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ORIGINAL ARTICLE **OPEN ACCESS**

Development and Validation of Analytical Method for Estimation of Vareniclinein Swab Samples

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ABSTRACT
The objective of the current study was to develop and validate simple and precise UV spectrophotometric method for estimation of Varenicline tartate (VRC)in the swab samples to validate cleaning procedure. The swabbing procedure was optimized in order to obtain a suitable recovery from stainless steel surface using 100% sterile cotton swab stick. Detection wavelength selected was 237.60 nm. The proposed method was validated in terms of Linearity, precision, accuracy, limit of detection and limit of quantitation. Linearity was studied over concentration range of 2-10µg / ml and correlation coefficient was found to be 0.9945 for regression line. A mean recovery obtained was 88.23 %.
Key words: Varenicline tartarate, Swab testing, spectrophotometric, cleaning validation.

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INTRODUCTION

Cleaning Validation is documented evidence that an approved cleaning procedure will provide equipment that is suitable for processing of pharmaceutical products or active pharmaceutical ingredients (APIs).For validation of cleaning procedure three methods of sampling that are considered to be acceptable, namely direct surface sampling (swab method), indirect sampling (use of rinse solutions) and placebo sampling.

A combination of the first two methods is generally the most desirable, particularly in circumstances where accessibility of equipment parts can mitigate against direct surface sampling. In Swab method the suitability of the material to be used forsampling and of the sampling medium should be determined. The ability to recover samples accurately may be affected by the choice of sampling material. It is important to ensure that the sampling medium and solvent are satisfactory and can be readily used. Rinse samples allow sampling of a large surface area. In addition, inaccessible areas of equipment that cannot be routinely disassembled can be evaluated. However, consideration should be given to the solubility of the contaminant. A direct measurement of the product residue or contaminant in the relevant solvent should be made when rinse samples are used to validate the cleaning process. Placebo sampling method provides simulation of actual production of subsequent batches.

FDA has not published specific guidelines to set acceptance criteria or method for determining whether a cleaning process is validated because of wide variation in the equipment and process used throughout finished and bulk products .Therefore pharmaceutical companies are expected to establish acceptance criteria based on specific and logical rationale and these criteria should be practical, achievable and verifiable and scientifically sound. The analytical methods used to detect residuals or contaminants should be specific for the substance to be assayed and provide a sensitivity that reflects the level of cleanliness determined to be acceptable by the company. Important is to define the sensitivity of the analytical method in order to set their reasonable limits. The acceptance criteria vary with the varying products or drugs which are processed, equipments used for processing, the potency of the drug and toxicity levels.

Cleaning Validation Protocol is required to define how the cleaning process will be validated. It includes objective of the validation process, responsibilities for performing and approving the validation study, description of the equipment to be used, the interval between the end of production and the beginning of the cleaning procedure, the number of lots of the same product, which could be manufactured during a campaign before a full cleaning is done, detailed cleaning procedures to be used for each product, each manufacturing system or each piece of equipment, the number of cleaning cycles to be performed consecutively, any routine monitoring requirement, sampling procedures, including the rationale for why

a certain sampling method is used, clearly defined sampling locations, data on recovery studies where appropriate, validated analytical methods including the limit of detection and the limit of quantitation of those methods, the acceptance criteria, including the rationale for setting the specific limits, other products, processes, and equipment for which the planned validation is valid according to a "bracketing" concept, change control and or re-validation.[1]

Varenicline (VRC, Figure 1); 7,8,9,10-tetrahydro-6,10-methano-6H-azepino[4,5-g]quinoxaline (2R,3R), is a novel agent that is a centrally acting as a highly selective partial agonist for the nicotinic acetylcholine receptor 1. VRC has mixed agonistic-antagonistic properties, thus it has the therapeutic benefit of relieving the symptoms of nicotine withdrawal and cigarette craving during abstinence while blocking the reinforcing effect of nicotine in those who lapse.It is soluble in water. Therefore the cleaning method was developed by using water as cleaning solvent. Literature survey revealed that only a few HPLC, HPTLC, Spectroscopic methods were reported for the estimation of VRC in the formulation and in bulk. No method is reported for estimation of Labetalolin swab samples. Therefore UV method is developed for the same. The proposed analytical method has been validated with respect to linearity, precision, accuracy, LOD and LOQ. The present work focuses on development and validation of spectroscopic method for analysis of swab samples of VRC.[2].

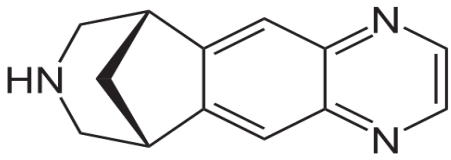

Fig 1: Chemical Structure of VRC (Source: ChemDraw Software)

MATERIAL AND METHODS

Reagent and Chemicals:

VareniclineTartarate working standard was obtained as the gift sample from Flemigo pharmaceutical Pvt. Ltd. All other reagents used were of analytical grade. Water was used as solvent for swab testing. The sample solution was passed through Whatman filter paper. Swab sampling was done by using 100% cotton sterile swab.

Instrumentation:

A UV Visible double beam spectrophotometer (Shimadzu model UV 1800) attached to computer UV probe 2.33 with spectral width of 2 nm, wavelength accuracy 0.5 nm and pair of 1 cm matched quartz cell was employed. Analytical balance (Schimadzu), Whatman filter paper. For the swab testing, instrument used was tablet compression machine

Recovery Studies of Vareniclinefrom Clean Tip Swabs and Stainless Steel Plate:

Stainless steel plate (30cm × 15cm) was used for the surface testing. The spiking solution was prepared by dissolving 50 mg VRCin 50 ml water to get the concentration of 1000 µg / ml. This was further diluted to get 10 µg / ml. Heads of the 100% cotton swabsticks were rinsed with water. Using calibrated graduated pipette, 1.6 ml, 2ml and 2.2ml solution having concentration 10 µg / ml were transferred on the three specified areas of recovery plate. These solutions were spread on the recovery plate in the area of 5 cm ×5 cm and were allowed to dry. Swabs sticks previously placed into glass test tube containing 5 ml of water were used for the swabbing the stainless steel plate. Swabbing was done first in horizontal and then in vertical direction.

Finally, swabs sticks were put again into glass test tube containing water and sonicated for 10 min at an ambient temperature and volume was made with the water. Finally, absorbance of these sample solutions was measured at the detection wavelength of 237.60 nm. [3]

Method for Cleaning the Instrument

Tablet compression machine was cleaned with dry cloth. To remove the traces of residue of drug, machine was then cleaned with 2% SLS solution twice and then wiped with water using cotton plug.

Method for Swab Testing:

Critical sites were selected and marked with area as shown in Table I. Each swab was dipped in 5 ml water. Swabs were taken in selected area using separate swab for different area carefully. Swabbing is done first in horizontal and then in vertical direction. Then swabs were again dipped in 5 ml water contained in 10ml test tube. These Test tubes were then sonicated for 10 min and then volume was made. Resultant solutions were filtered using Whatmann filter paper and analyzed at 237.60 nm. [4]

Preparation of Standard Solution

Stock solution of VRC was prepared by dissolving 50 mg of VRC in 50 ml water. This solution was further diluted suitably to get solution of concentration 10 µg / ml.

Determination of Absorption Maxima:

Standard solution 10 µg / ml were scanned between 200 - 400 nm. Spectrum was recorded and the suitable absorption maxima selected was237.60 nm.[5]

Development and Validation of Analytical Method [6]

Spectrophotometric method for the determination of VRC in swab samples was developed and validated by determining the linearity, precision, accuracy, LOD and LOQ. Detection wavelength selected for analysis was237.60 nm.

Linearity

Linearity was studied over a small drug concentration range from 2-10 µg / ml. The correlation coefficient (R^2=0.9945) obtained for regression line showed excellent linearity relationship between absorbance and concentration of VRC.

Precision

Precision of the method reported as % RSD, was estimated by repeatability, reproducibility and intermediate precision by measuring absorbance of six replicates of 2 µg / ml of VRC. % RSD values are less than 2% that illustrate the good precision of the analytical method.

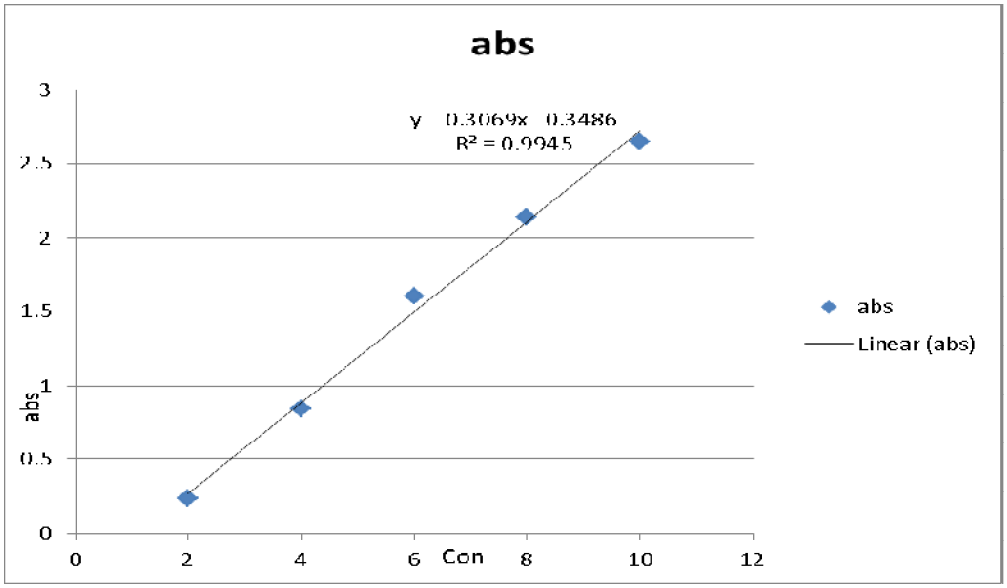

Fig. 2: Calibration curve for Varenicline

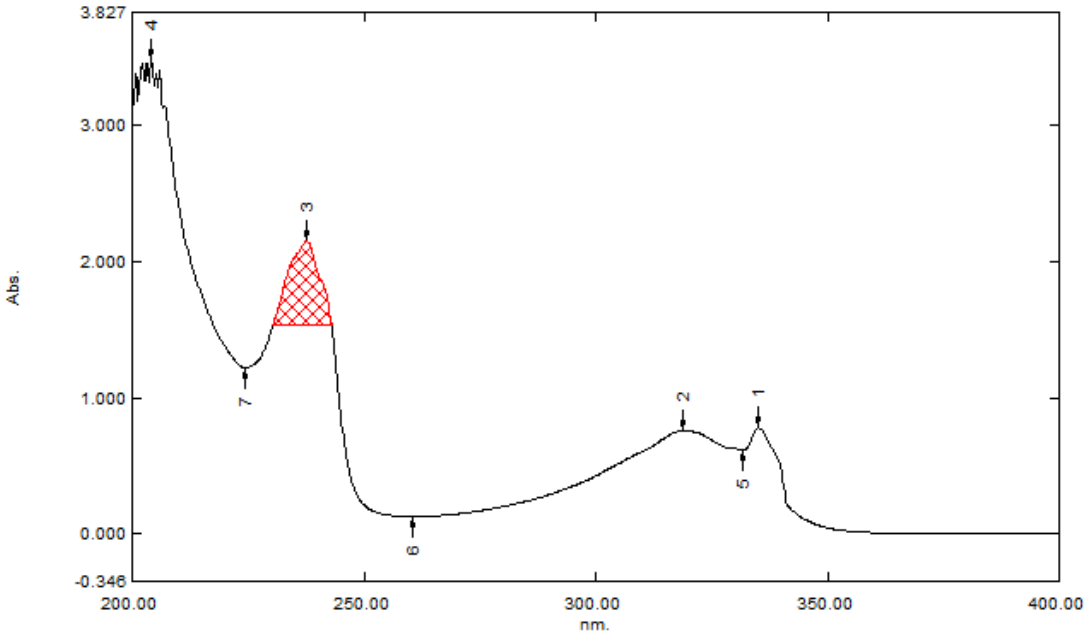

Fig.3: Absorption maxima for Varenicline

Accuracy

Accuracy of the procedure was determined by comparing the analytical amount determined Vs known amount spiked at 80%, 100% and 120% level of LOQ concentration with measurements for each concentration level achieved.

Limit of Detection and Quantitation [7]

The LOD and LOQ of VRC were estimated from the standard deviation of the response and the slope of the calibration curve by using following formula.

$$LOD = \frac{3.3 \times \sigma}{S}$$

$$LOQ = \frac{10 \times \sigma}{S}$$

Where σ = the standard deviation of the response

S = the slope of the calibration curve

LOD and LOQ were found to be 0.0002631 µg / ml [0.2631ng/ml] and 0.0025361 µg / ml [2.5361 ng/ml] respectively.

RESULTS AND DISCUSSION

Developed cleaning method removes even traces of residue of drug present on the instrument. Analytical method developed was found to be linear, precise, accurate and sensitive to detect even small quantity of drug residue.

All the results for validation parameter are tabulated in **Table I-III**.

Table I: Critical sites and area selected for UV Readings

Critical Sites Selected	Area for Swab Testing	Absorbance
Turret	2 cm x 2 cm	Not Detected
Upper Punch (12.5mm)	1 cm x 1 cm	0.0001
Lower Punch (12.5mm)	1 cm x 1 cm	0.0021
Die	1 cm x 1 cm	Not Detected
Upper Camp Tract	2 cm x 2 cm	Not Detected
Platform	2 cm x 2 cm	Not Detected

Table II : Linearity for VRC

Sr. No.	Concentration (µg/ml)	Absorbance
1	2	0.231
2	4	0.84
3	6	1.603
4	8	2.14
5	10	2.65

Table III. Summary for Validation Parameter of VRC

Sr. No.	Validation Parameters	Results
1	Linearity	R^2 0.9945
2	Precision a) Interday Precision b) Intermediate Precision c) Intraday Precision	(% RSD) 1.00% 1.20% 1.52%
3	Accuracy 80% 100%	Percentage Recovery 85.14% 89.62%
4	LOD	0.0002631 µg/ml
5	LOQ	0.0025361 µg/ml

The method was validated as per ICH guidelines for linearity, accuracy, precision, LOD and LOQ. Linearity was studied over a small drug concentration range from 2-10 µg / ml. The correlation coefficient (R2=0.9945). % RSD values are less than 2% that illustrate the good precision of the analytical method. Accuracy of the procedure was determined by comparing the analytical amount determined Vs known amount spiked at 80%, 100% and 120% level of LOQ concentration with measurements for each

concentration level achieved. LOD and LOQ were found to be 0.0002631 µg / ml [0.2631ng/ml] and 0.0025361 µg / ml [2.5361 ng/ml] respectively.

CONCLUSION

The proposed method is simple, rapid, sensitive and economic and hence can be used for the routine analysis of swabs.

ACKNOWLEDGEMENT

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