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Analytical Method Development and Cleaning Validation of Cefadroxil Dry Syrup Using TOC Apparatus.

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ABSTRACT

The systematic approach developed to assess the amount of residues left on manufacturing equipment surfaces from product carryover is known as cleaning validation. Current trends have seen increasing demand for rapid sample analysis time along with low detection limits for verification of cleaning validation samples. A total organic carbon (TOC) method is sensitive and is less time consuming than high performance liquid chromatography (HPLC). The purpose of this study is to demonstrate how to develop and validate a TOC method for cleaning applications. Validation of the cleaning procedures for manufacturing or processing equipment has been presented in this paper. A sensitive and reproducible method was developed and validated for the determination of Cefadroxil in swab samples. The method for determining residues of Cefadroxil on manufacturing equipment surfaces is validated for linearity, accuracy, precision, repeatability, limit of detection (lod) and limit of quantification (loq). The sampling procedure using cotton swabs was also validated. This method can be used to detect trace levels of Cefadroxil residue in production equipment area to confirm the efficiency of the cleaning procedure in pharmaceutical industries to avoid cross contamination.

Keywords: Cefadroxil, toc (total organic carbon), cleaning validation.

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INTRODUCTION

Current good manufacturing practices guidelines are clearly indicating that cleaning procedures should be in place for every activity involved in the manufacturing, storage, handling and distribution of the active pharmaceutical ingredients. Cleaning procedures should be validated in order to ensure that no carry over, contamination or cross contamination poses the high risk to API quality [1]. Cleaning validation is the process assuring that effective procedure is used to remove residue from pharmaceutical manufacturing equipment. The main rational for requiring clean equipment is to prevent contamination or adulteration of drug product. A proper cleaning validation program provides documented proof that one can consistently and effectively clean a system or piece of equipment [2]. In other words "The process of providing documented evidence that the cleaning methods employed within a facility consistently controls potential carryover of product (including intermediates and impurities), cleaning agents and extraneous material into subsequent product to a level which is below predetermined levels."

GMP regulations explicitly state that manufacturers of finished pharmaceuticals must properly clean their facilities and equipment to ensure product safety [3-4].

Cleaning validation is a prime customer requirement since it ensures the purity and safety of the product. It is a regulatory requirement in Active Pharmaceutical Ingredient product manufacture and also assures the quality of the process through an internal control and compliance [5]. Mostly, cleaning validation samples have been measured using high performance liquid chromatography (HPLC) methods, which are often time consuming and subject to a number of interferences. Total organic carbon (TOC) analysis is a new method which has previously been applied to only measurement of carbon residues on production surfaces for pharmaceutical equipment and for water quality checking. We have applied the TOC analysis method to examine the Cefadroxil residue. This developed and validated method offers extremely low detection capability in parts per billion (ppb), rapid sample analysis time and therefore quick turn-around of production, equipment and facilities. The method allows the measurement of extraneous materials such as process intermediates and cleaning agents, which are not possibly detected by other non specific or specific methods. TOC for cleaning validation has several advantages over specific methods. Only one method is needed for all cleaning validation analysis, the method is simpler to implement and easier to validate than chromatographic techniques and less time consuming. The method always produces a ''worst-case'' result, assuming that all residues are the active substance. Toc analysis demonstrated the better correlation to cleaning validation compounds in comparison to traditional analytical methods. Some qualities that make TOC a viable part of a cleaning validation include: high sensitivity, high recovery of samples, non-specific measurement and ease of use, minimal interferences and cost effectiveness [6-8].

MATERIALS AND METHODS

Chemical and reagents

All chemicals and reagents used for cleaning validation were of analytical grade.

METHODS

Sample preparation

25 sq. Cm. Stainless steel plates were used in the % recovery by swab technique test to simulate manufacturing equipment. One side of each plate was spiked with 0.1 ml solution of active substance Cefadroxil equivalent to Cefadroxil (3 mg/ml). The plates were allowed to dry completely overnight at room temperature. A texwipe alpha swab was moistened with water and the spiked plate surface was swabbed both vertically and horizontally. The swab end was cut off, placed into 100 ml volumetric flask containing purified water. The vial was capped tight, vortexes, and allowed to stand for one hour prior to analysis.

Preparation of standard stock solution of Cefadroxil

An accurately weighed Cefadroxil equivalent to Cefadroxil (10 mg) were transferred into 100 ml volumetric flask, dissolved in 50 ml of purified water and diluted up to mark with purified water to get concentration of Cefadroxil (100 ppm).

Standard solution of Cefadroxil

10 µg/ml of Cefadroxil standard solution was prepared by diluting 1 ml from above stock solution, made up to 10 ml with purified water into 10 ml volumetric flask**.**

Preparation of Cefadroxil solution for swab recovery study

An accurately weighed Cefadroxil equivalent to Cefadroxil (30 mg) was transferred into 10 ml volumetric flask, dissolved with 5 ml of diluent and diluted up to mark with diluent to get concentration of Cefadroxil (3 mg/ml).

Preparation of calibration curve for Cefadroxil

For cleaning validation of Cefadroxil injection in mixing tank by TOC, we require the linearity of Cefadroxil, make a solution of Cefadroxil by dissolving 10 mg Cefadroxil equivalent to Cefadroxil in one 100 ml volumetric flask and make a volume with purified water and then take 1 ml of this solution in 10 ml volumetric flask and make a volume with purified water, for further dilution take a dilution of 1, 3, 5, 7 and 9 ml solution in series of 10 ml volumetric flask and make a volume up to mark with purified water to get 1, 3, 5, 7 and 9 ppm of solution.

Validation parameters of traces for Cefadroxil by TOC method

Linearity and Range

The linearity response was determined by analyzing 5 independent levels of calibration curve in the range of 1, 3, 5, 7 and 9 ppm for Cefadroxil equivalent to Cefadroxil. Plot the calibration curve of % organic carbon versus respective concentration and find out correlation co efficient and regression line equation for Cefadroxil.

Accuracy

The accuracy of the method was determined by calculating the recoveries of Cefadroxil by the standard addition method. Known amounts of standard solutions of Cefadroxil was at added at 80, 100 and 120 % level to pre-quantified sample solutions of Cefadroxil. The amount of Cefadroxil was estimated by applying obtained values to the respective regression line equations, each sample was prepared in triplicate at each level and analyze. Record the % organic carbon from the peak area of drug, % recovery was calculated from regression equation of the calibration curve.

Precision

Repeatability

It was determined by analyzing Cefadroxil (10 µg/ml) six times.
The % organic carbon of six replicates standards was measured and % rsd was calculated.

Intraday precision

For intraday, Cefadroxil in the range of 8, 10 and 12 µg/ml were analyzed three times

On the same day and % rsd was calculated.

Inter day precision

For inter day, Cefadroxil in the range of 8, 10 and 12 µg/ml were analyzed three times

On three different days and % rsd was calculated.

Ruggedness

From standard solution, 10 µg/ml of Cefadroxil equivalent to Cefadroxil was prepared and analyzed six different analysts (three times) using similar operational environmental conditions. The % organic carbon was measured for same concentration solutions and calculate % rsd.

Sensitivity

limit of detection (lod)

Calculate the limit of detection for Cefadroxil by 3.3 x sd of intercept/average of Slope equation.

Limit of quantification (loq)

Calculate the limit of quantification for Cefadroxil by 10 x sd of intercept/average of Slope equation.

Solution stability in diluents

A standard solution of Cefadroxil was stored in the vials and in the volumetric flask. The solution was analyze initial and after 1 hour.

System suitability test

System suitability testing was essential for the assurance of the quality performance of The toc. Earlier prepared solutions were analyzed for system suitability testing. The relative standard deviation of six replicate standards should be less than 2.0 %.

RESULTS AND DISCUSSION

A cleaning validation method was developed for the simultaneous estimation of residual traces of Cefadroxil in dry powder syrup using TOC analyzer apparatus. The cleaning validation is the process of assuring that cleaning procedures effectively remove the residue from manufacturing equipment/facilities below a predetermined level. This is necessary to assure the quality of future products using the equipment, to prevent cross-contamination, and as a world health organization and good manufacturing practices requirement. Total organic carbon method was applied to number of pharmaceutical products. This method was developed for measuring residual Cefadroxil on surface of mixing vessel during manufacturing process. The proposed method has been statistically validated for linearity, accuracy, precision, repeatability and reproducibility, limit of detection and limit of quantification.

The linearity of developed method was achieved in the range of 1-9 µg/ml for Cefadroxil (r^2 = 0.999). The % recovery (accuracy) of drug was achieved in the range of 99.31±99.59% which was within the acceptance criteria. The % recovery is within limit (98.0-102.0%) so the method is accurate. The % rsd for repeatability was found to be 0.111% for Cefadroxil. The % rsd for intraday precision was found to be 0.109-0.013 % for Cefadroxil. The % rsd was found to be 0.536-0.694 % for Cefadroxil. The low % RSD indicates that the method is precise. Ruggedness was determined by preparing solutions and analyzed by six different (three times) analysts using similar Operational and environmental conditions. The % RSD was found to be 0.085075. The low % RSD value (< 2%) revealed that the proposed method is rugged. The limits of detection and limits of quantification were evaluated to be 0.0129 and 0.0392 µg/ml. In Solution stability testing, The solution was analyze Initial and after 1 hour. % degradation was found to be 0.27. The % recovery of Cefadroxil was found to be 99.45 by swab technique and 99.59 by rinse technique with method precision less than 2 % rsd. We found that the TOC method is applicable for determining residual Cefadroxil on equipment surfaces and will be

useful for cleaning validation. This method can be used to detect trace levels of Cefadroxil residue in production equipment area to confirm the efficiency of the cleaning procedure in pharmaceutical industries to avoid cross contamination.

Table 1: Validation parameters of Cefadroxil dry syrup

Parameters	Cefadroxil dry syrup
Linearity range	1-9 µg/ml
Equation	Y=0.527×-0.014
Slope	0.527
Intercept	0.014
Correlation coefficient	0.999
Accuracy(% recovered)	99.31-99.59
%recovery by swab ±% rsd	99.45±0.549
%recovery by rinse±%rsd	99.59±0.15
Intraday precision (%rsd)(n=3)	0.109-0.013
Interday precision(%rsd)(n=3)	0.028-0.174
Repeatability (%rsd)(n=3)	0.111
Reproducibility (%rsd)	0.850
Lod(% organic carbon)	0.012
Loq(%organic carbon)	0.039

CONCLUSION

A Cleaning validation method was developed for the simultaneous estimation of residual traces of Cefadroxil in Dry Powder Syrup using TOC Analyzer Apparatus. The cleaning validation is the process of assuring that cleaning procedures effectively remove the residue from manufacturing equipment/facilities below a predetermined level. This is necessary to assure the quality of future products using the equipment, to prevent cross-contamination, and as a World Health Organization and Good Manufacturing Practices requirement. Total Organic Carbon (TOC) analysis method was applied to number of pharmaceutical products. This method was developed for measuring residual Cefadroxil on surface of mixing vessel during manufacturing process. The proposed method has been statistically validated for linearity, accuracy, precision, repeatability and reproducibility, limit of detection (LOD) and limit of quantification (LOQ) as per ICH Q2 guidelines. It was found that the TOC method is applicable for determining residual Cefadroxil on equipment surfaces and will be useful for cleaning validation. This method can be used to detect trace levels of Cefadroxil residue in production equipment area to confirm the efficiency of the cleaning procedure in pharmaceutical industries to avoid cross contamination.

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