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Short communication

Cleaning validation in production area – development of analytical method for quantitative determination of Cefixime residues

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Introduction

Cleaning is considered a critical process in the manufacturing of pharmaceutical products. The cleaning process must reduce residues of previous product to levels that ensure patient safety and result in visibly clean equipment.

Cleaning validation is documented evidence that an approved cleaning procedure will reproducibly remove the previous product or other residues on product contact equipment surfaces below the scientifically set acceptance levels.

An analytical method is one of the deciding factors in establishing the cleanliness of pharmaceutical manufacturing equipment. It is, therefore, important that there be a high level of confidence in the results obtained using the method. A properly developed cleaning validation strategy includes analytical method validation, which defines the method parameters necessary in providing a high level of confidence in the cleaning results (Kaiser and Ritts, 2004).

Measuring cleanliness is a difficult task. Essentially, trace residues in surfaces are the target analytes. The residue must first be extracted from a surface, recovered from the extraction medium, and then suitably quantitated (Kaiser and Ritts, 2004).

API residue is typically tested, as it may be the high hazard component in the formulation. The primary consideration for the test method is that it is sensitive to levels lower than the cleaning limit for the analyst of interest. If the test method is not sensitive enough to test residue levels lower than the cleaning limit, the method sensitivity must be enhanced, a different test method must be employed, or the manufacturing equipment must be dedicated.

Product grouping is a way to reduce validation activities in sites with multiple products and processes. If a product in a group requires a more aggressive cleaning process, that product becomes a worst-case product in that group. The worst-case product should be determined by performing a risk assessment considering solubility, toxicological effect and cleanability. All the products in the group should be cleaned using the worst-case product parameters (Govind et al., 2018).

Cefixime granules for oral suspension 100mg/5mL was chosen on the basis of a worst-case rating approach.

The aim of this study was to validate simple analytical method for verification of cefixime residues on equipment after production of Cefixime granules for oral suspension 100mg/5mL.

Materials and methods

The HPLC-UV method for determination of cefixime residues on stainless steel surface was developed and validated in order to control a cleaning procedure after manufacturing of Cefixime granules for oral suspension 100mg/5mL. The HPLC method has been validated to show specificity, linearity and range, accuracy, precision, limit of quantification (LOQ) and limit of detection (LOD), as per ICH guideline Validation of analytical procedures: Text and Methodology Q2(R1).

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Chemicals and reference standards

Potassium dihydrogen phosphate, Tetrabutylammonium hydroxide, Sodium hydroxide, o-Phosphoric acid 85%, Acetonitrile, Methanol and Purified water were supplied from Merck KGaA, Darmstadt, Germany. Reference standard for Cefixime trihydrate was supplied from Alkaloid, AD Skopje.

Instrumentation and analytical conditions

The analysis was performed on Thermo Ultimate DAD 3000 and was controlled by Chromeleon CDS software version 7.2 SR5. The method was optimized by using column Symmetry C18, 150mm x 3.9mm, 5µm; with column temperature of 40 ºC; autosampler temperature of 23 ºC; at a 1.5 mL/min flow rate and 254 nm detection. Mobile phase: mixture od acetonitrile and buffer solution pH=6.5 in ratio 23 : 77% (*V/V*). The injection volume was 10 µL.

Results and discussion

The method was specific and distinguished the specific analyte of interest (cefixime) from the other ingredients of the formulation, potential degradants and the cleaning agent.

It exhibited good linearity between the responses of cefixime related to the concentrations of standards in the range of 0.4 µg/mL to 20 µg/mL (r=1.00).

The precision of the method was verified by repeatability and method precision. The repeatability was shown by six replicate injections of standard solution containing cefixime in the working concentration of 10 µg/mL (RSD=0.3%). The method precision was evaluated using six samples which are first extracted from a stainless steel coupons, recovered from the extracted medium and then suitably quantitated (RSD=0.9 %).

The LOD and LOQ were determined at a signal-to-noise ratio of 3:1 and 10:1, respectively. The limit of detection was 0.12 µg/mL and the limit of quantification was 0.4 µg/mL.

For cleaning validation, accuracy is measured through recovery of samples from equipment surface e.g. stainless steel and extraction of the recovered samples into testing solutions.

The test solution with known concentration was applied to the surface of the equipment (stainless steel coupons, size 25 cm^2). The residue was removed by two Texwipe TX715 swabs (one methanol wetted swab and the other one dry). The swabs were thereafter extracted with mobile phase for 15 minutes with sonication (Yang et al., 2005).

Accuracy was reported as % recovery of the amount of analyte in the recovered samples measured against the amount of analyte spiked onto the sample recovery surface.

The accuracy was performed at three concentration levels and the obtained mean recovery was 90.63% and RSD=3.61%. Acceptance criteria for recovery was 70.0-110.0% and RSD $\leq$ 15.

This parameter should be performed on all materials from which the production equipment is made.

It is necessary to use recovery factor to all individual results in cleaning validation of pharmaceutical manufacturing equipment. Recovery factor is the recovery of swabbed material from the equipment to the solution.

Conclusion

Proper development and validation of the analytical method helps assure that the cleaning procedure is effective and reproducible in preventing contamination and cross-contamination in production area.

Simple analytical method for quantitative determination of cefixime residues on equipment after production of Cefixime granules for oral suspension 100mg/5mL was validated. The linearity of the method covers the required sensitivity for residue detection and the accuracy of the method was proved by recovery of swabbed samples from equipment. The method can be applied to routine control of pharmaceutical equipment cleanliness by sampling from stainless steel surface areas of 25 cm^2.

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