Validation Of Cleaning Procedure for Obeticholic Acid Tablet Production

Ravina Rajpurohit[1], Aparna Arora[2], Anju Goyal[3], Hitesh Kothari[4]
[1,2,3,4]*Department of Pharmaceutical Quality Assurance, Bhupal Nobles' College of Pharmacy, Bhupal Nobles' University, Udaipur (Rajasthan) 313001*

***Abstract*—Cleaning validation is an essential requirement in pharmaceutical manufacturing to ensure that equipment used in production does not carry residues from previous batches that could compromise product quality and patient safety. The present study evaluates the effectiveness of a cleaning procedure applied to equipment used in the manufacture of obeticholic acid tablets. Considering the drug's potency and low aqueous solubility, a worst-case approach was adopted. Residue assessment was performed using both swab and rinse sampling techniques, followed by quantitative and microbiological analysis. Acceptance limits were defined using regulatory approaches such as the 10-ppm criterion and health-based exposure limits. Results obtained from three consecutive validation runs confirmed that the cleaning procedure consistently reduced residues and microbial contamination to acceptable levels. The findings demonstrate that the validated cleaning process is reliable, reproducible, and compliant with current regulatory expectations.**

***Index Terms*— Cleaning validation, Obeticholic acid, cross-contamination, MACO, pharmaceutical quality.**

I. INTRODUCTION

Cleaning processes in pharmaceutical manufacturing have gained significant regulatory and industrial focus due to the increasing potency of modern drugs and incidents of contamination causing serious harm.

Effective and validated cleaning procedures are essential to prevent cross-contamination, especially as many drugs can trigger severe allergic responses even at low exposure levels.

The primary objective of robust cleaning practices is to ensure consistent product quality and patient safety, which remains a key regulatory and industry requirement.[1-6]

Cleaning validation provides documented evidence with a high degree of assurance that equipment can be consistently cleaned to predetermined acceptable limits.

It ensures that residues from manufacturing processes and cleaning agents are effectively removed without posing any safety risk to patients.[7,8]

Obeticholic acid belongs to hepatoprotective category. It is a semi-synthetic bile acid, which acts as a farnesoid X receptor agonist and is used for treating primary biliary cholangitis. It was derived from a chenodeoxycholic acid. The key role of the farnesoid X receptor (FXR) as a regulator of bile and cholesterol metabolism in the liver.[9-16]

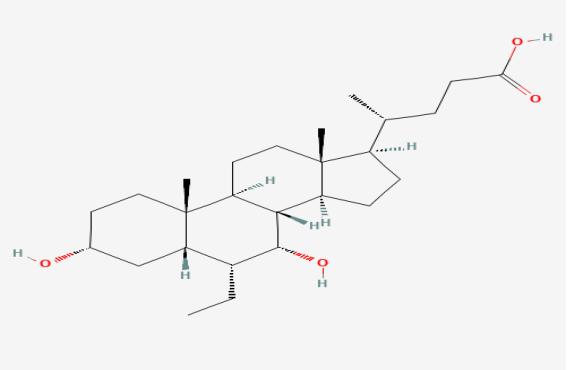
The farnesoid X receptor (FXR) is a nuclear receptor that plays a central role in regulation of bile acids and also regulation of metabolism. Activation of FXR can decrease hepatic fibrosis and also reduce inflammation. [16-20]

II. DRUG PROFILE

Chemical name: dihydroxy-5 beta-cholanic acid, 3 alpha-hydroxy steroid and 7 alpha-hydroxy steroids

Molecular Formula: $C_{26}H_{44}O_4$

Structure:



Structure Of Obeticholic Acid

Molecular weight: 420.6 gm/mol

This process is essential in pharmaceutical manufacturing to prevent cross-contamination and drug adulteration, thereby maintaining product quality and regulatory compliance. Obeticholic acid is a highly potent compound used in the management of liver-related disorders such as primary biliary cholangitis. Due to its pharmacological activity at low doses and its physicochemical characteristics, it is categorized as a challenging compound from a cleaning perspective. Therefore, establishing an effective and validated cleaning process is essential.[21-26]

Regulatory agencies emphasize the use of scientific and risk-based approaches for cleaning validation. These include identifying worst-case products, defining acceptable residue limits, and verifying cleaning effectiveness through analytical testing. The present work focuses on applying these principles to validate the cleaning process for equipment used in the manufacture of obeticholic acid tablets.[27-30]

III. OBJECTIVES

The objective of the cleaning validation is to verify the effectiveness of the cleaning procedure for removal of product residues, degradation products, preservatives, excipients, or cleaning agents as well as the control of potential microbial contaminants.

The objective of this study is to demonstrate the effectiveness of standard cleaning procedure for residues up to predetermined acceptance criteria for obeticholic acid 10 mg Tablets.

IV. DRUG OVERVIEW

General Characteristics

Obeticholic acid is a semi-synthetic bile acid derivative with significant pharmacological activity at low concentrations. It is formulated as oral tablets in low-dose strengths.[31]

Mechanism of Action

The drug acts by activating the farnesoid X receptor, which plays a key role in regulating bile acid synthesis and transport. This mechanism helps in reducing liver inflammation and improving bile flow.[32-33]

Pharmacokinetic Profile

Obeticholic acid is rapidly absorbed after oral administration and exhibits extensive protein binding. It undergoes hepatic metabolism and is primarily excreted through the fecal route. Its relatively long half-life supports once-daily dosing.[32-34]

V. MATERIALS AND METHODS

Equipment Involved

The study covered major equipment used in tablet manufacturing, including blending units, granulation systems, dryers, and compression machines.

Cleaning Procedure

A standardized cleaning procedure involving detergent washing followed by purified water rinsing was applied. The procedure was designed to ensure effective removal of residues from all product-contact surfaces.

Risk-Based Approach

A worst-case selection strategy was employed based on factors such as:

- Drug potency
- Solubility characteristics
- Toxicological profile
- Batch size and dosage

Sampling Techniques

Two complementary sampling methods were used:

- Swab sampling: to assess residues on specific surface areas
- Rinse sampling: to evaluate residues in hard-to-reach areas

Sampling locations were selected based on equipment design and potential residue accumulation points.

Acceptance Criteria

Acceptance limits were established using regulatory guidance:

- Chemical residue limits based on the 10-ppm approach and health-based exposure limits
- Microbial limits based on standard pharmacopeial requirements

VI. RESULT

Visual Inspection

Organoleptic techniques such as visual inspection, smell, and touch were employed as part of the cleaning

program and validation process. Visual examination, as required by cGMP regulations, was used to assess equipment cleanliness before use and during routine monitoring. Ultraviolet (UV) light was utilized to enhance detection of residues on equipment surfaces, confirming effective cleaning. All equipment used in the manufacture of obeticholic acid tablets was visually inspected across three consecutive batches and found to be clean after the cleaning procedure.

Visual Inspection Results of Dispensing Booth (After Cleaning)

All observed areas, including walls, floor, doors, scoops, reverse laminar airflow unit, platform balance, and other utensils, were found to be visually clean in all three validation batches.

No visible residues were detected, confirming the effectiveness and consistency of the cleaning procedure across Batch 1, Batch 2, and Batch 3.

Visual Inspection Results of Sifter (After Cleaning)

All critical equipment components, including the feed hopper, sieves, multi-mill blades, discharge chute, and screw conveyor, were visually inspected and found to be clean in all three validation batches.

The absence of visible residues across Batch 1, Batch 2, and Batch 3 confirms the effectiveness and consistency of the cleaning procedure.

Visual Inspection Results of Rapid Mixer Granulator (After Cleaning)

All critical components of the rapid mixer granulator, including the chopper, impeller, discharge chute, and adjacent areas, were visually inspected and found to be clean across all three validation batches.

Additional parts such as both view glasses and the RMG lid also showed no visible residues in any batch.

These results confirm the effectiveness and consistency of the cleaning procedure for the rapid mixer granulator.

Consistent results were obtained across three independent cleaning validation runs, indicating robustness of the cleaning process.

Visual Inspection Results of Fluidized Bed Dryer (After Cleaning)

All components of the fluidized bed dryer, including the bottom pan, FBD bowl product container, and retarding chamber, were visually inspected and found to be clean across all three validation batches.

The inner side of the view glass also showed no visible residues in any batch.

These observations confirm the effectiveness and consistency of the cleaning procedure for the fluidized bed dryer.

Visual Inspection Results of Conta Blender (After Cleaning)

The lid and inner surface of the Conta blender were visually inspected and found to be clean across all three validation batches.

No visible residues were observed on any surface after the cleaning procedure.

These results confirm the effectiveness and consistency of the cleaning process for the conta blender.

Visual Inspection Results of Compression Cubicle and Compression Machine (After Cleaning)

All areas of the compression cubicle and compression machine, including floor, ceiling, walls, doors, and electric panels, were visually inspected and found to be clean across all three validation batches.

Equipment components such as hopper, feed frame, turret, discharge chute, and metal detector also showed no visible residues.

The discharge chute of the metal detector (VO-RCM-06) was similarly clean, confirming the effectiveness and consistency of the cleaning procedure.

Visual Inspection Results of Coating Area and Coating Machines (After Cleaning)

All areas of the coating section, including floor, ceiling, walls, doors, and electric panels, were visually inspected and found to be clean across all three validation batches.

All coating pans (I to V) showed no visible residues following the cleaning procedure.

These findings confirm the effectiveness and consistency of the cleaning process for the coating area and equipment.

Visual Inspection Results of Blister Packing Room and Blister Packing Machine (After Cleaning)

All areas of the blister packing room, including floor, walls, and doors, were visually inspected and found to be clean across all three validation batches.

Equipment components such as hopper, spiral bowl, chute, feed box, and machine door showed no visible residues after cleaning.

The de-blistering machine chute was also clean, confirming the effectiveness and consistency of the cleaning procedure.

Results of Chemical and Microbiological Inspection Method

After visual inspection, all equipment was further evaluated using chemical and microbiological methods.

Results for all equipment used in the manufacture of obeticholic acid were within predefined acceptance limits across three consecutive batches.

Analysis of samples from the dispensing booth confirmed effective cleaning, with no fungal growth or pathogenic organisms observed.

Chemical and Microbiological Inspection Results of Dispensing Booth (After Cleaning)

Chemical analysis of dispensing booth samples showed that active drug residue levels for all locations were below the acceptance limit of 10 ppm across three batches.

Microbiological results (TBC) were within acceptable limits at all sampling points, indicating effective microbial control.

No pathogenic organisms or fungal growth were detected at any location, confirming the effectiveness of the cleaning procedure.

Chemical and Microbiological Inspection Results of Granulation Room (After Cleaning)

Chemical analysis of granulation room samples showed that active drug residue levels at all locations were below the acceptance limit of 10 ppm across three validation batches.

Microbiological results (TBC) were within acceptable limits for all sampled areas, indicating effective cleaning and microbial control.

No pathogenic organisms or fungal growth were observed, confirming the adequacy and consistency of the cleaning procedure.

Chemical and Microbiological Inspection Results of Sifter (After Cleaning)

Residue levels for the sifter components ranged from 0.00 to 9.37 ppm across three batches, remaining within the 10-ppm acceptance limit.

Microbiological counts ranged between 10 and 21 CFU, indicating acceptable microbial levels.

All sampled locations, including discharge chute, feed bowls, and sieves, complied with cleaning validation criteria.

Chemical and Microbiological Inspection Results of Sifter Cum Multi-mill (After Cleaning)

Residue levels for the sifter cum multi-mill components ranged from 0.00 to 4.15 ppm across three batches, well within the 10-ppm limit.

Microbiological counts were observed in the range of 4 to 18 CFU, indicating acceptable microbial levels.

All sampled locations, including discharge chute, feed hoppers, multimill screen, and screw conveyor, met the cleaning validation criteria.

Chemical and Microbiological Inspection Results of Rapid Mixer Granulator (After Cleaning)

Residue levels for the rapid mixer granulator components ranged from 0.00 to 7.09 ppm across three batches, remaining within the 10-ppm acceptance limit.

Microbiological counts were within acceptable limits, ranging from 11 to 25 CFU across all sampled locations.

These results confirm that the cleaning procedure for the rapid mixer granulator is effective, consistent, and compliant with validation criteria.

Chemical and Microbiological Inspection Results of Fluidized Bed Dryer (After Cleaning)

Residue levels for fluidized bed dryer components ranged from 2.41 to 8.03 ppm across three batches, remaining within the 10-ppm acceptance limit.

Microbiological counts were within acceptable limits, ranging approximately from 4 to 19 CFU across all sampling locations.

These results confirm that the cleaning procedure for the fluidized bed dryer is effective, consistent, and compliant with validation requirements.

Chemical and Microbiological Inspection Results of Conta Blender (After Cleaning)

Residue levels for conta blender components ranged from 0.00 to 8.06 ppm across three batches, remaining within the 10-ppm acceptance limit.

Microbiological counts were within acceptable limits, ranging from 10 to 28 CFU across all sampled locations.

These results confirm that the cleaning procedure for the conta blender is effective, consistent, and compliant with validation criteria.

Chemical and Microbiological Inspection Results of Compression Cubicle and Compression Machine (After Cleaning)

Residue levels for compression cubicle and compression machine components ranged from 0.01 to 9.44 ppm across three batches, remaining within the 10-ppm acceptance limit.

Microbiological counts were within acceptable limits, generally ranging from 3 to 29 CFU across all sampling locations.

These results confirm that the cleaning procedure for the compression area and equipment is effective, consistent, and compliant with validation criteria.

Chemical and Microbiological Inspection Results of Coating Room and Coating Machine (After Cleaning)

Residue levels for coating area and coating machine components ranged from 0.11 to 1.36 ppm across three batches, which are significantly below the 10-ppm acceptance limit.

Microbiological counts were within acceptable limits, generally ranging from 6 to 25 CFU across all sampled locations.

These results confirm that the cleaning procedure for the coating area and equipment is highly effective, consistent, and compliant with validation requirements.

Chemical and Microbiological Inspection Results of Blister Packing Room and Blister Packing Machine (After Cleaning)

Residue levels for blister packing room and machine components ranged from 0.01 to 7.98 ppm across three batches, remaining within the 10-ppm acceptance limit.

Microbiological counts were within acceptable limits, generally ranging from 6 to 25 CFU across all sampled locations.

These findings confirm that the cleaning procedure for the blister packing area and equipment is effective, consistent, and compliant with validation criteria.

VII. DISCUSSION

All results were within predefined chemical and microbiological limits, with no pathogens or fungal growth observed across three consecutive batches, confirming the effectiveness of the cleaning procedure.

Cleaning validation for new and existing products involves both similarities and differences, requiring cycle development, optimization, and sensitive analytical methods for residue detection.

Proper validation depends on well-designed cleaning cycles, calibrated monitoring instruments, suitable equipment selection, and thorough operator training with complete documentation to ensure reproducibility and compliance.

VIII. RESULT

Cleaning validation for obeticholic acid 10 mg tablets was successfully performed on three consecutive batches to demonstrate the effectiveness and consistency of the established B-type cleaning procedure.

All results complied with predefined acceptance criteria (≤10 ppm for product contact surfaces and acceptable microbiological limits), with no contamination or failures observed.

The study confirms that the cleaning method is robust, reproducible, and suitable for routine use, ensuring regulatory compliance and minimizing the risk of cross-contamination in a multi-product facility.

IX. CONCLUSION

The cleaning validation study confirms that the cleaning procedure used for obeticholic acid tablet manufacturing is effective and reproducible. Residual drug levels and microbial contamination were consistently within acceptable limits. The validated process meets regulatory expectations and can be adopted for routine manufacturing operations to prevent cross-contamination.

REFERENCES

[1] World Health Organization, *WHO Technical Report Series No. 986: Annex 2 – WHO Good Manufacturing Practices for Pharmaceutical Products*. Geneva, Switzerland: WHO Press, 2014.

[2] J. Agalloco and F. J. Carleton, *Cleaning Validation for the Pharmaceutical, Biopharmaceutical, Cosmetic, Nutraceutical,*

Medical Device and Diagnostic Industries, 2nd ed. New York, NY, USA: Informa Healthcare, 2008.

[3] D. A. LeBlanc, "Establishing scientifically justified acceptance criteria for cleaning validation of potent compounds," *Pharmaceutical Technology*, vol. 34, no. 7, pp. 62–74, 2010.

[4] European Medicines Agency, *Guideline on Setting Health-Based Exposure Limits for Use in Risk Identification in the Manufacture of Different Medicinal Products in Shared Facilities*. London, U.K.: EMA, 2014.

[5] J. W. Halloran, "Allergen and cross-contamination control in pharmaceutical manufacturing," *Journal of Pharmaceutical Sciences*, vol. 94, no. 8, pp. 1687–1696, 2005.

[6] International Council for Harmonisation, *ICH Q7: Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients*. Geneva, Switzerland: ICH, 2016.

[7] D. Jindal, H. Kaur, R. K. Patil, and H. C. Patil, "Validation in pharmaceutical industry: Equipment validation—A brief review," *Adesh University Journal of Medical Sciences and Research*, vol. 2, no. 2, pp. 94–98, 2020.

[8] P. D. Debaje, G. S. Chhabra, N. Gujarathi, and A. Jadhav, "Regulatory aspects of cleaning and cleaning validation in active pharmaceutical ingredients," *Asian Journal of Pharmaceutical Research and Development*, vol. 6, no. 3, pp. 69–74, 2018.

[9] S. Fiorucci, S. Cipriani, A. Mencarelli, F. Baldelli, G. Bifulco, and A. Zampella, "Farnesoid X receptor agonist for the treatment of liver and metabolic disorders: Focus on 6-ethyl-CDCA," *Mini Reviews in Medicinal Chemistry*, vol. 11, no. 9, pp. 753–762, 2011.

[10] L. Verbeke, R. Farre, J. Trebicka, M. Komuta, T. Roskams, and S. Klein, "Obeticholic acid, a farnesoid-X receptor agonist, improves portal hypertension by two distinct pathways in cirrhotic rats," *Hepatology*, vol. 59, no. 6, pp. 2286–2298, 2013.

[11] J. R. Walters, I. M. Johnston, J. D. Nolan, C. Vassie, M. E. Pruzanski, and D. A. Shapiro, "The response of patients with bile acid diarrhoea to the farnesoid X receptor agonist obeticholic acid," *Alimentary Pharmacology & Therapeutics*, vol. 41, no. 1, pp. 54–64, 2015.

[12] S. Akare, S. Jean-Louis, W. Chen, D. J. Wood, A. A. Powell, and J. D. Martinez, "Ursodeoxycholic acid modulates histone acetylation and induces differentiation and senescence," *International Journal of Cancer*, vol. 119, no. 12, pp. 2958–2969, 2006.

[13] R. E. Poupon, B. Balkau, E. Eschwege, and R. Poupon, "A multicenter, controlled trial of ursodiol for the treatment of primary biliary cirrhosis," *New England Journal of Medicine*, vol. 324, pp. 1548–1554, 1991.

[14] G. M. Hirschfield, A. Mason, V. Luketic, K. Lindor, S. C. Gordon, and M. Mayo, "Efficacy of obeticholic acid in patients with primary biliary cirrhosis and inadequate response to ursodeoxycholic acid," *Gastroenterology*, vol. 148, no. 4, pp. 751–761, 2015.

[15] C. Eipel, K. Abshagen, and B. Vollmar, "Regulation of hepatic blood flow: The hepatic arterial buffer response revisited," *World Journal of Gastroenterology*, vol. 16, no. 48, pp. 6046–6057, 2010.

[16] Z. Younossi and M. Abdelmalek, "Obeticholic acid for the treatment of nonalcoholic steatohepatitis: Interim analysis from a multicentre, randomised, placebo-controlled phase 3 trial," *The Lancet*, vol. 394, no. 10215, pp. 2184–2196, 2019.

[17] S. Modica, R. M. Gadaleta, and A. Moschetta, "Deciphering the nuclear bile acid receptor FXR paradigm," *Nuclear Receptor Signaling*, vol. 8, Art. no. e005, 2010.

[18] S. Fiorucci, E. Antonelli, G. Rizzo, *et al*., "The nuclear receptor SHP mediates inhibition of hepatic stellate cells by FXR and protects against liver fibrosis," *Gastroenterology*, vol. 127, no. 5, pp. 1497–1512, 2004.

[19] R. M. Gadaleta, K. J. van Erpecum, B. Oldenburg, *et al*., "Farnesoid X receptor activation inhibits inflammation and preserves the intestinal barrier in inflammatory bowel disease," *Gut*, vol. 60, no. 4, pp. 463–472, 2011.

[20] Y. D. Wang, W. D. Chen, M. Wang, D. Yu, B. M. Forman, and W. Huang, "Farnesoid X receptor antagonizes nuclear factor kappaB in

hepatic inflammatory response," *Hepatology*, vol. 48, no. 5, pp. 1632–1643, 2008.

[21] World Health Organization, *WHO Guidelines on Cleaning Validation*. Geneva, Switzerland: WHO Press, 2019.

[22] European Medicines Agency, *Guideline on Setting Health-Based Exposure Limits for Shared Facilities*. London, U.K.: EMA, 2014.

[23] U.S. Food and Drug Administration, *Guide to Inspections Validation of Cleaning Processes*. Silver Spring, MD, USA: FDA, 1993.

[24] International Council for Harmonisation, *ICH Q7: Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients*. Geneva, Switzerland: ICH, 2016.

[25] G. M. Hirschfield, A. Mason, V. Luketic, K. Lindor, S. C. Gordon, M. Mayo, *et al*., "Efficacy of obeticholic acid in primary biliary cholangitis," *New England Journal of Medicine*, vol. 375, no. 7, pp. 631–643, 2015.

[26] S. Mudaliar, R. R. Henry, A. J. Sanyal, L. Morrow, H. U. Marschall, M. Kipnes, *et al*., "Efficacy and safety of obeticholic acid in NAFLD," *Gastroenterology*, vol. 145, no. 3, pp. 574–582, 2013.

[27] European Medicines Agency, *Guideline on Setting Health-Based Exposure Limits for Use in Risk Identification in the Manufacture of Different Medicinal Products in Shared Facilities*. London, U.K.: EMA, 2014.

[28] World Health Organization, *WHO Guidelines on Cleaning Validation*. Geneva, Switzerland: WHO Press, 2019.

[29] U.S. Food and Drug Administration, *Guide to Inspections Validation of Cleaning Processes*. Silver Spring, MD, USA: FDA, 1993.

[30] International Council for Harmonisation, *ICH Q7: Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients*. Geneva, Switzerland: ICH, 2016.

[31] European Medicines Agency, *Ocaliva (Obeticholic Acid): EPAR Product Information*. London, U.K.: EMA, 2016.

[32] G. M. Hirschfield, A. Mason, V. Luketic, K. Lindor, S. C. Gordon, M. Mayo, *et al*., "Efficacy of obeticholic acid in primary biliary cholangitis," *New England Journal of Medicine*, vol. 375, no. 7, pp. 631–643, 2015.

[33] S. Mudaliar, R. R. Henry, A. J. Sanyal, L. Morrow, H. U. Marschall, M. Kipnes, *et al*., "Efficacy and safety of obeticholic acid in nonalcoholic fatty liver disease," *Gastroenterology*, vol. 145, no. 3, pp. 574–582, 2013.

[34] U.S. Food and Drug Administration, *Ocaliva (Obeticholic Acid) Prescribing Information*. Silver Spring, MD, USA: FDA, 2016.