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Research Article

Validation of Cleaning Procedures for Residual Determination of Drugs in Manufacturing

Bhavana Bairagi*, Dr. Kamble Ravindra Keshavrao

Department of Quality Assurance, Bhupal Nobles' College of Pharmacy (BNCP), Bhupal Nobles' University, Udaipur (Rajasthan) – 313002.

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ABSTRACT

Cleaning validation is a crucial process in pharmaceutical manufacturing to ensure equipment is free from harmful residues from previous products, including active pharmaceutical ingredients (APIs), excipients, and cleaning agents. This process ensures consistent removal of residues, preventing cross-contamination and maintaining product quality and safety. Key aspects of cleaning validation include adhering to regulatory guidelines, using analytical techniques like HPLC and TOC analysis, selecting a "worst-case" product for validation, using sampling techniques like swab and rinse sampling, defining acceptable residue levels based on toxicity and daily dose, and establishing a detailed validation protocol. The importance of cleaning validation lies in preventing cross-contamination, ensuring product quality and safety, complying with regulations, protecting brand reputation, and reducing the risk of product recalls and other costly consequences associated with contamination. It is mandated by regulatory bodies like the FDA, EMA, and WHO to adhere to Good Manufacturing Practices (GMP). Terbinafine, a synthetic allylamine antifungal drug, is highly lipophilic and tends to accumulate in skin, nails, and fatty tissues. It inhibits ergosterol synthesis by inhibiting the fungal squalene monooxygenase enzyme. Terbinafine hydrochloride was granted FDA approval on 30 December 1992. Validating a cleaning procedure for residual drug determination in manufacturing aims to demonstrate that the process consistently removes drug residues from equipment to levels below predetermined acceptance criteria, preventing cross-contamination and ensuring product purity and safety. This involves establishing residue acceptance criteria, selecting appropriate analytical methods, developing a robust cleaning process, conducting validation studies, demonstrating reproducibility and repeatability, identifying potential risks, ensuring patient safety, meeting regulatory compliance, and

***Corresponding Author:** Bhavana Bairagi
Address: *Department of Quality Assurance, Bhupal Nobles' College of Pharmacy (BNCP), Bhupal Nobles' University, Udaipur (Rajasthan) – 313002.*
Email ✉: bairagibhavna50@gmail.com

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maintaining product quality by preventing cross-ontamination between different drug products produced on the same equipment.

INTRODUCTION

Cleaning validation is a crucial process in pharmaceutical manufacturing to ensure equipment is free from harmful residues from previous products, including active pharmaceutical ingredients (APIs), excipients, and cleaning agents. This process ensures that cleaning procedures consistently remove these residues to predetermined levels, preventing cross-contamination and maintaining product quality and safety. Key aspects of cleaning validation include adhering to regulatory guidelines, using analytical techniques like HPLC and TOC analysis, selecting a "worst-case" product for validation, using sampling techniques like swab and rinse sampling, defining acceptable residue levels based on toxicity and daily dose, and establishing a detailed validation protocol. The importance of cleaning validation lies in preventing cross-contamination, ensuring product quality and safety, complying with regulations, protecting brand reputation, and reducing the risk of product recalls and other costly consequences associated with contamination. It is mandated by regulatory bodies like the FDA, EMA, and WHO to adhere to Good Manufacturing Practices (GMP). The process is essential for maintaining the reputation of the pharmaceutical company and ensuring product quality and safety (1-6). Terbinafine is a tertiary amine that is N-methyl-1-naphthalenemethylamine in which the amino hydrogen is replaced by a 3-(tertbutylethynyl)allyl group. An antifungal agent administered orally (generally as the hydrochloride salt) for the treatment of skin and nail infections. It has a role as an EC 1.14.13.132 (squalene monooxygenase) inhibitor, a P450 inhibitor and a sterol biosynthesis inhibitor. It is a tertiary amine, an acetylenic compound, a member of naphthalenes, an enyne and an allylamine antifungal drug. It is a conjugate base of a terbinafine(1+). Terbinafine hydrochloride (Lamisil) is a synthetic allylamine antifungal. It is highly lipophilic in nature and tends to accumulate in skin, nails, and fatty tissues. Like other allylamines, terbinafine inhibits ergosterol synthesis by inhibiting the fungal squalene monooxygenase (also called squalene epoxidase), an enzyme that is part of the fungal cell wall synthesis pathway. Terbinafine hydrochloride was granted FDA approval on 30 December 1992 (7-11). Validating a cleaning procedure for residual drug determination in manufacturing aims to demonstrate that the process consistently removes drug residues from equipment to levels below predetermined acceptance criteria, preventing cross-contamination and ensuring the purity and safety of subsequent drug products. This is achieved by establishing a reliable analytical method to detect and quantify residual drug levels and verifying that the cleaning procedure effectively reduces them to acceptable limits. The objectives include establishing residue acceptance criteria, selecting appropriate analytical methods, developing a robust cleaning process, conducting validation studies, demonstrating reproducibility and repeatability, identifying potential risks and mitigation strategies, ensuring patient safety, meeting regulatory compliance, and maintaining product quality by preventing cross-ontamination between different drug products anufactured on the same equipment. The process also involves assessing parameters like cleaning time, detergent concentration, and rinse procedures.

2. MATERIALS AND METHODS

2.1 Procurement of the Drug

Terbinafine hydrochloride, a medication from Intas Pharmaceutical Ltd Thane, is available in a

10g package with a purity of 99.8 to be used as Reference drug while, Sun Pharma Lab. Ltd India which contains 15 mg dosage of Terbinafine hydrochloride to be used as test drug.

2.2 Method and Procedure

2.2.1 Selection of Mobile Phase

The mobile phases tested include methanol: water (90:10), methanol: water (80:20), acetonitrile: water (90:10), acetonitrile: phosphate buffer 10mm (90:10), acetonitrile: phosphate buffer 10mm (80:20), and acetonitrile: phosphate buffer (75:25) with pH 4.5.

2.2.2 Chromatographic Conditions

The chromatographic conditions were established through trial and error, maintaining constant consistency throughout the method. The column was Inertsil 4.6 x 250 mm, with a particle size of 5 µm, stationary phases of C18 Inertsil, mobile phase of Acetonitrile: Phosphate Buffer (75:25), pH 4.5, and a sample size of 20 µL.

2.2.3 Validation of the Method

Adjusting several UFLC settings (FDA, 1995, 1997, 2000, 1994, 1987; USP, 2000) confirmed the reliability of the UFLC approach (16). Calibration plot least-squares linear regression analysis verified the UFLC method's linearity (17), the limits of detection and quantification for the medicines mentioned were determined to be three and five epochs, respectively, above and below the baseline noise, The process adhered to the guidelines established by the United States Pharmacopoeia (USP, 2000), specificity (17), precision (18) accuracy (19), robustness (20) and ruggedness (21) were determined.

3. RESULTS AND DISCUSSION

3.1 Characterization of the Drug

Pharmaceutical sciences rely on methods like organoleptic characterisation, melting point measurement, and solubility testing to evaluate drugs' physical and chemical properties. These methods detect physical changes caused by handling or storage, and determine the drug's solubility in different solvents. These techniques are crucial for developing effective dosage forms and pharmaceuticals that meet patient needs while being safe for use (Table 1). Terbinafine hydrochloride is a crystalline solid that exhibits a melting point of about 200.95±0.719°C. The melting point of Terbinafine hydrochloride is typically listed as 199-203°C.

3.2 Selection of mobile phase:

Each mobile phase was filtered through Whatman filter paper No. 42. Peak, well resolved peaks with symmetry within limits and significant Based on sample solubility & stability, various mobile phase compositions were evaluated to achieve acceptable separation using selected chromatographic conditions. From various mobile phases tried, mobile phase containing Methanol: Water (70:30) pH 4 was selected, since it gives sharp reproducible retention time for the drug.

3.3 Validation of the Method

The study conducted accuracy tests using the usual addition method for recovery and replicated drug estimations using the proposed technique. The method's specificity was determined by separating peaks from matrix components. The method achieved a concentration range of 80% to 120% of the test concentration, and the drug marketed formulation was linear within ± 20% of the test concentration. The system's suitability was reliable, and the limit of detection is the smallest detectable concentration of an analyte in a sample that cannot be precisely measured. The method was expanded for medication estimation in

commercialized tablet formulation, producing accurate and dependable results.

Table 1: Results and Statistical Data for Recovery study

S.NO.	Amount of Drug (mg/ml)	% of Recovery of Drug
1	0.5	99.56
2	1.0	98.78
3	1.5	99.03
4	2.0	99.99
5	2.5	94.65
6	3.0	98.89

Table 2: Results and Statistical Data of Precision Study

S. No.	Weight of the Sample (mg)	% Label Claim
1	100.5	99.22
2	101.0	97.78
3	101.5	98.03
4	102.0	98.88
5	102.5	98.65
6	103.0	99.89

Table 3: Observations of Linearity and range study

S. No.	% Label Claim	Peak Area
1	99.22	49997.90
2	97.78	50555.34
3	98.03	47345.55
4	98.88	44436.98
5	98.65	51980.44
6	99.89	49876.04

Table 4: Result of Robustness study

Condition	Parameter	RT
Change in Wavelength	**253 nm**	4.23
	255 nm	4.55
	257 nm	5.01
Change in Temperature	**30ºC**	4.33
	25 ºC	4.66
	20 ºC	5.00
Change in Mobile Phase	**75:25**	4.23
	70:30	2.57
	65:35	4.99

Table 5: Limit of detection (LOD) and Limit of quantization (LOQ)

Drug Name	LOD (µg/ml)	LOQ (µg/ml)
Terbinafine hydrochloride	0.056	1.004

4. CONCLUSION

Cleaning validation for terbinafine Hcl tablets manufactured by Dr. Reddy's Laboratories, Bollaram, Hyderabad by HPLC method is validated as per ICH guidelines The purpose of cleaning validation is to establish the documented evidence with high degree of assurance that the cleaning process followed as per standard operating procedure for cleaning the equipment HPLC used for processing of terbinafine Hcl tablets. The results of cleaning validation is found to be well within the acceptance criteria (based on dose criteria, 10 PPM criteria and visually clean criteria) and hence the objective of the company to have an effective cleaning programme is well documented and the desired results were achieved. The analytical method followed for terbinafine Hcl tablets (exifine tablets) meets the requirement of intended analytical application parameters.

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