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Research Article

THE INDUSTRIAL IMPORTANCE OF TECHNOLOGY TRANSFER FOR ANALYTICAL METHOD DEVELOPMENT AND VALIDATION–APPLICATION TO VILAZODONE HYDROCHLORIDE DOSAGE FORM

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ABSTRACT

Objective: The research aims to create a fast, economical, and efficient tech transfer method for analyzing bulk materials and pharmaceutical dosage forms.

Methods: The analysis was performed using an Acquity UPLC BEH C18 analytical column (130 Å, 1.7 µm, 3 mm x 100 mm) with detection of the analyte at 238 nm. The mobile phase flow rate was optimized at 0.3 ml/min, and an injection volume of 0.5 µl** was used. The isocratic mobile phase consisted of a blend of buffer (0.1% OPA) and acetonitrile at a ratio of 40:60% v/v.

Results: All validation parameters of the analytical method were acceptable. The analyte eluted at 3.08 min with satisfactory theoretical plates and a tailing factor. The recovery of the analyte was 99-100%, and the method's precision was 0.59 and 0.72% RSD. The technique showed no interference, indicating specificity. The linearity was demonstrated over the 20-60 µg/ml range, with a regression coefficient of 0.999.

Conclusion: The developed method is cost-effective, specific with minimal interference, and time-saving. It also reduces solvent consumption for quality control analysis of vilazodone hydrochloride samples. The method demonstrates good linearity, robustness, and accuracy.

Keywords: Vilazodone HCl, UPLC, ICH, Tech transfer, Validation

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INTRODUCTION

Vilazodone hydrochloride is the most common oral medicament and possesses potent and selective activities as a serotonin reuptake inhibitor an agent that acts as a potent, selective serotonin reuptake inhibitor and a partial agonist of the 5-HT1A receptor used for treating major depressive disorder caused by chemical changes in the brain triggered by life events or illness and the agent binds with enzyme allosterically. The drug vilazodone HCl was approved by the FDA in 2011[1] and the molecule was developed by Allegran with the trade name VIBRID. According to pharmacokinetics, it has good bioavailability with fatty and light food particles. Chemically5-[4-[4-(5-cyano-1-indol-3-butyl] piperazin-1-benzofuran-2-carboxamide; hydrochloride. The structure of the compound is given (fig. 1). The molecular mass is 477.9 g/mol^{-1}and the Pka value with 7.1weak base property after the partition coefficient between n-octanol and water study.

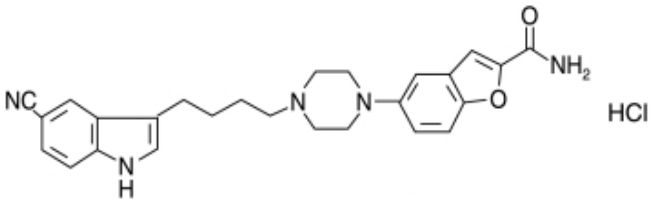

Fig. 1: Chemical moiety of vilazodone hydrochloride

Several analytical methods have been reported, which include HPLC-MS/MS [2-6], UPLC-MS/MS [7, 9], UFLC [8], HPTLC [15], HPLC [10-14], and spectrophotometric [13-20].

Previous developments in analytical methods for vilazodone hydrochloride have been criticized for their lengthy and tedious processes, as well as their insufficient sensitivity. Therefore, there is a need to develop an enhanced analytical method for vilazodone hydrochloride that offers improved sensitivity and efficiency while meeting the necessary criteria for accuracy.

In the current context of research work, the new analytical technique for vilazodone hydrochloride was developed and validated utilizing a sophisticated chromatographic system UPLC (Ultra Performance liquid chromatography) system because the system has many advantages among the conventional methods when compared to other factors like analysis run time and usage and consumption of solvent and withstanding high back pressure without experiencing any undesirable detrimental effects in the analytical column for being analyte separation and no sudden pressure development into the system. The proposed method was validated as per ICH guidelines.

MATERIALS AND METHODS

Materials and chemical reagents

Vilazodone Hydrochloride was provided as a complimentary sample by Dr. Reddy's Labs, located in Visakhapatnam, India. Milli-Q water was used for the study and prepared using the Milli-Q Integral water purification system. All chemicals and reagents utilized for method development were sourced in analytical reagent grade without additional purification steps.

Instrumentation

The Make Waters Aquity UPLC 2695 module with binary pumps setting UV detector with autosampler. Using the Waters Empower 2 software tool, data from experimental methodology is integrated into the separation technique.

Methods

Chromatographic conditions

The method development was carried out through a calibrated UPLC apparatus comprising an Acquity UPLC binary solvent manager equipped with an Acquity automatic sampler with a sample cooling facility for samples and a UV detector compassed from Waters (Waters Inc.). Empower software is used for data analysis and data integrity. Selected the analytical column for the separation of analyte with Aqcuity UPLC BEH C18 (130 Å, 1.7µm, 3 mm X 100 mm) and analyte detected at 238 nm. The flow rate by mobile phase was optimized as 0.3 ml/min and injection volume-0.5µl was employed. An isocratic mixture of mobile phase contains buffer (0.1% Orthophosphoric acid) and acetonitrile in the ratio 40:60 % v/v. A drastic change occurred and was observed at 3.05 min between a stationary phase and analyte being of interest due to the ionization state [8]. The run time of analysis was completed in about 6 min using isocratic mode operation under ambient temperature conditions along with stabilized pressure.

Preparation of standard solution and calibration curve

Transferred 25 mg API into 25 ml volumetric flask and dissolved using methanol as solvent and the concentration of solution is 1 mg/ml. Further, 100µg/ml was prepared from the same resultant solution. Appropriate standard dilutions for the methodology were prepared.

Preparation of pharmaceutical solid dosage form

Accurately weighed content amount of 20 VIBRID tablets powder corresponding to 20 mg relinquished into a 100 ml graduated flask. 1/3rd of the dilutant was added, and the flask contents were vortexed for 30 min to liberate the free form of API from the placebo. The volume of the flask was filled up to 100 ml with diluent, mixed well to get a clear solution, and filtered through the PVDF membrane to retain the placebo material into the membrane. Filtrate is used for analysis. The concentration of the prepared tablet solution was 100 µg/ml.

RESULTS AND DISCUSSION

Method development

We conducted various trials with pH and change of mobile phase composition. To get a fine and specific method. The optimized chromatogram is given in (fig. 2).

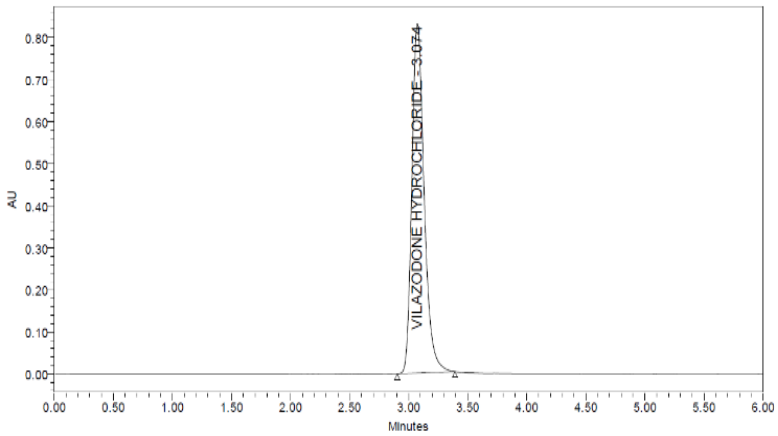

Fig. 2: Optimized typical vilazodone HCl chromatogram

Method validation

The optimized and developed method has been evaluated under the guidelines outlined in ICH Q2 (R1) from 2005.

The regulatory body (ICH) importance in the pharmaceutical industry (Technology transfer)

The objective of this regulatory body is to ensure safe, effective, and high-quality medicinal agent's development. The key elements of the method, specifically accuracy, precision, and limit of quantification, play a crucial role in technology transfer, along with specificity, linearity, and LOD. However, the limit of quantification (LOQ) is a very important parameter in the method development of API-related substances or impurities. During the long-term stability regular evaluation of product-related parameters by performing the following: dissolution, blend assay, related substances (RS) or impurity quantification, and assay quantification of the finished product, the purity of the sample and quantification recovery has been decreased, which resulted in not following the expected trend analysis. This is due to the impurity level exceeding the specified limit as per ICH and other regulatory bodies.

The limits of impurity noticed due to various reactions and other factors within the molecule are affected by exposure to climatic conditions such as high humidity, high temperature, and crystallinity during storage. Afterward, impurity must be qualified for the effect of which is safe or unsafe in the formulation. Numerous articles have been published by academics, encompassing a wide range of work that cannot be accurately defined by method developers in terms of analytical accuracy, precision, and quantification limits. The importance of this data is evident during technology transfer and in ensuring reproducible data is submitted to the USFDA when the product is launched globally. The accuracy parameter plays a critical role in the recovery of the API amount, as well as the placebo material, across the entire range of dosages. Additionally, this parameter provides insight into the compatibility or non-compatibility of products with excipients for achieving good recovery amounts. The method's precision was assessed using inter- and intra-laboratory facilities, and the reproducibility and stability of the method were verified by injecting bracketing standards. Through the analysis process, good reproducibility data was obtained for homogeneous samples via multiple injections. The method's specificity is indicated by the absence of interference during separation. Several methods have reported stability-indicating profiles without being exposed to light. When submitting the product development report to the USFDA, the agency will seek reproducibility of data and integrity before granting permission for global product distribution.

System suitability

The UPLC system was evaluated after calibration. The system's operation was confirmed by applying all routine system setup conditions, including purging and system pressure management, and ensuring the mobile phase supply channel lines, infrits, and detector were functioning properly. Next, six replicate samples were injected into the system to obtain chromatogram results. Equipment testing was conducted using USP 24 and NF19 standards. The recorded chromatogram results are provided (table 1).

Table 1: System suitability results

Name of the drug	Duration (Rt) (min)	Area (AU) RSD	Column efficiency plates	Symmetry factor
Vilazodone HCl	3.08 ±0.13	6153758±0.21	4282	1.28
Accepted limits [22,23,24]	RSD NMT 2	RSD NMT 2	>2000	NMT 2

Rt = Retention time, RSD = Relative Standard Deviation, NMT = Not More Than. N=6

Specificity

The specificity parameter provides information about the analyte being assessed unequivocally in the presence of other components [8]. The generated data has been represented (fig. 3).

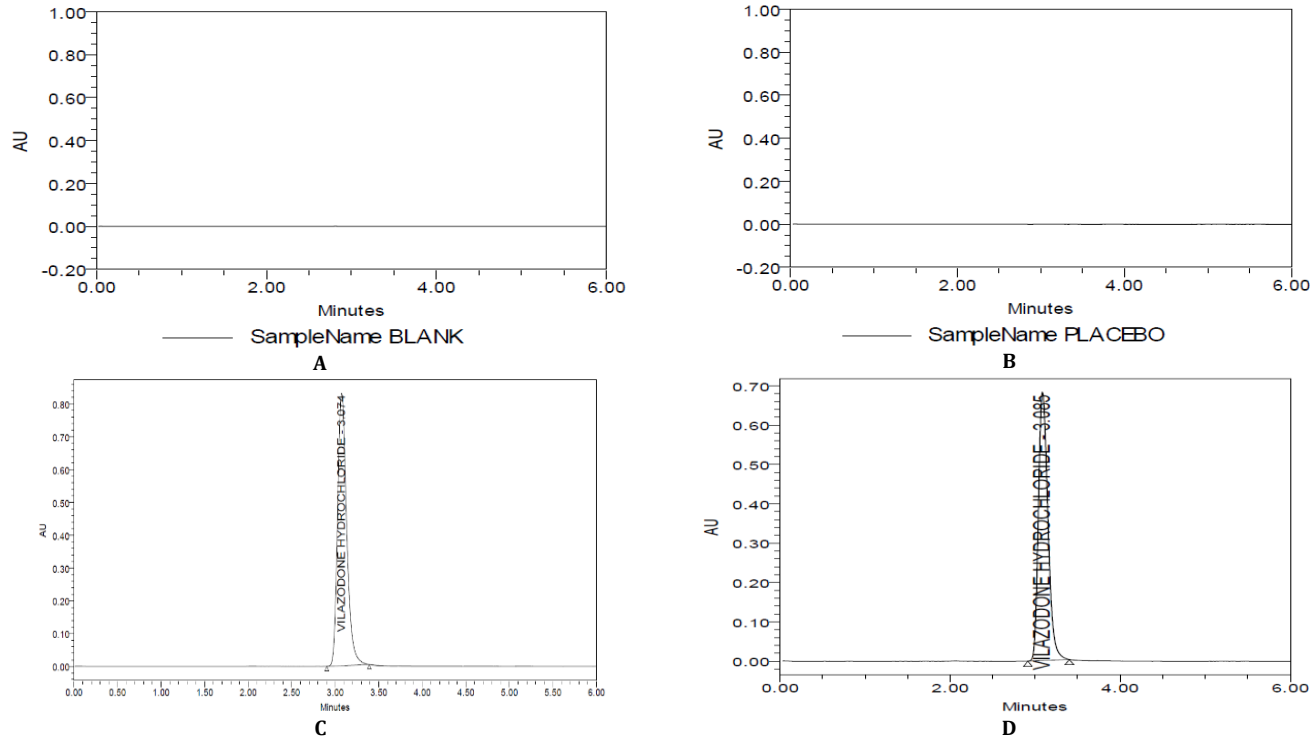

Fig. 3: A. Blank B. Placebo C. Formulated product chromatogram and D. Standard

Accuracy

The accuracy of the analytical procedure was determined by assessing the consistency or agreement between acceptable values, either a conventional true value or accepted reference value, using the standard addition method [11]. Accuracy was evaluated by adding known amounts of analyte (spiked) into a pre-analyzed tablet sample containing pure vilazodone hydrochloride at 50%, 100%, and 150% levels, and the samples were

injected in triplicate at each level and then calculating their % recovery at each level. The method demonstrated high accuracy and no interference with the formulated drug product. The results are presented (table 2).

Table 2: Findings from the accuracy

Spiked level	Sample area	Amount added	Amount found	% Recovery	% Mean	% RSD
50%	3040980	19.80	19.59	99	99%	**0.58%**
	3015257	19.80	19.42	98		
	3074516	19.80	19.80	100		
100%	6121063	39.60	39.43	100	100%	
	6127357	39.60	39.47	100		
	6136915	39.60	39.53	100		
150%	9251931	59.40	59.60	100	100%	
	9240771	59.40	59.40	100		
	9292355	59.40	59.40	101		

*mean area of three determinations.

Precision

Repeatability

The precision of the proposed method was investigated using homogeneous samples, and the degree of scatter, or proximity to agreement, between several measurements was measured under specified conditions [20]. The known concentration of standard drug solution is injected as six replicates on the same day and subsequently on the following day using the same column. Calculated and summarised with % RSD value against peak area response. The outcomes are given (table 3).

Table 3: Findings of reproducibility and within-day variability

Variable	% RSD for VLZ response (n=6)
Repeatability	0.59±0.41
Intermediate precision	0.72±0.28

n= six determinations, mean±SEM

Linearity and range

The analyte was tested to see if its test results were directly proportional to its concentration in the sample, ranging from 20 to 60 µg/ml. The linearity (R^2) was determined using regression analysis of the calibration curves, and the results are summarized (table 4). The graph plotted by taking concentration on the x-axis and peak response on the y-axis showed good linearity within the 20-60 µg/ml. (fig 4). The formula for the regression coefficient is given below.

$$a = \frac{n(\sum yz) - (\sum y)(\sum z)}{n(\sum y^2) - (\sum y)^2}$$

$$b = \frac{(\sum z)(\sum y^2) - (\sum z)(\sum yz)}{n(\sum y^2) - (\sum y)^2}$$

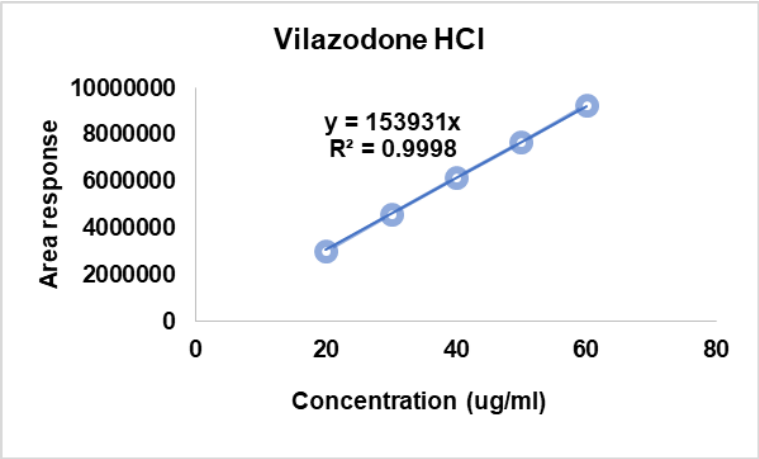

Fig. 4: Linearity curve

Detection of limit

The lowest statistically detectable analyte concentration can be determined with a signal-to-noise ratio of 3:1, and the LOD concentration is 0.249 µg/ml [15]. The chromatogram is shown below (fig. 5).

$$\text{LOD} = \frac{3.3 * \text{SD}}{\text{Slope}}$$

Quantification limit

The lowest detectable concentration of analyte in a sample, with a signal-to-noise ratio of 10:1 using the LOQ, is 0.075µg/ml [15]. The chromatogram is shown (fig. 5).

$$\text{LOQ} = \frac{10 * \text{SD}}{\text{Slope}}$$

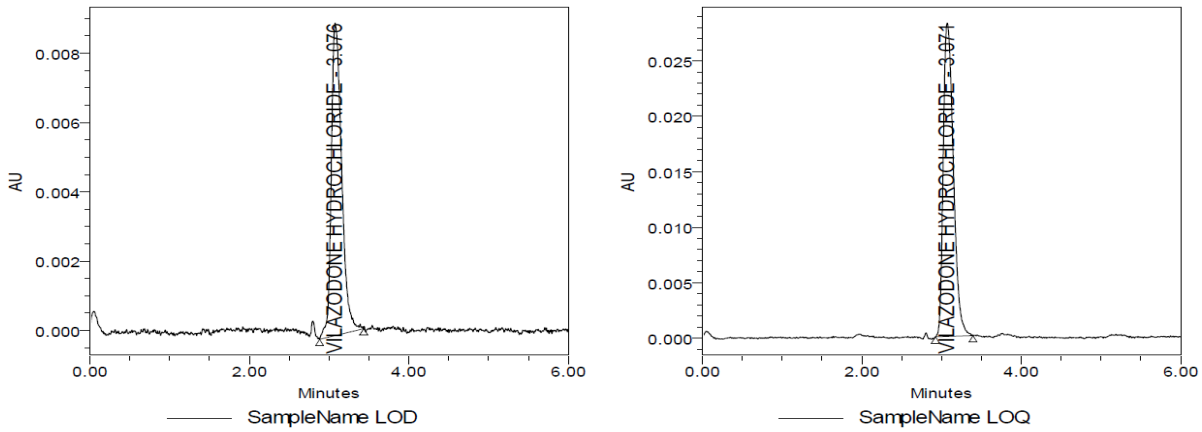

Fig. 5: LOD and LOQ chromatograms

Robustness

An analytical procedure's robustness is a measure of its ability to withstand slight, intentional changes in method parameters and demonstrate reliability under typical use [11]. Variables are presented (table 5).

Table 5: Parameters variation

Parameter	**Mobile phase variation**					
Variation	**+10%**			**-10%**		
Vilazodone HCl	Separated time	Analyte response	Tailing factor	Separated time	Analyte response	Tailing factor
	3.87	6815339	1.26	2.54	4927377	1.41
	Temperature variation					
	3.86	7087954	1.26	2.54	5043794	1.44

*Three determinations with±10% of temperature and mobile phase variations

CONCLUSION

The method we created has demonstrated excellent accuracy, repeatability, and sensitivity for routine analysis during tech transfer. In this method, the choice of organic modifier and aqueous solvent played a crucial role. Particularly, they had a noticeable effect when the analyte was separated by UPLC BEH C18 (130 A°, 1.7 µm, 3 mm x 100 mm) over a short period. An illumination study of at least 1.2 x 10^6 lux hours reveals the molecule's characteristics. Future work will benefit from the conclusion drawn from this study.

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Nil

AUTHORS CONTRIBUTIONS

Work design by Bhaskara rao, Plan and Execution by Mohan Gupta, drafting article by Sarika, Lakshmi Madhavi, and Prashanthi. Finally, all authors reviewed.

CONFLICT OF INTERESTS

The authors affirm that there are no conflicts of interest to disclose.

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