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Cleaning Validation of Losartan Potassium Tablets on Pharmaceutical Manufacturing Equipments

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ABSTRACT
This study is to establish the procedure of cleaning validation of Losartan Potassium tables on pharmaceutical manufacturing equipments and analytical method validation by UV spectroscopy. This study develops a procedure and validation analytical method by UV spectroscopy used in cleaning validation. This study is aimed to produce a simple and validated method by UV Spectrophotometer for cleaning validation and develop a system as compliance to the regulatory bodies like USFDA, MHRA, WHO, etc. The method gave good results as compared to official books and guidelines. The analysis of samples by UV is easy as compared to other sophisticated instruments like HPLC, TC. Samples are analyzed effectively by UV Spectrophotometer.

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Introduction

Validation is defined as the establishing of documented evidence which provides a high degree of assurance that a planned process will consistently perform according to the indented specified outcomes. The quality systems regulation defines process validation and establishing by objective evidence that a process consistently produces a result or product meeting its pre-determined specifications. The goal of a quality system is to consistently produce products that are fit for their indented use[1]. Cleaning validation is documented evidence that an approved cleaning procedure will provide equipment which is suitable for processing of pharmaceutical products. The cleaning of pharmaceutical equipments is an area of increasing regulatory importance within industry [2]. Inorder to evaluate a cleaning method, it is necessary to sample the product contact surfaces of the equipment and establish the level of residuals present. The six sampling methods are swab sampling, rinse sampling method, coupon sampling, placebo sampling, solvent sampling and product sampling. It is important to select an appropriate method for detection of residue in the cleaning sample. During validation of the cleaning procedure the test method used should be able to specifically quantify concentration of all compounds of interest that may be present in the sample. The specific analytical methods used for cleaning validation include UV spectroscopy, HPLC,GC, HPTLC, atomic absorption spectroscopy, flurimetry and plain photometry. Non-specific analytical methods commonly used for cleaning verification include visual examination, gravimetric analysis, pH, conductivity, microscopy, titration, total organic carbon method. The SOP for method validation would cover the following items – accuracy, precision, linearity, specificity, range, LOQ/LOD [3] . The scientific rationale is normally included in the limit section of the protocol for the cleaning validation. The scientific rationale which support the actual limit should be logical, comprehensive and easily understood[4].

Materials and Methods

List of chemicals used in Analytical Method Validation Losartan potassium (Reference std.), Methanol (Rankem), Purified water.

Procedure for Analytical Method Validation

Selection of Analytical Performance Characteristics

Following analytical performance characteristics have been selected for analytical method validation use for analysis of cleaning swab samples: Detection of λ max, Blank swab interference analysis, Linearity, and Range, Precision, Recovery of drug from spiked SS plates (accuracy), LOD and LOQ

1. Detection of λ Maxima for Losartan Potassium

Weighed accurately 50mg of working standard and transferred into 100 ml volumetric flask and made up the volume with water to 100 ml. Took 2 ml of above solution in another 100 ml volumetric flask and made up the volume to 100 ml with water (10ppm).

2. Blank Swab Interference Analysis

Blank swab solution:

Took 6 Texwipe swabs in different stopper test tubes containing 100 ml water. Sonicated for 2 min., removed the swab from sample solution. Made a homogenous solution
Measured absorbance of standard solution (10 ppm), blank solution and blank swab solution at of λ max determined by scanning of 10ppm standard solution.

3. Linearity

Prepared the test solution using Losartan Potassium working standard at concentration level 2, 4, 6, 8 and 10 ppm. Measured the absorbance of all solutions at determined maximum wavelength in duplicate. Plot the graph between absorbance (y-ordinate) and concentration (x-abscissa) and determined the regression and correlation coefficient (r^2).

4. Precision

4.1. Repeatability of Measure of Absorbance

To check repeatability, measurement of absorbance 10 ppm solution of drug was measured 6 times at λ max and % RSD was calculated.

4.2. Reproducibility of Measurement of Absorbance

To check reproducibility, the absorbance of different

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concentration in three replicates was performed.

4.2.1. Intraday analysis

Intraday analysis was determined by analyzing the 5 drug concentration in triplicate at same day and % RSD was calculated. In this study 2,4,6,8 and10 ppm solution was prepared in triplicate form and the absorbance was determined at λ max of drug.

5. Recovery of drug from Spiked SS Plates

Determined the recovery of the method by applying the method to SS plates to which known amount of analyte (Losartan Potassium) has been added.

Spiking with solution of 50, 100 and 200 ppm:

Spiked uniformly three 5 X 5 cm^2 three separate SS plate (316 SS grade) with 400 µl solution of 50, 100 and 200 ppm standard solutions respectively with the help of a micro pipette and allowed the surfaces to dry. This procedure was performed in triplicate.

Test solutions

Took out the swabs from stoppered test tubes and squeezed the excess swabbing solvent by pressing it with the wall of the test tube. Swabbed the dried spiked plate as per procedure of sampling of swab on equipment (vertically and horizontally). Using single swab from one spiked location (plate). Placed this spiked swab in stopper test tube containing 10 ml of water and sonicated the test tube for about 10 min. to extract the drug in solution. Swabbed at 9 plates (3 concentrations in triplicate). Measured the absorbance of each of the swab test solutions at determined λmax. Compared all these swabbed solutions of 50, 100 and 200 ppm with standard solution of 2, 5, 10 ppm and % recovery should not be less than 80 %. The amount of drug found in test solute was calculated as per the formula given

$$\text{Amount of drug found (µg/swab)} = \frac{AT \times WS \times 10 \times 1000}{AS \times DS}$$

AT = average absorbance of drug in sample solution, AS = absorbance of drug in std. solution

WS = weight of drug (working std.) taken in mg, DS = dilution for std. solution

% recovery of drug was calculated as per the formula:

$$\%\ \text{Recovery} = \frac{\text{Amount of drug found (µg)} \times 100}{\text{Amount of drug spiked (µg)}}$$

6. Limit of Detection

Preparation of standard solution (10 ppm)

Took 50 mg of drug (working standard) to 100 ml volumetric flask and made up to 100 ml with water. 2 ml of this solution was taken in 100 ml volumetric flask and made up 100 ml with water. From stock solution prepared 100 ml each of 0.1, 0.2, 0.3, 0.4, 0.5 ppm by suitable dilutions. Took the absorbance of all the above concentration and calculated the LOD by using following formula

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

σ = standard deviation of the response, S = slope of calibration curve

7. Limit of Quantitation

From the absorbance obtained from the Limit of Detection, determined the concentration at which the analytical method can able to quantify the analyte. LOQ can be calculate by using following formula

$$LOQ = \frac{3.3\sigma}{S}$$

Selection of swab sampling points of equipments

It is very important step in the cleaning validation. In this we selected the sampling point on the equipments which are the most difficult to clean. It includes various parts of equipments which mostly comes in direct contact with raw material and products. The active residue content as found from the sampled area is multiplied with the overall surface area in order to get the maximum amount of residue in the equipment surface. Likewise residue is calculated for the other equipment in the same equipment train. Following are the swab sampling point for the cleaning validation:-

A. Granulation Area: Vibro Sifter, Multimill, Rapid Mixer Granulator, Fluidised Bed Drier, Bin Blender, IPC, Tipper

B. Compression Area:Compression Machine,Deduster (LHS), Metal detector (LHS), Deduster (RHS), Metal detector (RHS)

C. Inpection Area: Tablet capsule sorter,

D. Coating Area:Auto coater, Roll Compactor

F. Packaging Area:Blister Packing Machine

Procedure of swab sampling from the equipment

Swab samples were collected from the different locations of the equipments

- Swab samples was done in the following manner

Sampling area = 5 X 5 cm = 25 cm^2

Sampling patterns

Wiped the defined area in both the directions as shown in the figure. Applied only one time. The surface was not rubbed in to and forward movement. Swabbed the specified area and stored in a test tube containing 10 ml of water then stoppered the test tube. This sample was then analyzed by the UV spectrometer.

Calculation of Maximum Allowable Residue (MAR)

MAR was calculated by following formula

$$MAR = \frac{\text{Smallest therapeutic dose (mg) X safety factor for the dosage form X smallest batch size amongst all subsequent products (kg) X 1000 X 1000}}{\text{Average weight X largest daily dose (mg) (Amongst the next products to be manufactured in the same equipment}}$$

Estimation of acceptance limit for each swab

The acceptance limit for each swab was calculated according to the respective equipment surface area using following formula

$$\text{MAR value (per swab)} = \frac{\text{Maximum allowable residue X 25 } (cm^2)}{\text{Total contact surface area in } (cm^2)}$$

Procedure for Analysis of the Samples

Preparation of standard solution (10 ppm): About 10 mg of losartan potassium was taken in 100 ml volumetric flask. Then made up with water and placed in sonicator to prepare uniform solution. Took 10 ml of this solution in 100 ml volumetric flask and made up with water. Took the absorbance in UV spectrophotometer.

Preparation of sample solution_swab is placed in a test tube filled with 10 ml of water and sonicated for 10 min. Took the absorbance of solution in UV spectrophotometer.

The amount of drug present in each swab was calculated by using the following formula:

Absorbance of sample	Wt. of std. drug	10	10	Potency of drug
Absorbance of std.	100	100	1	100

The amount of drug present in each swab was calculated with recovery factor by using the following formula:

$$\frac{\text{Drug present in each swab} \quad X \quad 100}{\text{Recovery factor}}$$

Results

1. Detection of Maxima of Losartan Potassium

The 10 ppm solution was scanned and λmax was found at 205 nm.

2. Blank swab interference

This study was performed to check the interference on the absorbance of Losartan Potassium at the maxima due to swab and cleaning agent

Table. Absorbance of Blank Swab

Solution	Standard solution	Swab solution 1	Swab solution 2	Swab solution 3	Swab solution 4	Swab solution 5	Swab solution 6
Absorbance at 205 nm	0.9950	0.0005	0.0009	0.0012	0.0011	0.0017	0.0005

3. Linearity

Linearity of the analytical method was its ability to elicit test results that are directly proportional to the concentration of the drug substance taken for test, within a given range of 2 – 10ppm.

Table. Linearity study

Conc. (ppm)	2	4	6	8	10	Cor. Coff.	Intercept	Slope
Absorbance	0.1836	0.4011	0.5746	0.8142	0.9918	0.9979	-0.0158	0.1015

4. Precision

Precision is the measure of either degree of reproducibility or repeatability of analytical method. It is expressed as std. dev. or coefficient of variance.

Table: Repeatability of absorbance

S No.	1	2	3	4	5	6
Absorbance	0.9956	0.9961	0.9967	0.9971	0.9940	0.9950
Mean + std. dev.	0.9957 + 0.0012					
% CV	0.1205					

Reproducibility of absorbance (2, 4, 6, 8, 10 ppm)

a. Intraday Analysis

Intraday precision was determined by analyzing drug as per procedure for three times in the same day.

Table. Intra day analysis.

Sl. no	**Conc. (ppm)**	**Absorbance**			**Mean**	**Std. Dev**	**% CV**
		A	**B**	**C**			
1	2	0.2001	0.1985	0.1992	0.1993	0.0008	0.4014
2	4	0.3982	0.3995	0.3971	0.3982	0.0012	0.3014
3	6	0.5978	0.5997	0.5978	0.5984	0.0011	0.1838
4	8	0.8019	0.8021	0.7982	0.8007	0.0022	0.2747
5	10	0.9993	0.9967	0.9967	0.9976	0.0015	0.1504

b. Inter day Analysis

Inter day precision was determined by analyzing drug as per procedure daily for three days. Reproducibility was evaluated by coefficient of variation

Table. Inter day analysis

S. no	**Conc. (ppm)**	**Day 1**	**Day 2**	**Day 3**	**Mean**	**Std. Dev**	**% CV**
1	2	0.2006	0.1985	0.2001	0.1997	0.0011	0.5508
2	4	0.3994	0.4023	0.4010	0.4009	0.0015	0.3742
3	6	0.5994	0.5992	0.6018	0.6001	0.0014	0.2332
4	8	0.7982	0.8019	0.8011	0.8004	0.0019	0.2374
5	10	0.9977	0.9967	0.9956	0.9967	0.0010	0.1003

5. Recovery study (accuracy)

Recovery study was performed by spiking the different concentration solution on the SS Plate and then swabbed by swab sticks. Then analysis in UV and compared the absorbance of test solution with standard solution results.

Table. Recovery study

Conc.	**Abs. 1**	**Abs. 2**	**Abs. 3**	**Mean**	**Std. abs.**	**% Recovery**	**Mean Recovery**
2 ppm	0.1704	0.1689	0.1650	0.1681	0.1980	84.89	84.99
5 ppm	0.4315	0.4302	0.4287	0.4301	0.4991	86.17	
10 ppm	0.8469	0.8297	0.8395	0.8387	0.9993	83.92	

6. Limit of Detection

It was calculated based on standard deviation of response and slope of calibration curve

Table. Results of limit of detection

Conc. (ppm)	Absorbance		Mean Absorbance
	Absorbance 1	Absorbance 2	
0.1	0.0105	0.0106	0.01055
0.2	0.0221	0.0217	0.0219
0.3	0.0306	0.0308	0.0307
0.4	0.0422	0.0422	0.0422
0.5	0.0524	0.0516	0.0520

7. Limit of Quantitation

$$LOD = \frac{3.3 \times 0.01633}{0.1032} = 0.05222\ \mu g/ml$$

$$LOQ = \frac{10 \times 0.01633}{0.1032} = 1.8254\ \mu g/ml$$

Calculation of Maximum Allowable Residue

MAR is calculated by following formula

$$MAR = \frac{2.5 \times 0.001 \times 135 \times 1000 \times 1000}{1920} = 175.78\ mg$$

Estimation of Acceptance Limit for Each Swab

The acceptance limit for each swab is calculated according to the respective equipment surface area using following formula

$$\text{MAR value (per swab)} = \frac{175.78 \times 25}{408430.62} = 0.0707\ mg/swab$$

Table Results of Swab from vibrosifter

Sl. No.	Sampling point	Absorbance	Drug Precision (mg/swab)	Drug with recovery factor (mg/swab)
a	Hopper	0.0731	0.0073	0.0086
b	Bowl	0.0636	0.0063	0.0074
c	Gasket	0.0540	0.0054	0.0063
d	Chute	0.0453	0.0045	0.0053
e	Ring	0.0532	0.0053	0.0062
f	Sieve	0.0604	0.0060	0.0071

2. Multimill:

Table Results of Swab from Multimill

Sl. No.	Sampling point	Absorbance	Drug Precision (mg/swab)	Drug with recovery factor (mg/swab)
a	Hopper	0.0458	0.0046	0.0054
b	Rotor blade	0.0592	0.0059	0.0069
c	Sizing chamber	0.0342	0.0034	0.0040
d	Discharge Port	0.0406	0.0040	0.0047

3. Rapid Mixer Granulator:

Table Results of Swab from Rapid Mixer Granulator

Sl. No.	Sampling point	Absorbance	Drug Precision (mg/swab)	Drug with recovery factor (mg/swab)
a	Inlet Chute	0.0679	0.0068	0.0080
b	Impeller	0.0691	0.0069	0.0081
c	Chopper	0.0729	0.0072	0.0085
d	Discharge Port	0.0759	0.0075	0.0088
e	Gasket	0.0767	0.0076	0.0089
f	Internal Surface	0.0517	0.0051	0.0060
g	Landing Port	0.0568	0.0056	0.0066
h	Lid	0.0476	0.0047	0.0055

4 Fluidized Bed Drier

Table Results of Swab from Fludised Bed Drier

S No.	Sampling point	Absorbance	Drug Precision (mg/swab)	Drug with recovery factor (mg/swab)
a	Sieve	0.0754	0.0075	0.0088
b	Bowl	0.0470	0.0047	0.0055
c	Retarding Chamber	0.0450	0.0045	0.0053
d	View Window	0.0376	0.0037	0.0043
e	Plenum Bottom	0.0551	0.0055	0.0065

5. IPC

Std. Abs (10 ppm) = 0.9987

Wt. of Std Drug = 9.997 mg

Table Results of Swab from IPC

Sl. No.	Sampling point	Absorbance	Drug Precision (mg/swab)	Drug with recovery factor (mg/swab)
a	Inner Surface	0.0745	0.0074	0.0087

6. Bin Blender

Table Results of Swab from Bin Blender

Sl. No.	Sampling point	Absorbance	Drug Precision (mg/swab)	Drug with recovery factor (mg/swab)
a	Inner Surface	0.0491	0.0049	0.0058
b	Discharge Port	0.0395	0.0039	0.0046
c	Lid of Sampling Port	0.0465	0.0046	0.0054

7. Tipper

Table Results of Swab from Tipper

S No.	Sampling point	Absorbance	Drug Precision (mg/swab)	Drug with recovery factor (mg/swab)
a	Internal Surface	0.0243	0.0024	0.0028

A. Compression Area:

Std. abs (10ppm) = 0.9950

Wt. of Std. Drug = 9.960 mg

1. Compression Machine:

Table Results of Swab from Compression Machine

Sl. No.	Sampling point	Absorbance	Drug Precision (mg/swab)	Drug with recovery factor (mg/swab)
a	Connector	0.0289	0.0029	0.0034
b	Powder Hopper (LHS)	0.0435	0.0043	0.0051
c	Powder Hopper (RHS)	0.0374	0.0037	0.0044
d	Feed Frame	0.0590	0.0059	0.0069
e	Tablet discharge port (LHS)	0.0536	0.0053	0.0062
f	Tablet discharge port (RHS)	0.0721	0.0072	0.0085
g	Turret	0.0610	0.0061	0.0072

2. Deduster (LHS):

Table Results of Swab from Deduster (LHS)

Sl. No.	Sampling point	Absorbance	Drug Precision (mg/swab)	Drug with recovery factor (mg/swab)
a	Turret	0.0780	0.0078	0.0092
b	Drum	0.0676	0.0067	0.0079

3. Deduster (RHS)

Table 7.3.1 Results of Swab from Deduster (RHS)

Sl. No.	Sampling point	Absorbance	Drug Precision (mg/swab)	Drug with recovery factor (mg/swab)
a	Turret	0.0759	0.0076	0.0089
b	Drum	0.0745	0.0074	0.0087

4. Metal Detector (LHS):

Table Results of Swab from Metal Detector (LHS)

S No.	Sampling point	Absorbance	Drug Precision (mg/swab)	Drug with recovery factor (mg/swab)
a	Outlet chute	0.0428	0.0043	0.0051
b	Feeding chute	0.0752	0.0075	0.0088
c	Hopper	0.0433	0.0043	0.0051
d	Vibration plate	0.0743	0.0074	0.0087
e	Rejection box	0.0649	0.0065	0.0076

5. Metal Detector (RHS):

Table Results of Swab from Metal Detector (RHS)

S No.	Sampling point	Absorbance	Drug Precision (mg/swab)	Drug with recovery factor (mg/swab)
a	Outlet chute	0.0377	0.0038	0.0045
b	Feeding chute	0.0402	0.0040	0.0047
c	Hopper	0.0459	0.0046	0.0054
d	Vibration plate	0.0455	0.0045	0.0053
e	Rejection box	0.0514	0.0051	0.0060

C. Inspection Area:

Std. abs (10ppm) = 0.9940

Wt. of Std. Drug = 9.97 mg

1. Tablet Capsule Sorter:

Table Results of Swab from Tablet Capsule Sorter

S No.	Sampling point	Absorbance	Drug Precision (mg/swab)	Drug with recovery factor (mg/swab)
a	Hopper	0.0551	0.0055	0.0065
b	Vibration plate	0.0549	0.0055	0.0065

c	Inspection roller	0.0587	0.0059	0.0069
d	Outlet plate	0.0638	0.0064	0.0075

D. Coating Area:

1. Auto Coater:

Table Results of Swab from Auto Coater:

S No.	Sampling point	Absorbance	Drug Precision (mg/swab)	Drug with recovery factor (mg/swab)
a	Inner surface of coating pan	0.0690	0.0069	0.0081
b	Baffle	0.0068	0.0068	0.0080
c	Discharge chute	0.0054	0.0054	0.0063

E. Packaging Area:

Std. abs (10ppm) = 0.9950

Wt. of Std. Drug = 9.975 mg

1. Blister Packing Machine:

Table Results of Swab from Blister Packing Machine

S No.	Sampling point	Absorbance	Drug Precision (mg/swab)	Drug with recovery factor (mg/swab)
a	Hopper	0.0603	0.0060	0.0071
b	Vibration plate	0.0731	0.0073	0.0086
c	Feeding box	0.0515	0.0051	0.0060

Discussion

The Maximum Allowable Residue (MAR) is 175.78 mg calculated as per the formula. The Maximum Allowable Residue (MAR) for each swab is 0.0107 mg/swab. All sampling point samples are analyzed UV microscopy. Results of all swabs are below the MAR. So it shows that the cleaning validation of Losartan Potassium is found acceptance limit. The analytical method validation is performed by UV spectrophotometer. In the experimental work we found linearity range is 2-10 μg/ml as per Beer Lambert Law. The correlation coefficient is 0.9979. It is calculated by calibration curve. The slope of given results is 0.1015 and intercept is -0.0158. For the precision study the test applied on 6 replicate at same sample. The result of repeatability in terms of percentage of coefficient variance is 0.1205 and standard deviation is 0.0012. The result of intraday reproducibility in terms of percentage coefficient of variance is 0.2323. The result of interday reproducibility in terms of percentage of coefficient of variance is 0.2992.

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