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Development and validation of new HPLC method for dissolution studies of novel Antidepressant capsules

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Abstract:

A new stability indicating HPLC method developed and validated for the dissolution analysis of Venlafaxine hydrochloride in its pharmaceutical dosage forms. In this method Kromasil C 18 column was used, mobile phase combination used was sodium acetate buffer-acetonitrilein the ratio of 75:25 with UV-detection at 227 nm. This method was validat2ed as per ICH guidelines for specificity, linearity, precision and accuracy. Forced degradation studies were performed on the bulk sample using 0.5 N HCl, 0.1 N NaOH, 33 % H_2O_2 and heat (50 ºC).

Keywords*:* venlafaxine hydrochloride, solution stability; forced degradation study; antidepressant.

Introduction:

The chemical name of Venlafaxine hydrochloride is [1-{(2-dimethyl amino)-1-(4-methoxy phenyl) ethyl} cyclohexanol hydrochloride]. Venlafaxine chloride belongs to a second generation antidepressant and it is administered as racemic mixture. The mechanism of action of Venlafaxine hydrochloride is serotonin and nor-adrenaline reuptake inhibitor (SNRI), but in contrast to other tricyclic amines (TCAs), it does not interact with cholinergic, adrenergic or histaminergic receptors[1-2]. Different methods have been reported in literature for monitoring plasma levels of Venlafaxine hydrochloride. Most of the analytical methods carried out by HPLC to determine venlafaxine were aimed to quantifying it in biological fluids [3-26]. Therefore it is necessary to develop a simple, specific, rapid and sensitive analytical method for the quantification of Venlafaxine hydrochloride in dissolution fluids. The developed method was found to be fast, accurate as compared to already reported methods. The present work followedthe validation according to ICH guidelines with acceptable characteristics of suitability, reliability and feasibility.

Experimental:

Chemicals:

All chemical used were of HPLC grade and supplied by Ranbaxy Research Laboratories. Ranbaxy Research Laboratories Gurgaon, had supplied samples of venlafaxine hydrochloride. Venla (25mg) capsules from Solus were used as formulation. High pure water was prepared by using Millipore Milli-Q plus purification system.

Instrumentation:

The assay for venlafaxine hydrochloride was performed by using C 18 Kromasilcolumn (250 X 4.6 mm, particle size 5 µ). The HPLC system used for forced degradation studies, method development and method validation was Waters with PDA detector set at 225 nm. Data acquisition and output signal was monitored and processed by using Empower Pro Software.

Chromatographic conditions:

The mobile phase combination used was consisted of 10 mM buffer of pH 5.5 and acetonitrile in the ratio of 75:25. Buffer of pH 5.5 was prepared by dissolving 1.64 g of sodium acetate in 1000 ml of water and pH was adjusted with acetic acid, filtered through 0.45µm membrane filter, degassed with spurge and pumped to the column at a flow rate of 1 ml/min. The run time was set at 7 minutes and column temperature was ambient. The volume of injection loop was 20 µl. Before the injection of the drug solution the column was equilibrated for at least 20 minutes with the mobile phase. The eluents were monitored at 227 nm. Mixture of Water and acetonitrile in the ratio of 75:25 was used as diluent.

Sample preparation and analysis:

The stock solution of 1000 µg/ml was prepared by dissolving the appropriate amount of venlafaxine hydrochloride in diluent (Water and acetonitrile: 75:25). Stock solution was further diluted with diluent to obtain a standard solution of 100 µg/ml for assay. Similarly test solutions were prepared for the analysis.

Generation of stress sample:

For Acid hydrolysis the drug solution in 0.5 N HCl was kept at room temperature for 72 hrs; for neutral hydrolysis drug solution in water was kept at room temperature for 10 days. For alkali hydrolysis drug solution in 0.1 N NaOH was kept at room temperature for 72 hrs. For stress study under oxidative conditions the drug solution was kept in 33 % hydrogen peroxide at room temperature for 72 hrs ; for thermal stress testing, the bulk drug was subjected to dry heat at 105 ºC for 72 hrs, while for photo degradation bulk drug was subjected to UV-254 nm for 10 days.

Results and Discussion:

Peak purity test results confirm venlafaxine hydrochloride was homogeneous in all the stress conditions tested. There was no degradation observed for venlafaxine hydrochloride bulk and formulation samples during stress conditions. The mass balance of venlafaxine hydrochloride on stress sample was 100 % (% assay + % degradation). Typical retention time of venlafaxine hydrochloride was 3.1 min. In Fig.1 the chromatogram of venlafaxine hydrochloride standard is shown. System suitability parameter results are presented in Table 1.Assay method precision study was evaluated by carrying out independent assay of venlafaxine hydrochloride test sample against qualified reference standard and % RSD of six consecutive assays was found within the acceptable limits (RSD<2 %). The limit of detection represents the concentration of analyte that would yield a signal to noise ratio of 3 and limit of quantification represents the concentration of analyte that would yield a signal to noise ratio of 10.Linearity for venlafaxine hydrochloride was evaluated by regression analysis. The method exhibited linearity in concentrations ranging from 70 µg/ml to 130 µg/ml with a high degree of statistical significance (r^2>0.99). Accuracy of the assay method was evaluated in triplicate at three concentration levels, 80,100,120 % in bulk drug sample. The % recovery was calculated from the slope and y-intercept of the calibration curve obtained during linearity study of assay method. The % recovery of venlafaxine hydrochloride in bulk drug samples found within the acceptable limits (>97%). The robustness wasdetermined by injecting triplicate sample solution at different conditions with respect to control conditions. Robustness of method was checked by varying the instrumental conditions such as flow rate (± 10%), organic content in mobile phase ratio (± 2%), and wavelength of detection (± 5nm). The results are shown in Table 2.

Conclusion:

A simple RP-HPLC method has been developed and validated for the determination of Venlafaxine hydrochloride in dissolution fluids using Kromasil column at 225 nm. This method is simple, precise, and accurate. It is useful for the routine stability studies of venlafaxine hydrochloride in formulation during storage.

	USP PLATE COUNT	**USP TAILING**
System Precision	8532	0.99
Method Precision	9872	1.00
Accuracy	8875	0.98
Linearity	8782	1.01
Specificity	9214	1.02
Ruggedness	8778	0.99
Stability in Solution	8335	1.01

Table 1. System suitability of venlafaxine hydrochloride

S.NO.	SET-1	SET-2	SET-3	SET-4	SET-5	SET-6	SET-7	SET-8	SET-9	SET-10	SET-11
1	24.97	24.90	25.43	25.23	24.92	24.94	25.26	24.93	25.22	24.9	25.32
2	24.88	25.46	25.42	25.33	25.3	24.94	24.41	24.94	25.31	24.93	25.09
3	24.89	25.3	25.27	25.3	25	25.29	24.94	25.27	24.91	24.95	25.04
Mean	24.88	25.22	25.37	25.29	25.19	25.06	24.87	25.07	25.15	24.93	25.18
SD	0.01	0.28	0.09	0.04	0.16	0.20	0.43	0.18	0.21	0.03	0.21
% RSD	0.04	1.12	0.35	0.15	0.64	0.80	1.70	0.70	0.83	0.10	0.79

Table 2. Robustness of venlafaxine hydrochloride

Set-1: Control Sample, Set-2: Sample λ max222nm, Set-3: Sample λ max232m, Set-4: Flow rate 1.35 ml/min, Set-5: Flow rate 1.65 ml/min, Set-6: Mobile phase ratio 70:30, Set-7: Mobile phase ratio 80:20, Set-8: Sample temperature 30 ºC, Set-9: Sample temperature 40 ºC, Set-10: Buffer pH 5.48, Set-11: Buffer pH 5.52

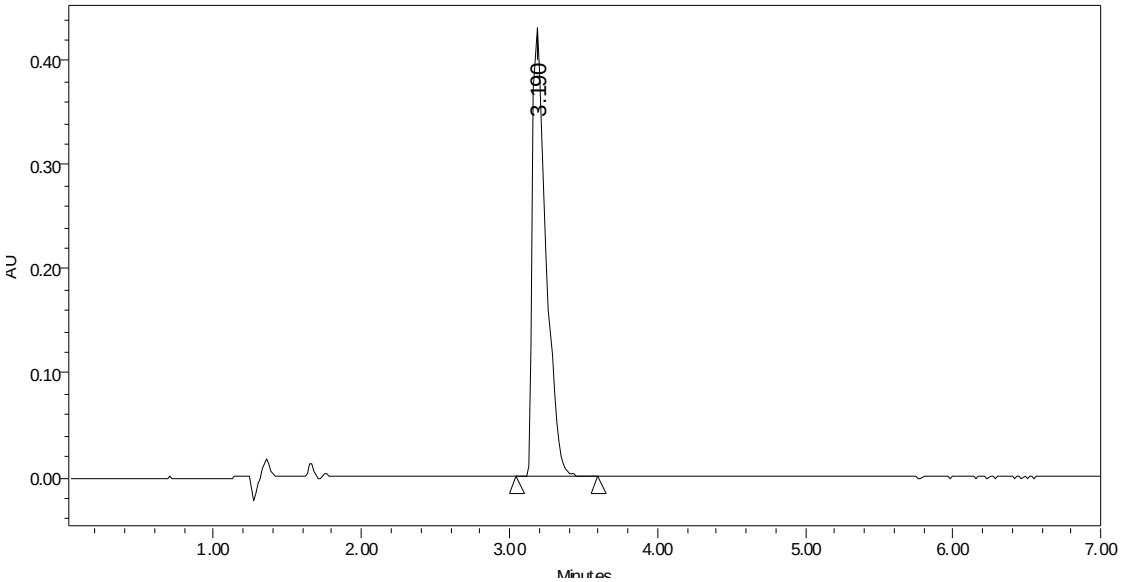

Fig.1.Chromatogram of Venlafaxine Hydrochloride Standard.

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