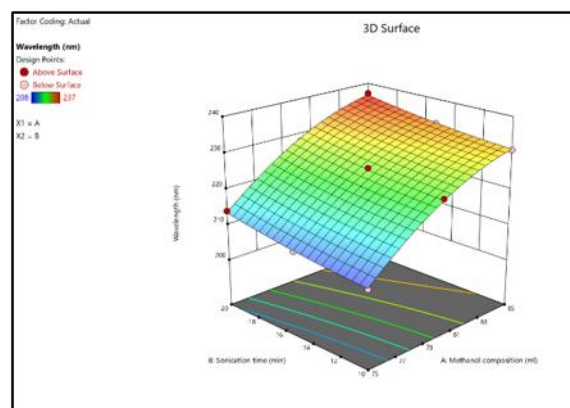


Fig No. 7: Effect of Methanol composition and sonication time on wavelength presented by response surface plot

(c) Validation of developed analytical method by using UV-spectrophotometry

1. Linearity

The samples were scanned at concentration range of 5, 10, 15, 20, 25 µg/ml.

Table No. 12: Results of calibration for Venlafaxine HCl

Conc. (µg/ml)	Absorbance	Regression equation	Intercept	Slope	Correlation coefficient (r ²)
5	0.389	Y=0.0298x+0.2432	0.2432	0.0298	0.9992
10	0.541				
15	0.702				
20	0.833				
25	0.989				

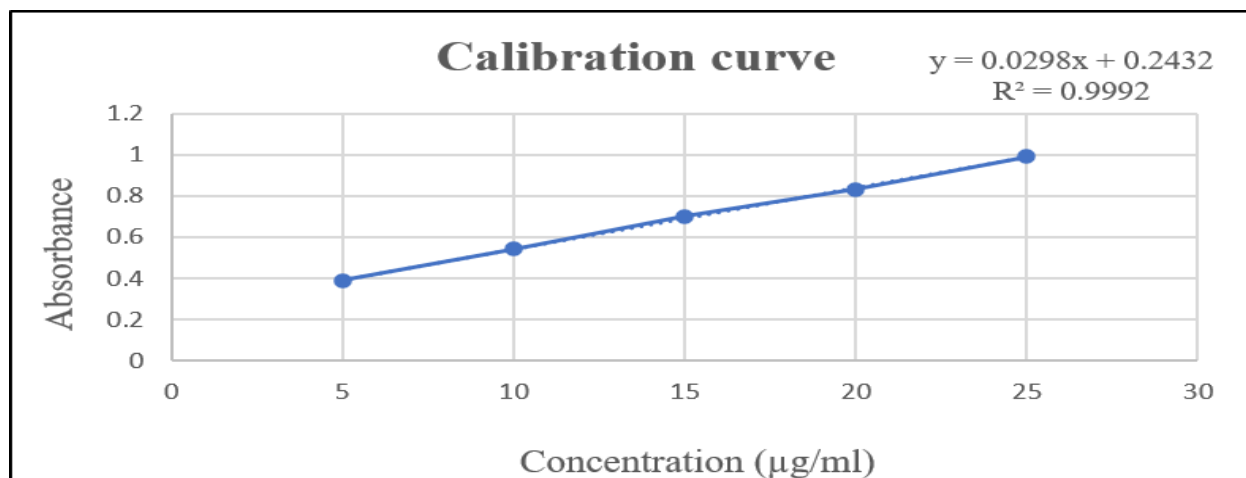


Fig No. 8: Calibration curve of Venlafaxine HCl

2. System precision

Absorbance was measured at a concentration of 15µg/ml using six replications of the sample solution on the same day.

Table No. 13: System precision of Venlafaxine HCl

Concentration (µg/ml).	Absorbance	Concentration found (µg/ml).	mean	SD	%RSD
15	0.713	15.76	15.57	0.148	0.95
	0.711	15.69			
	0.709	15.63			
	0.707	15.56			
	0.704	15.46			
	0.701	15.36			

3. Method Precision

Precision was carried out on Intraday and Interday at 3 various concentration and measurements were taken in triplicate for both studies.

Table No. 14: Intra-day method precision of Venlafaxine HCl

Concentration (µg/ml)	Absorbance	Concentration found (µg/ml)	mean	SD	%RSD
5	0.399	5.22	5.11	0.101	1.98
	0.395	5.09			
	0.393	5.02			
15	0.711	15.69	15.57	0.115	0.74

25	0.707	15.56	25.13	0.220	0.87
	0.704	15.46			
	0.999	25.36			
	0.992	25.12			
	0.986	24.92			

Table No. 15: Inter-day method precision of Venlafaxine HCl

Concentration (µg/ml)	Absorbance	Concentration found (µg/ml)	Mean	SD	%RSD
5	0.39	4.92	4.85	0.065	1.34
	0.388	4.85			
	0.386	4.79			
15	0.708	15.59	15.51	0.086	0.55
	0.706	15.53			
	0.703	15.42			
25	0.997	25.29	25.19	0.1	0.39
	0.994	25.19			
	0.991	25.09			

4. Robustness

Robustness determined by subjecting change in the wavelength. The method was found to be robust and the results are shown in Table 23

Table No. 16: Robustness of Venlafaxine HCl

Concentration (µg/ml)	Wavelength	Absorbance	Concentration found (µg/ml)	Mean	SD	%RSD
15	223	0.698	15.26	15.07	0.162	1.0
		0.691	15.02			
		0.689	14.95			
	225	0.71	15.66	15.52	0.135	0.8
		0.706	15.53			
		0.702	15.39			
	227	0.711	15.69	15.54	0.198	1.2
		0.709	15.63			
		0.700	15.32			

5. Ruggedness

Ruggedness was established by analyzing the samples by two distinct analysts.

Table No. 17: Ruggedness of Venlafaxine HCl

Analyst	Concentration (µg/ml)	Absorbance	Concentration found (µg/ml)	Mean	SD	%RSD
Analyst 1	15	0.716	15.86	15.69	0.152	0.9
		0.71	15.66			
		0.707	15.56			
Analyst 2	15	0.715	15.83	15.69	0.152	0.9

		0.712	15.73			
		0.706	15.53			

6. Accuracy

The recovery study was carried out at three distinct percentage: 80%, 100%, and 120%

Table No. 18: Result of Accuracy of Venlafaxine HCl

Brand name	Level	Actual amount of Venlafaxine HCl added in mg	Actual amount of Venlafaxine HCl found in mg	% Recovery	Mean	SD	%RSD
Venx 75	80%	13.5 µg/ml	12.11	98.10	100.0	1.78	1.78
	100%	15 µg/ml	14.98	100.55			
	120%	16.5 µg/ml	17.61	101.59			

7. LOD & LOQ

Table No. 19: LOD & LOQ data

LOD	$3.3 \times 0.00788 \div 0.02984$	0.87 µg/ml
LOQ	$10 \times 0.00788 \div 0.02984$	2.64 µg/ml

(d) Forced degradation study of API by using UV spectrophotometry

Table No. 20: Results for Degradation of API

Stress condition	Time (min/ Day)	Absorbance of standard	Absorbance of degraded sample (Mean ± SD)	Degraded up to %	Actual % degradation
Acid	30	0.541	0.780±0.003	3.9	3.9
	60		0.755±0.012	7.0	3.1
	90		0.730±0.018	10.1	3.1
	Day3		0.706±0.009	13.1	3.0
	Day5		0.680±0.0011	16.3	3.2
Alkali	30		0.769±0.014	5.3	5.3
	60		0.735±0.010	9.5	4.2
	90		0.700±0.006	13.8	4.3
	Day3		0.665±0.008	18.1	4.3
	Day5		0.630±0.010	22.4	4.3
Oxidation	30		0.758±0.005	6.6	6.6
	60		0.720±0.007	11.3	4.7
	90		0.682±0.004	16.0	4.7
	Day3		0.654±0.006	20.6	4.6
	Day5		0.606±0.008	25.4	4.8

Thermal	Day1	0.792±0.003	2.5	2.5
	Day3	0.757±0.004	6.8	4.3
	Day5	0.743±0.005	8.5	1.7
Photolytic	Day1	0.797±0.003	1.8	1.8
	Day3	0.768±0.005	5.4	3.6
	Day5	0.756±0.006	6.9	1.5

Table No. 21: % degradation of API at 48 hrs in all stress conditions

Stress condition	Time (min/ Day)	% Degradation	Actual % degradation
Acid	5 th day	16.3	3.2
Alkali		22.4	4.3
Oxidative		25.4	4.8
Thermal		8.5	1.7
Photolytic		6.9	1.5

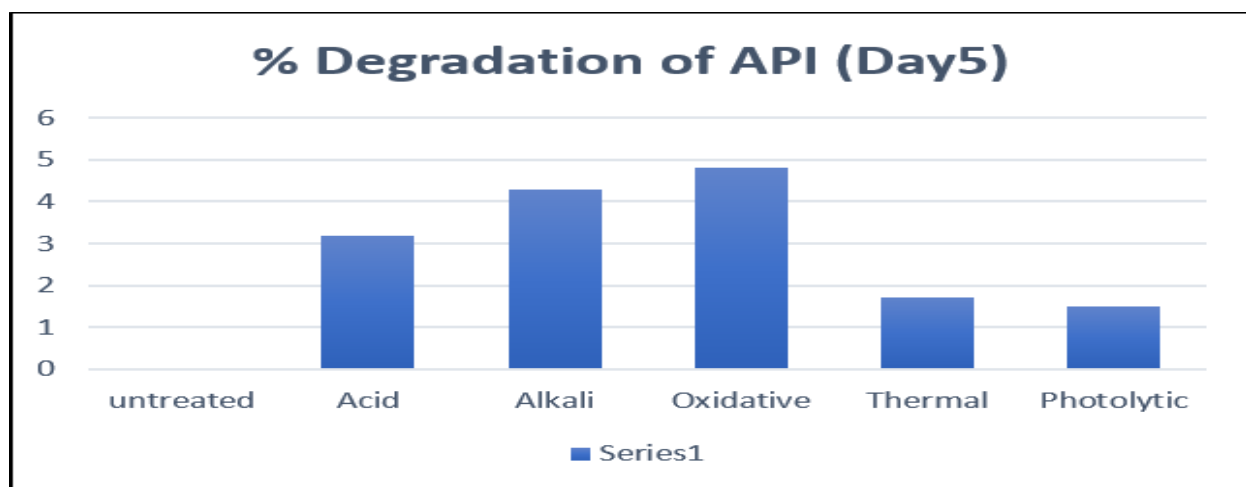


Fig No. 9: Graphical representation showing % degradation of API

IV. CONCLUSION

The present study successfully developed and validated a simple, accurate, precise, and economical UV spectrophotometric method for estimation of Venlafaxine Hydrochloride in bulk and pharmaceutical dosage form. The method showed maximum absorbance at 225 nm and obeyed Beer-Lambert's law in the concentration range of 5–25 µg/ml. Validation as per ICH Q2 (R1) guidelines confirmed that the method was reliable, robust, and suitable for routine analysis. Forced degradation studies indicated that the drug undergoes degradation under acidic, alkaline, oxidative, thermal, and photolytic conditions, with maximum degradation observed under acidic and oxidative stress conditions.

Overall, the developed method was found to be suitable for routine quality control and stability studies of Venlafaxine HCl.

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