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Cleaning Validation and Residual Analysis of Telmisartan Drug

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Abstract

Introduction: Cleansing validation is a foremost and complete activity which is used for industrial purposes to provide maximum protection to evolve medicinal products, such as removing particulate matter, chemicals, and adulterant microorganisms that lie in active substance of medicinal products in a part of machines that is produced or being manufactured. Cleansing validation has long been recognized as the gold standard for ensuring the effectiveness, quality, and constancy of manufacturing machines and produced goods of guaranteed standard. **Materials and Methods:** In order to quantify Telmisartan residues in samples from various parts of the equipment surfaces after Telmisartan 40mg tablets were manufactured, a swab sampling and HPLC method have been developed and verified. **Results:** The residual sample recovery was found to be less than 80 % limit. The HPLC method was prepared using mobile phase preparation, a temperature in the column of 40℃, and 298 nm detector wavelength. The detection and quantification limits were discovered to be 0.05 mcg/ml and 0.14 mcg/ml, respectively. During the analysis of residues, no contamination occurred with the swab solution or samples. **Conclusion:** As a result, after the production of Telmisartan 40 mg tablets, this method can be used to quantify Telmisartan residues.

Key Words:
Telmisartan, Cleaning Validation, Swab Solution.

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INTRODUCTION:

Medicinal items are the most important component of healthcare and must be manufactured with the highest level of quality, safety, and efficacy. Multiple principles for achieving such quality are currently of particular relevance in medicinal industry. Medicinal products and active substances can be adulterated by a variety of pharmaceuticals or APIs, cleansing agents, germs, or other factors such as aerial particles, dirt, basic materials, intermediary, and so on. Cleaning procedures are the processes that ensure that potentially hazardous chemicals are efficiently removed from equipment. This can be reduced by cleaning the equipment, apparatus, and processing area thoroughly. As a result, validation of cleaning techniques is required to verify the compliance with regulatory criteria in pharmaceutical product manufacture, as well as the protection, effectiveness, and standard of successive group of medicinal product [1].

The best cleaning practice during drug substance manufacture provide suitable operator safety precautions, systematic calibration, representation of equipment, and equipment surveillance, sample selection, approval standard, and analytical method identification standard [2]. Cleaning validation is a

recorded procedure that shows that the cleaning methods utilized are effective inside a facility consistently control cross contamination. To ensure compliance with cGMP rules, pharmaceutical producers must validate their cleaning procedure [3]. Pharmaceutical products and drug compounds must be manufactured under strict supervision to reliably replicate the intended product quality, with cross-contamination control playing a vital role. Residual components from a prior similar product or another product can be used over the following lots of the same product, affecting its impurity profile. An efficacious cleansing system must prepare recorded documentation at a facility's cleansing techniques constantly manage every possible residual outcome (intermediary and adulterants), cleansing agents, and external substance in future outcome with below the predetermined levels [4].

To assure the protection, efficiency & the standard of consequent packages of the drug products, its critical to validate cleaning procedures that strictly adhere to the guidelines and methods developed for the same [5,6]. Contamination and cross contamination in the pharmaceutical sector are conceivable as a result of insufficient cleaning of equipment, apparatus, processing regions, or beginning materials, which can result in significant risks. As a result, we cannot afford any contamination or cross contamination in the pharmaceutical industry. This can be reduced by cleaning the equipment, apparatus, and processing area thoroughly. With the assistance of GMP, the industry aims to fulfil these primary objectives [7]. Cleaning and cleaning validation are two procedures that help to reduce patient risk by keeping cross-contamination between things to acceptable levels. By introducing the residual from the preceding batches, cleansing agents, and other extrinsic substances into the manufacturing process, or incomplete or faulty cleansing might lead to a contaminated product. Cleansing validation is essential, since the number of potent and complicated medicinal compounds and biotechnology products increases [8]. To ensure compliance with cGMP rules, pharmaceutical manufacturers must validate their cleaning procedure. Enhancing the equipment off-peak periods has a significant prospect to improve pharmaceutical manufacturing efficacy and profitability. Cleaning validation is also helpful in associated research like packing component cleaning validation [9].

Validation for cleaning a group of chemicals was accomplished using swab sampling and rinse solution techniques, as well as HPLC for analyte separation and detection. The significance of the sampling method, the characteristics of the swab, the solvent, the swabbing method, and the material content of the contact surfaces of the product in the manufacturing equipment has been examined for the swab and rinse sampling method, the quantitative cleaning verification method, and the API level and nature. Assessment of Swab and Rinse Sampling Methods & Determination of Recovery Rates in Cleansing Validation contemplating the Different Surfaces, Quantity & Types of Residues and impurities [10]. The cleansing validation technique has sparked substantial debate in the pharmaceutical business. Several goods have been recalled in the last 10 years because of recontamination and poor cleansing efforts [10]. Cleansing Validation is a formalised procedure that demonstrates how thoroughly, and consistently pharmaceutical production equipment is cleaned [11, 12]. Cleansing validation is the recorded procedure in the pharmaceutical sector for an integrated documented authentication to achieve homogeneous safe product development [13]. Cleaning validation is an observed technique that verifies the potential and constancy of cleansing pharmaceutical production equipment, as well as a specific cleaning process's capacity to offer consistent and reproducible cleaning outputs that fulfil a predefined standard Contaminants related to bacteria, previous outcomes (such as residues API and excipient), Decontaminants residues, aerial pollutants such as fine particles or matters, that can react with the medicinal products [3]. Cleansing validation demonstrates that an approved cleaning operation produces equipment suitable for the processing of pharmaceutical products. In terms of regulatory compliance, cleaning pharmaceutical equipment is becoming increasingly critical. A sample of the product contact surfaces of the equipment must be taken to ascertain the amount residuals present in order to evaluate the cleaning procedure [13]. Cleansing Validation is an approach used to assure that a cleansing operation removes residuals of a product's active pharmaceutical components generated from parts of tools, as well as the cleansing assists utilized in the cleansing process and the cleansing process microbiological characteristics. All remains are eliminated in pre-established amounts assuring that the preceding product's waste does not degrade the succeeding product's standards that are being generated. [14]. Cleaning validation is critical in lowering the risk of product contamination from pharmaceutical manufacturing facilities. The key objective of the cleansing process validation is to guarantee adherence with the

Government policies and Federal regulations [10]. Cleansing validation should be undertaken whenever drug products may come into touch with the equipment to ensure any cleansing treatment's efficacy. The pharmaceutical manufacturing industry realizes that after each manufacturing process of drug products, cleaning the manufacturing equipment and the manufacturing area is required by regulatory bodies [5]. It's a critical systematic obligation of the pharmaceutical industry's quality management system, and this process assures that the cleansing operation efficiently eliminates residual processing equipment and production area below a pre-estimated threshold. This process assures the standards of various products & also is a valuable tool that meets the requirements of EUGP and the USFDA [15]. In general, regulatory agencies and frequently practicing pharmaceutical industries approved of two sorts of sampling procedures. The two most common ways of sample collection of the manufacturing equipment is direct sample & the other one is to employ rinse sampling. The two benefits of rinsing samples are to cover wider space and unreachable areas/parts. The disadvantages are that the particulate matter might be insoluble or clogged on the production surface area. [15].

Telmisartan is an anti-hypertensive white to slightly yellowish solid-state drug, that is water insoluble, & in the pH range 3-9, sparingly soluble in strong acid (except hydrochloric acid), and fully soluble in strong base, with a melting point 261-263℃. Its purity factor is 99.80%w/w and available in 20-80 mg [16].

Telmisartan is an angiotensin II non-peptide antagonist that works on the AT-I receptor subtype. The ACE kinase II transforms angiotensin-I into angiotensin-II. Vasoconstriction is caused by angiotensin II, activation of aldosterone production and release, stimulation of heartbeat, as well as salt reabsorption by the kidneys. Telmisartan blocks angiotensin II's vasoconstrictor actions. It's an angiotensin II receptor with a binding ability 3000 times higher than AT-II antagonist with a greater bond for the Angiotensin-I receptor (AT-1). Of all ARBs, Telmisartan has the extensive half-life compared to any other substance (24 hours) and highest distribution volume. Apart from suppressing RAS, it selectively modulates the activity of PPAR, a crucial insulin and glucose metabolism regulator. With regard to diabetes and cardiovascular disease (CVD), the dual method of action of telmisartan is anticipated to offer protection against vascular and kidney damage [16].

MATERIALS AND METHOD:

REAGENTS & CHEMICALS:

Telmisartan (Reference std.), Distilled water, Sterile cotton swab sticks by Himedia Laboratories Pvt.Ltd Mumbai, Methanol HPLC, AR Grade Ammonium dihydrogen phosphate, AR Grade Sodium hydroxide, AR Grade Orthophosphoric Acid, Water HPLC Grade, C18 column, HPLC system with UV detector, 10 x10 cm stainless steel plate, Teflon plate, Silicon rubber, FBD Bag cloth Required glass wares.

INSTRUMENTATION:

The experiments were carried out in HPLC system, Lab solution software, auto sampler, column C-18, UV detector [10, 12, 13, 17].

SELECTION OF ANALYTICAL VALIDATION PARAMETERS:

The stated systematic method for the measurable determination for Telmisartan in swab samples from drug product production of the Telmisartan tablets equipment surface area after manufacturing was validated according to the guidelines. [15] The analytical parameters chosen for the validation technique for collection through the swab samples: Specificity, Accuracy, Linearity, Repeatability, LOD&LOQ [9, 18, 19, 20].

HPLC method

Preparation of Standard: In a 50 mL volumetric flask, accurately weigh 20 milligrams of Telmisartan WRS. 10 mL Methanol of is added to dissolve, and the volume is made up against the remaining Methanol and shaken rigorously. Pipette out 5 mL of this solution into a 200 mL volumetric flask, dilute it and make up the volume with Methanol. Methanol should be used to dilute 5 mL to 50 mL.

Sample preparation: Wipe a defined area of 10 x10 cm in the area required with a cotton swab which is wetted with Methanol and Transfer it to a 10 ml stoppered test tube filled with Methanol. Close the stopper and shake vigorously. Filter.

Chromatographic Parameters:

Developed method was utilized by using a C18 column (4 cm×4.0 mm), mobile phase (70:30), 5 micrometres, methanol. Mobile phase was prepared using Ammonium dihydrogen phosphate buffer with pH adjusted to 3.0 With a column temperature of 40°C, the flow rate was 0.7 ml/min., wavelength to be detected at 298 nm and sample injection volume of 5µL [15].

Procedure: Inject the prepared standard and sample solution in 6 replicates separately into the liquid chromatogram and observe for the main peak areas.

ANALYTICAL METHOD VALIDATION PARAMETERS:

SPECIFICITY: The Specificity put-forth by this strategy is demonstrated by appropriately separating and computing the peak of interest. The method's

specificity was tested by injecting standard solution, environment control and a negative swab sample. Disperse uniformly 1 ml of Methanol on a stainless-steel plate of dimension 10 × 10 cm. Air dry the plate. Swab the plate by means of a cotton swab wet with Methanol. Then pour the same into a stoppered test tube with 10 ml of Methanol. Analyse the solution for the presence of telmisartan. There should not be any response at the retention time of Telmisartan or the area obtained should be less than the area of LOD solution [17].

ACCURACY:

The accuracy of the method was evaluated by comparison between the computed analytical quantity and a known amount spiked at different concentration levels with measurements for each concentration level obtained [12].

Sample Preparation for Stainless steel plate/Teflon plate/Silicon rubber:

Prepare a solution containing 10mcg/ml Telmisartan in Methanol. Disperse uniformly 1 ml of the solution on a stainless steel plate/Teflon plate/Silicon rubber of dimension 10×10 cm. Air dry the plate. Swab the plate by means of a cotton swab wet with Methanol. Then pour the same into an enclosed test tube with 10 ml of Methanol. Mix it well and analyse by HPLC. Compare against a standard solution as given under the procedure. Calculate the recovery against the amount that was sprayed. Repeat the procedure twice. Similarly, calculate the recovery by spraying 0.5 ml - 1.5 ml of the standard solution three times each. 1ml corresponds to 10ppm, 0.5 ml and 1.5 ml corresponds to 5ppm and 15ppm respectively.

Sample Preparation for FBD bag cloth:

Prepare a solution containing 10mcg/ml Telmisartan in Methanol. Disperse uniformly 1 ml of the solution on a FBD bag cloth of dimension 10×10 cm, placed inside the Petri dish. Air dry the plate and pour 10 ml of the diluent to FBD bag placed inside the Petri dish. Swirl and Sonicator and analyse by HPLC. Compare against a standard solution as given under the procedure. Calculate the recovery amount that was sprayed. Repeat the procedure twice.

Similarly, calculate the recovery by spraying 0.5 ml - 1.5 ml of the standard solution three times each. 1 ml corresponds to 10 ppm, 0.5 ml and 1.5 ml corresponds to 5 ppm and 15 ppm respectively.

Standard Preparation: Prepare as given under method of analysis.

Calculate the amount sprayed as follows:

$$\frac{\text{Weight of WRS taken} \times 5 \times 1000 \times \text{Volume Sprayed} \times \text{Purity of WRS}}{100 \qquad 100 \qquad 100}$$

Calculate the amount obtained by the analysis:

$$\frac{\text{Test Area} \times \text{Std wt} \times 5 \times 5 \times \text{Purity of WRS}}{\text{Std area} \qquad 50 \qquad 200 \quad 50 \qquad 100}$$

Recovery is not less than 80.0% at each spike level. RSD at each spike level is not more than 10.0%.

LINEARITY:

Linearity has been examined across a narrow drug concentration range of 0.5 to 1.5 mcg/ml. The regression line's correlation coefficient (R2 =0.999) indicated an acceptable association between absorbance and Telmisartan concentration.

The maximum Telmisartan content limit in swab is 10 mcg which corresponds to 1 mcg/mL in the sample preparation. Prepare concentrations ranging from 50% to 150% of 1mcg/mL. (0.5 mcg/mL, 0.8 mcg/ml, 1.2mcg/ml, and 1.5mcg/ml). Analyse the solutions and record the areas obtained. Plot the concentration against area obtained. Calculate the coefficient of correlation square [12].

REPEATABILITY:

Repeat the method as performed under Accuracy, by a second analyst.

DETECTION AND QUANTIATION LIMIT:

To assess the concentration limits as LOD and LOQ, a range of linearity solutions from 0.01 mcg/mL to 0.8 mcg/mL concentrations were made, and the correlation coefficient' square, slope of the curve, and y-intercept were determined. The response standard deviation and slope were used to calculate the LOQ. Prepare standard solution and dilute them volumetrically to give solutions having concentrations ranging from 1.0 mcg/ml to 1 mcg/ml. Inject into the HPLC system and note down the areas.

From the residual sum of squares method, determine

LOD and LOQ:

i. LIMIT OF DETECTION (LOD):

$$\frac{10 \times \text{Residual standard deviation}}{\text{Slope}}$$

ii. LIMIT OF QUANTIATION (LOQ):

$$\frac{3.3 \times \text{Residual standard deviation}}{\text{Slope}}$$

RESULTS:

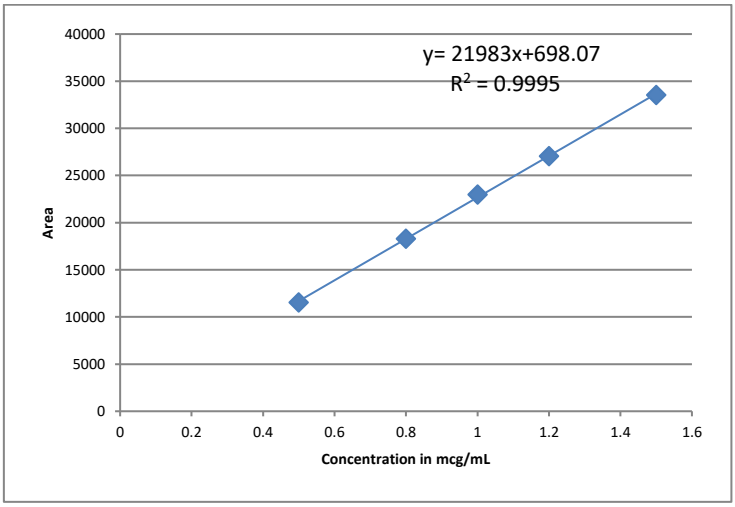

Figure 1. Linearity curve of Telmisartan

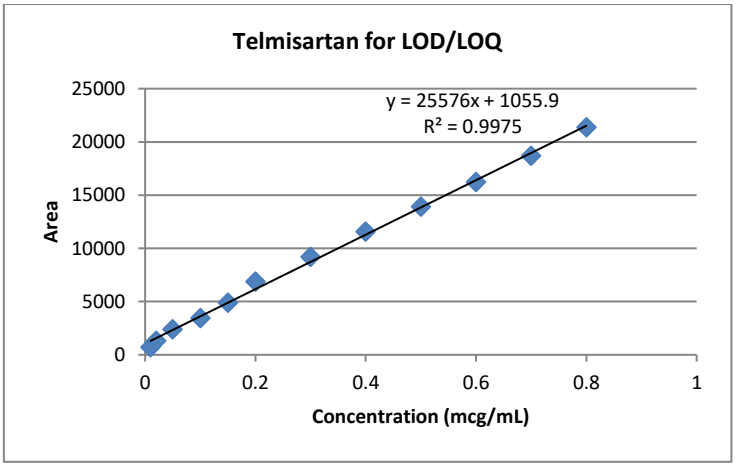

Figure 2. LOD &LOQ

DISCUSSION:

The methods of analysis have been developed to identify the linearity, precision, accuracy, specificity and sensitivity well enough to detect the traces of contaminants in minimal amounts. This analytical technique was performed for determining the metrics mentioned in the above statement and LOD & LOQ and Repeatability.

SPECIFICITY:

During the procurement time of the analyte, NIL intervention was observed from the extracted blank swab or the extraction solvent. There was no response at the Telmisartan retention time. The method is unique to Telmisartan.

ACCURACY:

In accuracy the concentration were spiked at different levels and their recovery percentage is obtained from the range of 50-150%. Recovery was

found greater than 80% at each spike level and RSD at each spike level is less than 10.0%. Method is Accurate (Tables 1, 2, 3).

LINEARITY:

Linearity was evaluated at concentrations ranging from 0.5 to 1.5 mcg/ml and the drug concentration observed in the areas obtained. Coefficient of correlation square is found to be 0.997. It was bound to be linear in the operating range from 50 -150 %(Table 7 & Figure 1).

REPEATABILITY:

Repeat the method as performed under Accuracy, by a second analyst. Recovery was found greater than 80 % at each spike level and RSD at each spike level is less than 10.0 %. Method is accurate (Tables 4, 5, 6).

LIMIT OF DETECTION AND LIMIT OF QUANTIATION:

It was determined using residual sum of squares method by residual standard deviation and slope. The LOD value obtained is 0.05 mcg/ml LOQ is 0.14 mcg/ml (Table 8 & Figure 2).

TABLES:

Table 1. Accuracy Result of Telmisartan in stainless steel plate

50% Recovery	100% Recovery	150% Recovery
98.17 %	99.71 %	96.12 %
100.60 %	99.34 %	95.96 %
97.25 %	100.23 %	96.44 %
RSD= 1.76%	**RSD = 0.45%**	**RSD=0.25%**

Table 2.Accuracy Result of Telmisartan in Sillicon Rubber

50% Recovery	100% Recovery	150% Recovery
96.17 %	96.81 %	98.20 %
98.16 %	97.49 %	97.48 %
94.89 %	96.29 %	97.56 %
RSD= 1.71%	**RSD= 0.62%**	**RSD= 0.40%**

Table 3.Accuracy Result of Telmisartan in FBD Bag Cloth

50% Recovery	100% Recovery	150% Recovery
103.14 %	98.45 %	95.88 %
101.54 %	99.56 %	95.86 %
98.86 %	100.27 %	96.39 %
RSD =2.14%	**RSD = 0.93%**	**RSD = 0.31%**

Table 4.Repeatability Result of Telmisartan in Stainless steel plate

50% Recovery	100 % Recovery	150% Recovery
97.46 %	98.81 %	95.30 %
99.28 %	98.31 %	96.76 %
98.83 %	100.32 %	95.48 %
RSD = 0.96 %	**RSD = 1.06 %**	**RSD = 0.83 %**

Table 5. Repeatability Result of Telmisartan in Teflon plate

50 % Recovery	100 % Recovery	150 % Recovery
103.96 %	95.03 %	102.49 %
104.43 %	95.50 %	104.07 %
105.73 %	97.04 %	102.58 %
RSD = 0.87%	**RSD = 1.10%**	**RSD = 0.86%**

Table 6.Repeatability Result of Telmisartan in FBD Bag cloth

50 % Recovery	100 % Recovery	150 % Recovery
99.74 %	99.67 %	96.26 %
100.91 %	99.72 %	97.83 %
100.03 %	100.98 %	96.35 %
RSD = 0.61 %	**RSD = 0.74 %**	**RSD = 0.91 %**

Table 7. Linearity results of Telmisartan as follows:

Concentration (mcg/ml)	0.5	0.8	1	1.2	1.5
Area	11545	18290	22980	27048	33542

Table 8.Limit of Quantification & Limit of Detection follows:

S.No	Concentration (mcg/mL)	Area
1.	0.01	702
2.	0.02	1322
3.	0.05	2403
4.	0.1	3463
5.	0.15	4895
6.	0.2	6869
7.	0.3	9195
8.	0.4	11563
9.	0.5	13918
1(	0.6	16241
1:	0.7	18690
1:	0.8	21367

CONCLUSION:

To validate the cleaning procedure, swab sampling and HPLC were used to quantify Telmisartan residues on various parts of equipment surfaces following the manufacture of Telmisartan 40 mg tablets. This method was considered appropriate based on the specificity, accuracy, and linearity of the swab samples collected. During the residue analysis, there was no interference from the swab solution or samples. As a result, The method indicated that the cleaning procedures used were effective in eliminating leftover residues from equipment surfaces while keeping contamination levels below the contamination limit. After assessing the numerous parameters, it is determined that the produced results meet the pre-established acceptance standards. As a result, the technique was used for swab testing after cleaning of equipment used after the manufacture of Telmisartan tablets 40 mg is approved and suitable for regular analysis. It's important to note that this is a general outline, and specific details and requirements may vary depending on regulatory guidelines and company-specific protocols. Therefore, it is recommended to consult relevant guidelines and regulatory authorities for a more detailed understanding of the cleaning method validation process for Telmisartan Tablet 40 mg in solid dosage form using HPLC.

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CONFLICTS OF INTEREST:

There is no competing interest.

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