International Journal of Chemical and Pharmaceutical Analysis
Volume 1, Issue 2, 2014, PP.63-66
www.ijcpa.in

Research Article

Quantitative Determination and Sampling of Valsartan Residues for Cleaning Validation in Production Area

Pravin Jadhav[1], Surekha Jadhav[1], Kavita Mehra[1], Harsha Katre[1], Chhaya Varkhade[1], Harshal Pawar[2]

[1]Research Scholar, [2]Assistant Professor and Head (Quality Assurance), Dr. L. H. Hiranandani College of Pharmacy, Ulhasnagar, India.

ABSTRACT
Cleaning validation is a Process of providing documented evidence that the cleaning methods employed within a facility consistently controls carryover of product. The aim of the present study was to validate simple analytical method for verification of residual Valsartan in equipment's used in the production area and to confirm efficiency of cleaning procedure. UV spectrophotometric method was developed and the detection was made at 233 nm. A cleaning verification assay was validated by using rinsing sampling technique. Recovery studies were carried out on stainless steel surface. The calibration curve was linear over a concentration range from 0.1 to 10.0 µg /mL with a correlation coefficient of 0.999. Detection limit and quantitation limit was detected by UV visible spectroscopy as 0.2 and 0.98 µg/mL .The developed UV spectroscopic method can be used successfully for routine analysis of valsartan residues on cleaned surface in production area.

Key words: Cleaning Validation, Valsartan residues, Quantitative Determination, UV- spectroscopy, LOQ.

1. INTRODUCTION

"Equipment and utensils be cleaned, maintained and sanitized at appropriate intervals to prevent malfunctions or contamination that would alter the safety, identity, strength, quality or purity of the drug product"[1].

Cleaning of pharmaceutical equipment is an essential step in pharmaceutical production to prevent contamination from one batch to another. Cleaning validation is done to ensure purity, patient safety and as regulatory control to avoid carryover of product. The safety of patients is the primary objective and product contamination presents serious problem matters for any pharmaceutical manufacturer. Hence it is important to develop a precise but easy method to validate the process of cleaning.

Valsartan is an anti-hypertensive drug. It is chemically N-(1-oxopentyl)-N-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-L-valine. It has molecular weight of 435.52. It is white to practically white fine powder. It is slightly soluble in water and has good solubility in methanol and ethanol[2].

Valsartan is a non-peptide, orally active and specific angiotensin II receptor blocker acting on AT_1 receptor subtype. It selectively inhibits the binding of angiotensin II to AT_1, which is found in many tissues such as vascular smooth muscle and the adrenal glands. This effectively inhibits the AT_1-mediated vasoconstrictive and aldosterone-secreting effects of angiotensin II and results in a decrease in vascular resistance and blood pressure. Inhibition of aldosterone secretion may inhibit sodium and water reabsorption in the kidneys while decreasing potassium excretion. It is used to treat high blood pressure and congestive heart failure.

During the cleaning validation factors like equipment construction material, sealing part and parts that offers greater risk of contamination should be taken into consideration. An acceptable residue limit should be established.Generally the limit for maximum accepted residue of active ingredient is based on mathematical formulae, therapeutic doses, and toxicological profile and kept at general limit of 10 ppm[3].

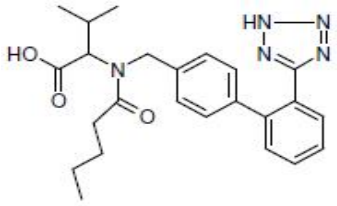


Figure 1: Chemical structure of Valsartan

Various methods like HPLC-UV, Liquid Chromatography – Mass spectroscopy, HPLC-DAD, Image analysis have been used however they are costly and time consuming UV provides a simple method for estimation of residues in equipment[3-6]. Different methods of sampling like swab sampling, rinsing have been used for cleaning validation however swab sampling may not be possible in case of equipment having surfaces which are not easily accessible. Hence rinsing presents a straight forward and trouble-free method.

The objective of the present work was to develop and validate a UV Spectroscopic method for analysis of valsartan residues in cleaning samples obtained from production equipment.

2. MATERIALS AND METHOD

2.1 Drug and chemical reagents

Valsartan was obtained as a gift sample from Unichem Labs, Mumbai. Ethanol and other reagents used were of analytical grade.

2.2 Instrumentation

UV spectrophotometric analysis was performed on double beam UV-Visible spectrophotometer (Shimadzu, model 1700) having two matched quartz cells with 1 cm path length.

2.3 Preparation of Standard Solution

Stock solution of valsartan was prepared by dissolving 10 mg of valsartan in 100ml of ethanol which gives 100 ppm concentration. Standard solution was prepared by transferring 1ml of stock solution in to 100 ml volumetric flask and the volume was made up with ethanol to produce concentration of 1ppm.

2.4 Determination of λmax

The solution was prepared by diluting 1 ml to 10ml with ethanol. The solution of 10 ppm hence obtained was scanned in UV-Visible spectrophotometer from 200-400 nm using ethanol as blank. The wavelength corresponding to maximum absorbance (λmax) was noted.

2.5 Linearity

Various aliquots were prepared from the stock solution in range 1-10 ppm. The samples were scanned in UV-Visible Spectrophotometer against ethanol as blank. The solutions were made in triplicate and Absorbance was noted.

2.6 Detection limit (DL) and quantitation limit (QL)

The detection limit (DL) and quantitation limit (QL) were determined based on the standard deviation amongst response and slope of the curve at low concentration levels.

2.7 Precision and intermediate precision

Precision of the method was demonstrated by intra-day and inter-day variation studies. In intra-day variation study five different solutions of concentration 5ppm were analyzed two times in a day the absorbance is noted. Precision at LOQ was done at 1 ppm. From the absorbance result mean, standard deviation and %RSD was calculated. In the inter-day variation studies, solution of same concentration 5ppm were analyzed on two different days and the absorbance result mean, standard deviation and %RSD was calculated.

2.8 Specificity

Specificity is the ability of the method to accurately measure the analyte response in the presence of all potential sample components (excipients) [7]. Sample solutions containing 40 µg/mL of valsartan were prepared using 200 mg tablet. The results were compared with those obtained in analysis of placebo and standard solution. No interference from excipients was observed at the wavelength of 233 nm.

2.9 Robustness

Robustness of the method was determined by carrying out by analyzing sample in triplicate under different wavelength (±) 2 nm.

2.10 Solution Stability

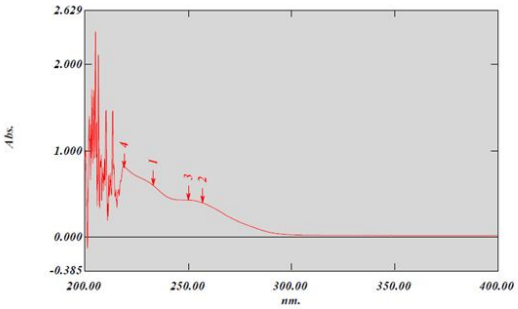
Solution stability of standard and sample solution was performed at room temperature. The absorbance's were noted for every one hour till 24 hrs.

2.11 Recovery of samples from stainless steel plates:

Stainless steel plates were contaminated with 1 ml of solution containing 2.5,5 and 7.5 µg/mL of valsartan and plates were dried at room temperature. Sampling was done using rinsing method.

3. RESULTS AND DISCUSSION

It was found that valsartan shows linearity between the ranges of 1-10 µg /mL with correlation coefficient of 0.998.The DL and QL were found to be 0.2 and 0.98 µg/mL respectively. Absorbance at 5ppm showed percentage relative standard deviation less than 2% and hence the method was found to be precise. There was no interference from excipients as shown in table. Percent Recovery was found to be 90%.



No.	Wavelength	Absorbance
1	233	0.598
2	250	0.396
3	257	0.428
4	219	0.805

Figure 2: UV-Spectrum of Valsartan in ethanol

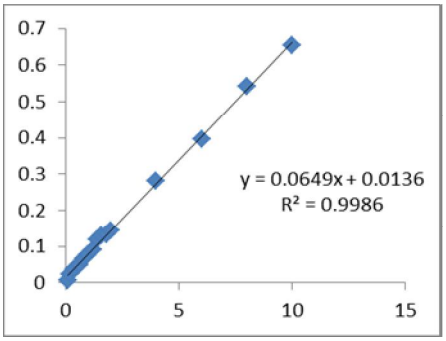


Figure 3: Calibration Curve of Valsartan

Table 1: Precision and intermediate precision at 5 ppm

Absorbance of Drug Solution at 5 PPM			
DAY 1		DAY 2	
Sample no.	Absorbance	Sample no.	Absorbance
1	0.1981	1	0.1996
2	0.1944	2	0.2039
3	0.1942	3	0.203
4	0.1959	4	0.2018
5	0.195	5	0.2
6	0.1974	6	0.198
Mean	0.195833333	Mean	0.20105
SD	0.001613278	SD	0.002235844
% RSD	0.82366	% RSD	1.0622
Mean of 12 samples			0.198442
Standard deviation of 12 samples			0.003158
% RSD of 12 samples			1.59

Table 2: Precision and intermediate precision at 1 ppm (LOQ)

Absorbance of Drug Solution at 1 PPM			
DAY 1		DAY 2	
Sample no.	Absorbance	Sample no.	Absorbance
1	0.0473	1	0.045
2	0.0478	2	0.0449
3	0.0457	3	0.0415
4	0.045	4	0.0412
5	0.0497	5	0.0411
6	0.0432	6	0.0446
Mean	0.04645	Mean	0.04305
SD	0.002294995	SD	0.001962396
% RSD	4.94%	% RSD	4.56%
Mean of 12 samples			0.04475
Standard deviation of 12 samples			0.002701
% RSD of 12 samples			6.04%

Table 3: Robustness Data

Absorbance of Drug Solution at 5 PPM			
231 nm		235 nm	
Sample no.	Absorbance	Sample no.	Absorbance
1	0.2277	1	0.1928
2	0.2249	2	0.1951
3	0.2264	3	0.1944
Mean	0.226333	Mean	0.1941
SD	0.001401	SD	0.001179
% RSD	0.618999	% RSD	0.6068

Table 4: Recovery Data

Amount added(µg/ml)	Amount found(µg/ml)	% Recovery	Mean Recovery %
2.5	2.18	87.2	90
5	4.61	92.2	
7.5	6.8	90.66	

4. CONCLUSION

Cleaning validation provides a means of providing that contamination levels have been reduced below contamination acceptance limits. It is concluded that the above method can be used as an effective method for validation of cleaning.

The simplicity and effectiveness of UV spectrophotometric method makes it useful method for routine analysis of valsartan residues on cleaned surface as compared to other methods.

5. ACKNOLEDGMENT

Authors are very much thankful to Dr. Paraag Gide, Principal of Hyderabad Sindhi National Collegiate Boards (HSNCB's) Dr. L. H. Hiranandani College of Pharmacy, Ulhasnagar for his continuous support and encouragement.

REFERENCES

1. Ravindra U, Chavan V, Saraf N, Sable P. Cleaning Validation: Important Aspect in Pharmaceutical Industry. IJPRD, 2011; Vol 2012;4(02). [Google Scholar]
2. http://www.rxlist.com/diovan-drug.htm (Accessed on 15th November 2012)
3. Akl MA, Ahmed MA, Ramadan A. Validation of an HPLC-UV method for the determination of ceftriaxone sodium residues on stainless steel surface of pharmaceutical manufacturing equipments. Journal of Pharmaceutical and Biomedical Analysis 2011;55(2):247-252. Available from: http://linkinghub.elsevier.com/retrieve/pii/S0731708511000458 PubMed PMID: 21330092. doi: 10.1016/j.jpba.2011.01.020. [Google Scholar]
4. Liu L, Pack BW. Cleaning verification assays for highly potent compounds by high performance liquid chromatography mass spectrometry: Strategy, validation, and long-term performance. Journal of Pharmaceutical and Biomedical Analysis 2007;43(4):1206-1212. Available from: http://linkinghub.elsevier.com/retrieve/pii/S0731708506006789 PubMed PMID: 17156961. doi: 10.1016/j.jpba.2006.10.008. [Google Scholar]
5. Dubey N, Dubey N, Mandhanya M, Jain DK. Cleaning validation for residual estimation of olmesartan medoxomil on stainless steel surface of pharmaceutical manufacturing equipments using swab sampling and HPLC-DAD method. Bulletin of Faculty of Pharmacy. 2013;51(1):95-100. [Google Scholar]
6. Zámostný P, Punčochová K, Vltavský Z, Patera J, Bělohlav Z. Dry-Swabbing/Image Analysis Technique for the Pharmaceutical Equipment Cleaning Validation. Procedia Engineering 2012;42:447-453. Available from: http://linkinghub.elsevier.com/retrieve/pii/S1877705812028366 doi: 10.1016/j.proeng.2012.07.436. [Google Scholar]
7. Maria. Inˆes Rocha Miritello Santoro.Quantitative determination and sampling of azathioprine residues for cleaning validation in production area. Journal of Pharmaceutical and Biomedical Analysis 2007;43(4):1495-14. Available from: http://linkinghub.elsevier.com/retrieve/pii/S0731708506007084 doi: 10.1016/j.jpba.2006.10.016. [Google Scholar]