RESEARCH ARTICLE

Laboratory Glassware Cleaning Validation by Liquid Chromatographic Quantitation of Betamethasone Valerate Residues

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ABSTRACT

Use of clean glassware ensures reliability of analyses that are carried out in laboratories. Glassware should be free of contaminants and residues from previous tests. It is therefore necessary to demonstrate the efficiency of glassware cleaning procedure through validation. This study aimed to evaluate the cleaning efficiency of laboratory glassware by quantitation of betamethasone valerate residues in cleaned glassware. Betamethasone ointment was selected through a risk ranking process as the worst to clean product. Glassware used in analysis of this drug product was cleaned manually and residues evaluated using high performance liquid chromatography. The analysis method was validated at concentration levels of 1 - 8 µg/ml for specificity, accuracy, precision, linearity, limit of detection and limit of quantitation. The method demonstrated residue recovery of 97%. Repeatability and inter-mediate precision expressed as relative standard deviation were 1.2% and 1.4%, respectively. The calibration curve was linear over a concentration range from 2.04 to 6.13 µg/ml with a correlation coefficient of 0.9997. The detection limit and quantitation limit were 0.11 µg/ml and 0.34 µg/ml, respectively. No residue was detected in glassware that was sampled for the cleaning validation. The results indicate that the manual cleaning method is effective as the level of betamethasone residues in cleaned glassware was below detection limit and thus will not interfere with analysis of the subsequent analyte.

Key Words: betamethasone, cleaning, glassware, validation

I. INTRODUCTION

Cross contamination in pharmaceutical production can impact both product safety and quality. Good Manufacturing Practices (GMP) demand control and prevention of contamination at every step of production (Sutton, 2012). In multi-product manufacturing facilities, prevention of possible cross-contamination is a key component of quality assurance during manufacturing (Khan et al., 2020; Velkovska et al., 2020). Non-dedicated equipment should be effectively cleaned to avoid contamination of subsequent product (Sargent et al., 2016). Cleaning methods employed within a facility should consistently control potential carryover of drug substance and cleaning agents into subsequent product (Raj Pal et al., 2018). Consequently, pharmaceutical manufacturers must validate cleaning processes to ensure compliance with GMP regulation (Datta & Abdullahi, 2020). Cleaning validation is a documented process that demonstrates the effectiveness and consistency in cleaning pharmaceutical production equipment (Sandagar & Mulik, 2019). It is a tedious procedure and validation of every cleaning process used in production is impractical. The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Q7A simplifies cleaning validation by use of the worst-case product and the choice should be justified (Raj, 2014; Porto et al., 2016). A risk matrix approach is used to select the worst-case product for the validation (Badawi et al., 2016). An appropriate analytical method should be selected, with ability to detect very low concentration of residues and produce a result that has a logical, scientific link with the target residue (Ramandi & Asgharian, 2020; Zaheer & Zainuddin, 2011). The method should be evaluated for accuracy, reproducibility and interferences including cleaning agents**.**

Cleaning validation applies to procedures that are used to clean equipment employed during the various steps of a manufacturing process. United States Food and Drug Administration (USFDA) regulations CFR 211.67 exempts laboratory glassware from the processing equipment cleaning validation program. Nonetheless, the USP pharmacopoeia stipulates that glassware must be clean and requires verification that the cleaning procedure is appropriate for the particular test or assay. In multiproduct facilities and research laboratories, a well performed process may give erroneous results if insufficiently cleaned glassware is used. Glassware that is not properly cleaned makes it difficult to determine if the source of aberrant analytical results is related to the inadequately uncleaned glassware or residues from manufacturing equipment (Hughes et al., 2007)). Pharmaceutical firms are expected to maintain laboratory glassware in a clean and sanitary manner to provide confidence in the analytical results (Pluta, 2007). It is therefore important to demonstrate the efficiency of glassware cleaning procedure through a validation program (Polonini et al., 2011; Sandale et al., 2016). The objective of cleaning efficiency testing is to provide the evidence that the glassware is consistently cleaned of product, to prevent possible cross-contamination (General European QM document, Polonini et al., 2011).

In this study, cleaning validation of laboratory glassware was performed at Elys Chemical Industries Ltd., Kenya. Elyvate ointment containing betamethasone valerate 0.1% w/w was identified as the worst-case product for validation. Glassware cleaning efficiency of this product was executed as per the validation protocol of product processing equipment and acceptance criteria. Betamethasone residues were extracted from the cleaned glassware and recovered from the extraction solvent. High performance liquid chromatography (HPLC) technique was used to

quantify betamethasone residues in cleaned glassware. The method was validated according to I*nternational Council for Harmonisation* (ICH) Q2 (R1) guidelines for specificity, accuracy, precision, limit of detection and quantitation, range and linearity (Hassouna & Mohamed, 2019); ICH, 2005).

II. METHODOLOGY

A. Materials

HPLC grade absolute ethanol was purchased from Chemoquip Limited, Kenya. Freshly distilled water was prepared at Elys' quality control laboratory, betamethasone valerate working standard was qualified against betamethasone valerate CRS EP standard. Analytical solutions were filtered through 0.45 µm hydrophilic nylon filter membranes.

B. Methods

Identification of worst to clean product

The worst-case product was identified through a risk ranking process. Three risk parameters in cleaning process; solubility of drug substance in water, degree of difficulty in cleaning of the product based on experience (interviews with operators) and type of dosage form were used to calculate the risk score. For each product, a number was assigned to each of the three risk parameters depending on severity of the associated risk as presented in Tables 1-3. A scale scoring of 1-5 was adopted for type of dosage form, 1-7 for solubility of drug substance and 1-2 for cleanability of the product. An insoluble drug substance was assigned a high score than a freely soluble one. Solubility of the drug substances was obtained from the British and USP pharmacopoeias. A high score was assigned to colored products and oil-based dosage forms. For each product, the risk values obtained from the three parameters considered were multiplied to arrive at risk priority number (RPN). A product risk matrix was prepared for all the products that were assayed at the facility (Table 4). The product with the highest RPN score was selected as the worst-case for the cleaning validation.

Sample preparation

Elyvate ointment containing betamethasone valerate 0.1% w/w was identified as the worst-case product. Sample and standard solutions for the study were prepared in the specified glassware as directed in the assay monograph of betamethasone valerate ointment. The prepared solutions were discarded and the glassware to be evaluated for cleanliness selected at every step of analysis as follows: 2 x 25 ml and 2 x 100 ml volumetric flasks, 2 x 100 ml beakers and 2 x 5 ml bulb pipettes. Two HPLC sample vials were also selected. The glassware was cleaned immediately after use as directed in the laboratory standard procedure. The glassware was first cleaned with hot water to remove the ointment base. This was followed by thorough cleaning using freshly prepared Teepol solution 1% v/v and rinsed with tap water and then 3 rinses with deionized water. The glassware was dried on laboratory draining rack. Recovery of residues was carried out by rinsing the cleaned and dry glassware with absolute ethanol as the extraction solvent. Glass beakers were rinsed with 25 ml of the extraction solvent, 25 ml and 100 ml volumetric flasks were filled to mark with the solvent and shaken, the HPLC vails were rinsed with 1.5 ml of the solvent, while bulb pipettes

were rinsed with a quantity of solvent equivalent to their respective capacity. The Accepted criterion for carryover *residues* was set at not more than 0.11 ppm (limit of detection).

Betamethasone valerate analytical method

Chromatographic analyses of samples were performed with Shimadzu *LC*-20A*D* HPLC system equipped with PDA detector, degasser, quaternary pump and an auto sampler. The output signals were monitored and processed using LC solution software. The chromatographic conditions included a Phenomenex column C_{18} 4.6 mm x 150 mm with particle size of 5 µm. The mobile phase was a filtered and degassed mixture of absolute ethanol and water in the ratio 42:58, with flow rate set at 1.0 ml/min. The column temperature was maintained at 45 °C. Sample injection volume was 10 µl and the eluted compound was monitored at a wavelength of 238 nm. The standard was prepared by dissolving an appropriate amount of betamethasone valerate working standard in absolute ethanol to obtain an initial stock solution of 0.2 mg/ml which was diluted to obtain a final concentration of 0.004 mg/ml.

Analytical method validation

The ICH Q2 (R1) method validation guideline was followed to assess specificity, accuracy, precision, linearity, limit of detection and limit of quantitation.

System suitability test

System suitability test (SST) was verified by Injecting 5 replicate injections of the standard solution into the chromatograph and calculating the Relative Standard Deviation (RSD) of retention time and Area. The RSD of retention time and area should be less than 2.0%.

Specificity

Specificity was demonstrated by injecting the cleaning agent, blank, sample and comparing the peaks observed in sample solution with standard solution.

Precision

The precision of the method was assessed by analyzing six individual samples of betamethasone valerate at 100% of the test concentration and calculating the relative standard deviation of the peak areas.

Accuracy

Accuracy for the residue recovery was established on three concentration levels (50%, 100% & 125%) analyzed and the percentage recovery calculated. Stock solution of the betamethasone valerate material was prepared. Three samples at each concentration level above were prepared by spiking 0.5 ml, 1.0 ml and 1.2 ml for 50%, 100% & 125% concentration levels respectively and separately in to 50 ml glass volumetric flask and left to dry. The residue was recovered by rinsing the 50 ml glass volumetric flask with ethanol.

Linearity

Linearity of the detector response was established by analysing standard solution at five concentrations; 50%, 75%, 100%, 125% & 150% equivalent to 2, 3, 4, 5, & 6 µg/ml respectively.

Limit of Detection (LOD) and Limit of Quantitation (LOQ)

The LOD and LOQ were determined based on the Standard Deviation of the Response and the Slope.

C. Ethical considerations

This study was performed as an obligation for compliance with Good Manufacturing Practices and continuous quality improvement and qualified for ethical exemption.

III. RESULTS

A. Identification of worst to clean drug product

Three risk parameters in glassware cleaning process; solubility of drug substance in water, degree of difficulty in cleaning of the product and dosage type and the respective risk scores are presented in Tables 1-3. High risk score was assigned to drug substances that are practically insoluble, oil-based formulations, coloured drug products and those products reported by operators to be difficult to clean. Very soluble drug substances for example, ascorbic acid was assigned a score of 1 whereas insoluble ones such as betamethasone and frusemide were assigned a high score. Table 4 presents the risk matrix for identification of worst-case drug product for validation and the deduced RPN values of drug products manufactured at the facility. Elyvate (betamethasone valerate 0.1% w/w) ointment and sulphur ointment were identified as hard to clean products with the same RPN score of 70. Elyvate ointment was selected as the worst- case product for the cleaning validation due to high selectivity and sensitivity of HPLC technique employed in analysis of this product.

Table 1:

Solubility Risk Ranking

Drug substance solubility (Part of solvent per part of solute)	Risk score
< 1	1
1-10	2
10-30	3
30-100	4
100-1000	5
1000-10000	6
>10000	7

Table 2:

Dosage Form Risk Ranking

Dosage form	Risk score
Syrup	1
Suspension	2
Tablet	3
Cream	4
Ointment	5

Table 3:

Cleanability Risk Ranking

Cleanability	Risk score
Easy to clean	1
Difficult to clean	2

Table 4:

Risk Matrix for Identification of Worst-Case Validation Drug Product

Product	Dosage form	Solubility	Cleanability	RPN
1. Cotrimoxazole Suspension	2	7	2	28
2. Cotrimoxazole Tablets	3	7	2	42
3. Ascorbic Acid Tablets	3	1	1	3
4. Aspirin Tablets	3	5	2	30
5. Hyoscine Tablets	3	1	1	3
6. Clotrimazole Tablets	3	7	2	42
7. Clotrimazole Cream	4	7	2	56
8. Chlorpromazine Tablets	3	2	1	6
9. Ciprofloxacin Tablets	3	3	1	9
10. Chlopheniramine Syrup	1	1	1	1
11. Chlopheniramine Tablets	3	1	1	3
12. Cold Capsules	3	4	1	12
13. APC Tablets	3	5	2	30
14. Doxycycline Capsules	3	2	1	6
15. Erythromycin Tablets	3	7	2	42
16. Erythromycin Syrup	2	7	2	28
17. Metronidazole Tablets	3	5	2	30
18. Metronidazole Suspension	2	5	2	20
19. Chloramphenical Capsules	3	5	2	30
20. Chlopheniramine Suspension	2	5	2	20
21. Hydrocortisone Cream	4	7	2	56
22. Paracetamol Suspension	2	4	1	8
23. Mepyramine Cream	4	3	1	12
24. Betamethasone Cream	4	7	2	56
25. Betamethasone Ointment	5	7	2	70
26. Levamisole Tablets	3	7	2	42
27. Levamisole Suspension	2	7	2	28
28. Folic acid Tablets	3	7	2	42

29. Frusemide Tablets	3	7	2	42
30. Nystatin Cream	4	6	2	48
31. Nystatin Tablets	3	7	2	42
32. Nystatin Suspension	2	7	2	28
33. Griseofulvin Tablets	3	7	2	42
34. Ibuprofen Tablets	3	7	2	42
35. Ibuprofen Suspension	2	7	2	28
36. ORS	3	1	1	3
37. Aspirin/Caffeine Tablets	3	5	2	30
38. Ibuprofen/Paracetamol Tablets	3	7	2	42
39. Nitrofurantoin Tablets	3	6	2	36
40. S/P Tablets	3	7	2	42
41. Promethazine Tablets	3	3	1	9
42. Quinine Mixture	3	1	1	3
43. SS Cream	4	7	2	56
44. Antacid Tablets	3	7	2	42
45. Sulphur Ointment	5	7	2	70
46. Tinidazole Tablets	3	7	2	42
47. Sulbutamol Syrup	1	1	1	1
48. Whitfield's Ointment	5	5	2	50

RPN= Risk Priority Number

B. Analytical method validation

System suitability test

The retention time and peak areas for 5 replicate injections of the standard solution are presented in Table 5. The relative standard deviation obtained for the two parameters is less than 2%.

Table 5:

System Suitability Results

Injection Number	Standard retention time (minutes)	Standard Area
1	6.418	69787
2	6.412	69496
3	6.407	70087
4	6.418	69766
5	6.445	69610
Mean	6.420	69749
RSD: NMT 2%	0.23%	0.32%

Specificity

The standard chromatogram of betamethasone valerate and sample chromatogram of betamethasone valerate recovery have a retention time of 6.5 minutes as indicated in Figures 1 and 2. No interference was observed at the retention time of the analyte.

Figure 1:

Standard Chromatogram of Betamethasone Valerate

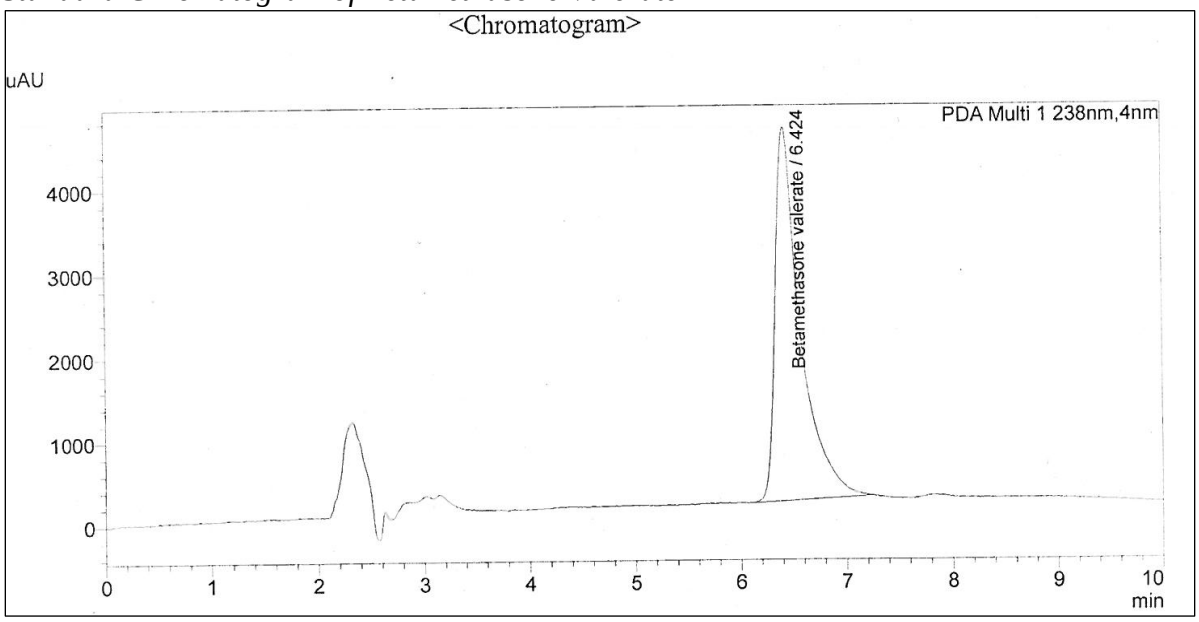
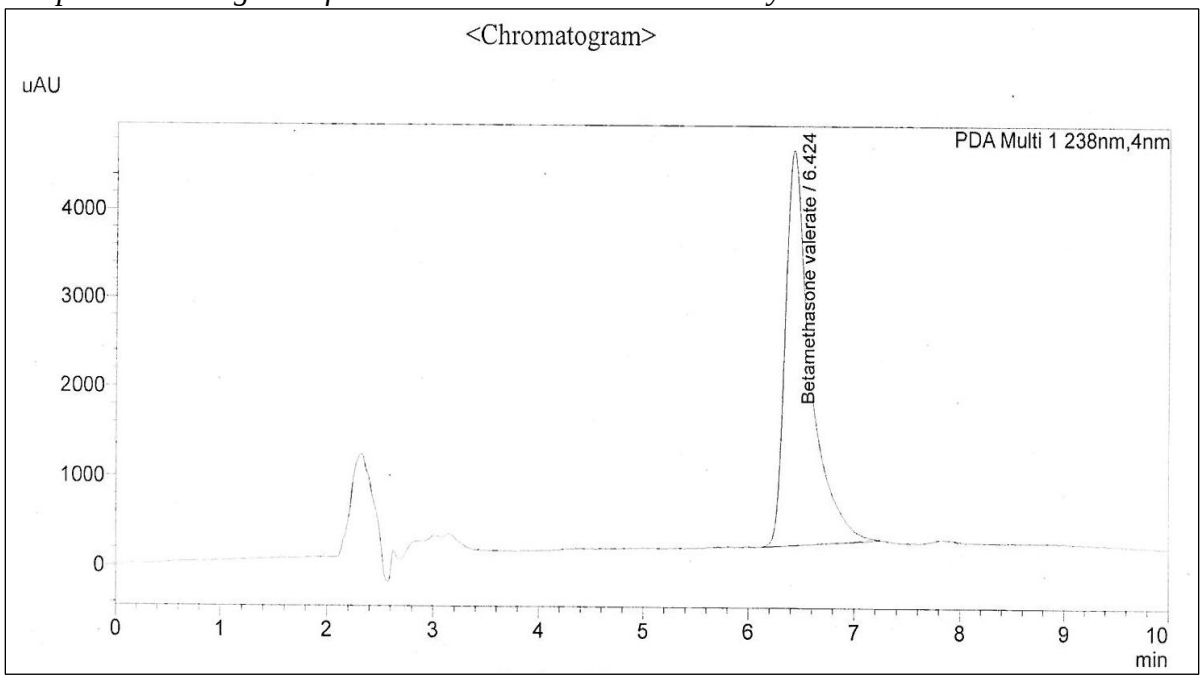


Figure 2:

Sample Chromatogram of Betamethasone Valerate Recovery



Precision

The precision of the method from analysis of six individual samples of betamethasone valerate at 100% of the test concentration is shown in Table 6. The relative standard deviation (RSD) obtained for the peak areas is below 2%.

Table 6:

Repeatability of Results

Solution	Area
Sample I	70694
Sample II	70170
Sample III	71634
Sample IV	70361
Sample V	70092
Sample VI	69525
RSD (Less than 2%)	1.01%

Accuracy

Accuracy for the residue recovery at three concentration levels (50%, 100% & 125%) is presented in Table 7. The mean recovery and the relative standard deviation were 96.99% and 1.94%, respectively.

Table 7:

Accuracy of Residue Discovery

Amount spiked	% Recovery
	97.08
50%	100.15
	99.12
	97.59
100%	94.01
	95.04
	97.08
125%	96.23
	96.65
Mean recovery	96.99%
RSD (Less than 2%)	1.94%

Linearity

The correlation coefficient of 0.9997 was obtained for concentration values of 2-8 ppm as shown in Figure 3. This demonstrated the linear correlation between the peak areas and the concentration at the low concentration values.

Limit of quantitation and Limit of detection

The limit of quantitation and limit of detection was found to be 0.34 ppm and 0.11 ppm respectively. The relative standard deviation of six replicate injections at LOQ and LOD was 2.02% and 4.42% respectively.

D. Results of betamethasone residue quantitation

None of the tested glassware showed detectable residues of betamethasone as indicated by the peak areas of clean glassware rinses in Table 8.

Figure 3:

Plot of Peak Area Versus Concentration

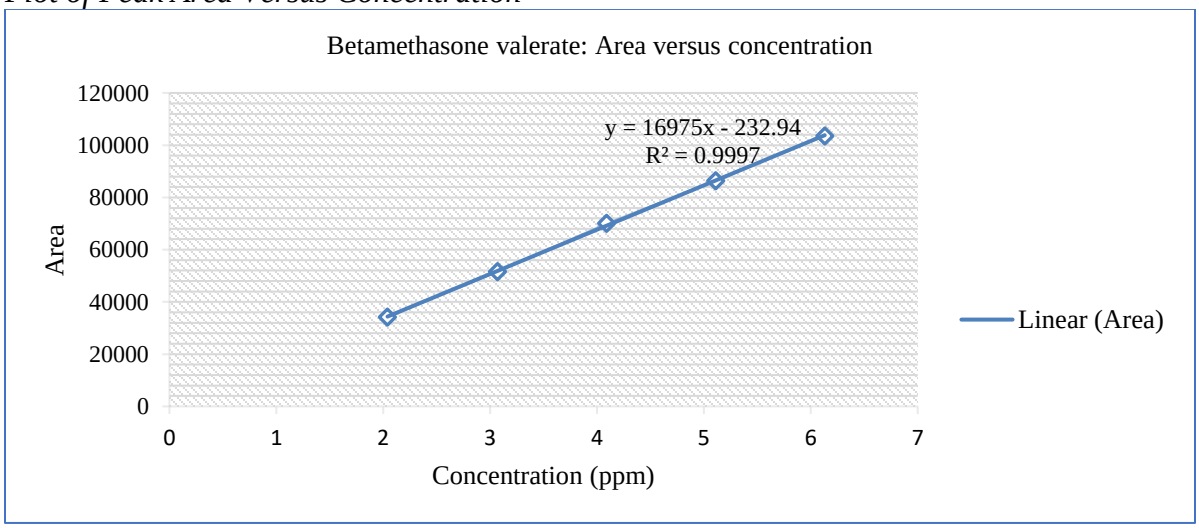


Table 8:

Peak Area of Glassware Recovery Residues

Glassware	Peak area
25 ml	No peak detected
100 ml volumetric flasks	No peak detected
100 ml beakers	No peak detected
5 ml bulb pipettes	No peak detected
HPLC sample vials	No peak detected
Standard solution	42256

IV. DISCUSSION

Possibility of carryover glassware contamination exists in multi-product facilities and research laboratories. Regulatory authorities require verification that a cleaning procedure is appropriate (Gowik, 2009). Also, the method employed in analysis of residues in cleaned glassware should be validated to confirm that it works as intended. The manual glassware cleaning method was validated by chromatographic quantitation of betamethasone residues in cleaned glassware. Pharmaceutical cleaning validation is complicated and labour intensive in multiproduct facilities. Forty-eight drug products were manufactured at the facility necessitating the application of risk-based approach to determine the worst-case product for the validation exercise. Elyvate (betamethasone) ointment and sulphur ointment were identified as the hard to clean products with the same RPN value of 70. Betamethasone valerate and sulphur drug substances are practically insoluble in water. The ointment base in the two formulations acts as a vehicle for the ingredients and also imparts occlusive and protective characteristics that are necessary for its intended use (Maru & Lahoti, 2019). Nonetheless, in regard to cleaning, the ointment base may inhibit wetting by cleaning agents, thereby making it difficult to clean the residual product and hence the high RPN score for ointments. Elyvate ointment was selected for the validation study due to selectivity and sensitivity of HPLC technique that is utilized in analysis of the drug substance compared to the titration method for sulphur ointment.

The system suitability test values obtained for performance parameters of the HPLC (RSD <2%) prior to the validation and quantitation exercise indicates that the system was functioning appropriately and therefore reliable to perform the analyses accurately and with precision. Failure of SST is mainly due to degradation of the HPLC column, incompetent analyst and poor maintenance of the HPLC system. The method of analysis of residues should provide high level of confidence in the results obtained. The validation results in this study demonstrate that the method that was used to quantify betamethasone valerate residues is reliable. From the chromatograms, it is evident that there was no interference of betamethasone valerate by blank and cleaning agent. The method is specific, able to measure the analyte in the presence of components. The RSD under precision testing and analyte recovery results of 96.99% demonstrate repeatability and accuracy of the method. This establishes that the method of analysis is adequately precise and accurate for the quantitation of betamethasone valerate residues in the tested glassware. Linearity was established with a correlation coefficient of 0.9997. This shows the ability of the method to elicit a direct response that is proportional to changes in concentration of the analyte over the stated range. The LOD and LOQ were 0.11 and 0.34 µg per ml, respectively, and RSD for the peak areas of six replicate injections at LOQ and LOD of 2.02% and 4.42% respectively demonstrating that the method is sensitive to detect residues of betamethasone valerate in laboratory glassware.

Glassware cleaning methods vary depending on the type and characteristics of the contaminant. Sandle et al (2016) established that a 5% solution of neutral detergent, followed by two rinses was the most efficient method in cleaning glassware in the pharmaceutical microbiology laboratory. Cleaning of glassware containing cyanocobalamin which has high molar absorptivity requires a more robust procedure involving the use of water, detergent, soaking in 0.1 M sodium hydroxide, rinsing 3 times with water and ethanol. Quantitation of residues in cleaned glassware is assayed to verify the cleaning efficiency. Mmakeletso (2012) developed and validated HPLC methods for the detection of drug and detergent traces on laboratory glassware. The mean recovery of the method was 99.5%. The HPLC method developed for the detection of drug traces recovered

from laboratory glassware was efficient and reliable. In another study, Valavala et al (2019) developed a liquid chromatography method for quantitation of dipyridamole in samples obtained from the equipment surface after the manufacture of dipyridamole modified release capsules. The calculated percent recovery was in the range of 99% to 100%. The HPLC method for quantitation of betamethasone residues in cleaned glassware in this study has a mean recovery level of 96.99%. No residues were detected in any of the tested glassware which shows that the cleaning procedure is efficient.

V. CONCLUSION

In this study, glassware cleaning validation was performed by HPLC quantitation of betamethasone valerate residues in cleaned glassware. The glassware used in the analysis of betamethasone ointment were cleaned manually following a standard procedure and analysed for any carryover residues of betamethasone valerate. The method of analysis was validated for specificity, accuracy, precision, limit of detection and quantitation, range and linearity. All the glassware recorded residues below the limit of detection of the method. This shows that the procedure used for cleaning of the glassware is appropriate and provides the desired level of cleanliness.

VI. RECOMMENDATIONS

In terms of the initial objectives, this study shows that the glassware cleaning method is effective. Nevertheless, we recommend a subsequent study to improve on the cleaning validation method by developing justifiable toxicity-based acceptance limits for carryover residues of the drug substance and cleaning agent.

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