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Validation of an HPLC-UV method for the determination of ceftriaxone sodium residues on stainless steel surface of pharmaceutical manufacturing equipments

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ABSTRACT

In pharmaceutical industry, an important step consists in the removal of possible drug residues from the involved equipments and areas. The cleaning procedures must be validated and methods to determine trace amounts of drugs have, therefore, to be considered with special attention. An HPLC-UV method for the determination of ceftriaxone sodium residues on stainless steel surface was developed and validated in order to control a cleaning procedure. Cotton swabs, moistened with extraction solution (50% water and 50% mobile phase), were used to remove any residues of drugs from stainless steel surfaces, and give recoveries of 91.12, 93.8 and 98.7% for three concentration levels. The precision of the results, reported as the relative standard deviation (RSD), were below 1.5%. The method was validated over a concentration range of 1.15–6.92 μg ml^{-1}. Low quantities of drug residues were determined by HPLC-UV using a Hypersil ODS 5 μm (250 × 4.6 mm) at 50 °C with an acetonitrile:water:pH 7:pH 5 (39–55–5.5–0.5) mobile phase at flow rate of 1.5 ml min^{-1}, an injection volume of 20 μl and were detected at 254 nm. A simple, selective and sensitive HPLC-UV assay for the determination of ceftriaxone sodium residues on stainless steel surfaces was developed, validated and applied.

1. Introduction

An important step in the manufacture of pharmaceutical products is the cleaning of equipment and surfaces. The cleaning procedures for the equipment must be validated according to good manufacture practice (GMP) rules and guidelines. The main objective of cleaning validation is to avoid contamination between different productions or cross-contamination. This cleaning is verified by determining the amount of residues on surfaces involved in the manufacture process. Cleaning validation consists of two separate activities: the first is the development and validation of the cleaning procedure used to remove drug residues from manufacturing surfaces and the second involves the development and validation of methods for quantifying residuals from the surfaces of manufacturing equipment. Furthermore, many sampling points of the manufacturing facility and the manufacturing equipment have to be tested to verify the occurrence of contamination.

For these reasons, an analytical method for residue monitoring should also be rapid and simple [1].

The acceptable limit for residue in equipment is not established in the current regulations. According to the FDA, the limit should be based on logical criteria, involving the risks associated with residues of a determined product. The calculation of an acceptable residual limit, the maximum allowable carryover of active products in production equipment should be based on therapeutic doses, the toxicological index and a general limit (10 ppm). Several mathematical formulas were proposed to establish the acceptable residual limit [2–4].

Ceftriaxone (Scheme 1) is (6R, 7R)-3[(acetyl-oxy) methyl]-7-[[2Z)-(2-amino-4-thiazolyl)(methoxyamino)-acetyl]amino]-8-oxo-5-thia-1-azabicyclo[4.2.0.]oct-2-ene-2-carboxylicacid [5]. Ceftriaxone is a water soluble cephalosporin beta-lactam antibiotics used in the treatment of bacterial infections caused by susceptible, usually gram positive organism. The bactericidal activity of ceftriaxone results from the inhibition of the cell wall synthesis and is mediated through ceftriaxone binding to penicillin binding proteins (PBPs). It inhibits the mucopeptide synthesis in the bacterial cell wall. The beta lactam moiety of ceftriaxone binds to caboxypeptidase, endopeptidase, transpeptidase, in the bacterial cytoplasmic membrane. These enzymes are involved in cell wall synthesis and cell division. By binding these, ceftriaxone results in the formation of defective cell walls and cell death.

Several methods have been used for determination of ceftriaxone sodium which includes High Performance Thin Layer Chromatography (HPTLC) [6], High Performance Liquid Chromatography (HPLC) [7–12], Capillary Electrophoresis (CE) [13,14].

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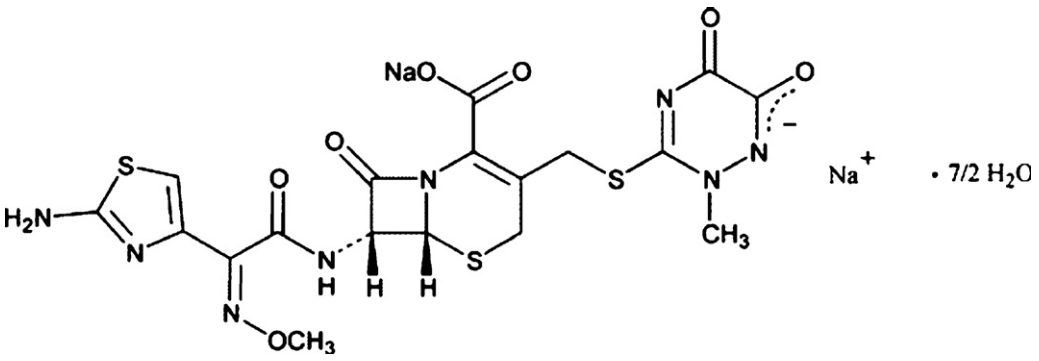

Scheme 1. Structural formula of ceftriaxone sodium.

A literature survey revealed that no validation of cleaning methods for ceftriaxone sodium residues, on stainless steel surfaces of pharmaceutical equipments, is to be found. Due to their high sensitivity and selectivity, analytical methods such as liquid chromatography were previously reported to be used for the determination of residues to control cleaning procedures [2–4,15–20].

Taking the above-mentioned considerations into account, the aim of this study was to develop and validate a simple analytical method that allows the determination of trace levels of ceftriaxone sodium residues in production area equipment and to confirm the efficiency of the cleaning procedure. The analytical method reported was validated considering selectivity, linearity, accuracy, precision and limits of detection (LOD) and quantification (LOQ). The stability of ceftriaxone sodium samples was also studied.

2. Experimental

2.1. Reagent and chemicals

Ceftriaxone sodium reference standard and ceftriaxone sodium E-Isomer of United States Pharmacopoeia (USP) were bought from Sigma, United States. Ceftriaxone sodium (USP) [21] is soluble in water. A fixed dose combination (FDC) was obtained from manufacturer, Venus Remedies Limited, India. Each vial contains 1 g ceftriaxone sodium. Chromatographic grade dibasic potassium phosphate, monobasic potassium phosphate, 85% phosphoric acid, potassium hydroxide, sodium citrate, citric acid, tetraheptylammonium bromide and acetonitrile were obtained from Merck, Germany. All other chemicals were of analytical reagent grade unless specified. HPLC grade water was prepared by taking reverse osmosis water and passing it through a Milli-Q System (Millipore, Milford, USA).

A pH 7.0 buffer, was prepared by dissolving 13.6 g of dibasic potassium phosphate with 4.0 g of monobasic potassium phosphate in 1000 ml of water then adjust pH (USP). pH 5.0 buffer was prepared by dissolving 25.8 g of sodium citrate in 1000 ml of water after adjusting pH with citric acid solution (USP). The extraction recovery sampling was realized with Alpha Swab polyester on a propylene handle-TX714A (ITW Tex wipe, Mahwah, USA).

2.2. Equipment

Chromatographic separation was performed on Agilent 1100 series liquid chromatographic system consisted of a degasser G1322A, quaternary pump G1311A, an automatic injector G1313A, a column oven G1316A and multiwavelength detector G1315A, all 1100 Series from Agilent Technologies, which were controlled by HP Chem-station software. The separation was carried out in Hypersil-ODS analytical column (250 mm × 4.6 mm, 5 μm, Thermo Hypersil, USA). In the sample preparation procedure, ultrasonic instrument (China) and Orion Ross combination pH electrode (Model 81-02) was used for all pH measurements.

2.3. Chromatographic conditions

The mobile phase consisted of 3.2 g of tetraheptylammonium bromide, 390 ml acetonitrile, 55 ml of pH 7 buffer, 5 ml of pH 5 buffer and 550 ml water. The mobile phase solution was filtered through 0.45 μm membrane filter (Millipore) and degassed prior to use. Extraction solution consisted of mobile phase solution (50% v/v) and water (50% v/v).

All chromatographic experiments were performed in isocratic mode. The mobile phase was pumped at flow rate of 1.5 ml min^{-1} with 20 μl injection volume. The column temperature was at 50 °C. UV detection was performed at λ_{max} 254 nm. All calculations were carried out on microcomputer under the Windows XP operating system.

2.4. Standard solution preparation

The stock solution of standard was prepared by accurately weighing ceftriaxone sodium reference standard (with water content 8%) and transferring into a 50 ml volumetric flask. Approximately 25 ml of diluting solvent was added and content of flask was sonified for 30 min. The solution in the flask was diluted to volume with diluting solvent and then 10 ml was diluted to 100 ml with diluting solvent the final concentration being 0.045 mg ml^{-1}.

Resolution solution was prepared accurately weighing 6 mg ceftriaxone sodium reference standard and 6 mg ceftriaxone sodium E-Isomer RS then transferred into a 100 ml volumetric flask, 50 ml of diluting solvent were added and the contents of flask were sonified for 30 min and the solution in the flask was diluted to volume with diluting solvent.

2.5. Sample solution preparation

The selected surfaces (10 cm × 10 cm) of stainless steel, previously cleaned and dried, were sprayed with 250 μl of stock standard solution, for the positive swab control at all concentration levels, and the solvent was allowed to evaporate. The surface was wiped in one direction with wet cotton swab soaked with extraction solution (5 ml water and 5 ml of mobile phase, ceftraxione sodium is soluble in water and mobile phase according to USP) was pipette into swab tube. The background control sample was prepared from the extraction solvent. The negative swab control was prepared in the same way as the samples, using swabs, which had not been in contact with the test surface. In addition, test and excipient solutions were prepared according to the content of vials powder to assure that they did not interfere with ceftriaxone sodium determination. Subsequently, the tubes were placed in an ultrasonic bath for 10 min and the solutions were analyzed by HPLC-UV.

3. Results and discussion

3.1. Acceptance limit calculation

In the filed of industrial pharmacy one of the more time and labor-intensive processes is the cleaning validation of reaction vessel that needs to take place after a particular product has been prepared. Careful examination of the vessel for trace residues is vital to the pharmaceutical manufacturing process as residues can contaminate subsequent products. The maximum allowable carryover (MACO) is the acceptable transferred amount from the previous to the following product. The MACO is determined based on the therapeutic dose, toxicity and generally 10 ppm criterion. Once the maximum allowable residue limit in the subsequent product was determined, the next step was the determination of the residue limit in terms of the contamination level of active ingredient per surface area of equipment. The total surface area of the equipment in direct contact with the product was accounted for in the calculation. The limit per surface area was calculated from the equipment surface area and the most stringent maximum allowable carryover. The 0.1% dose limit criterion is justified by the principle that an active pharmaceutical ingredient (API) at a concentration of 1/1000 of its lowest therapeutic dose will not produce any adverse effects on human health. The calculated limit per surface area (LSA) in the case of ceftriaxone was 1.2 μg/swab pro 100 cm^2. A stainless steel surface area of 10 cm × 10 cm was chosen for practical reasons.

3.2. Optimization of the chromatographic conditions

To obtain the best chromatographic conditions, the wavelength for detection, mobile phase composition, column temperature and flow rate were adequately selected. The main objective was to develop an HPLC-UV method that, running in the isocratic mode, allowed the determination of ceftriaxone residues collected by swabs, without interference of impurities originating from the swabs, plated and extraction media.

For analysis, the combination of water, tetraheptylammonium bromide, pH buffer 7, pH buffer 5 and acetonitrile is frequently used as the mobile phase. The amount of water was varied from 49% to 59% and flow rate varied from 1.2 ml min^{-1} to 1.7 ml min^{-1}. The sufficient separation, tailing factor and plate number were achieved with the proposed mobile phase (3.2 g of tetraheptylammonium bromide, 450 ml acetonitrile, 55 ml of pH 7, and 5 ml of pH 5 and 490 ml water) at flow rate 1.5 ml min^{-1}. Wavelength 254 nm was selected for detection because the drug has a sufficient absorption and low quantities of ceftriaxone can be detected correctly. Furthermore, the calibration curve obtained at 254 nm showed good linearity. Regarding the chromatographic procedure, different C18 columns were evaluated but the Hypersil ODS 5 μm (250 mm × 4.6 mm) was preferred to improve the peak symmetry, plate number and resolution. The column temperature was varied from 40 to 56 °C but the analysis at 50 °C was preferred to improve the peak symmetry, plate number and resolution.

3.3. Optimization of the sample treatment

Cotton swabs were spiked with different quantities of ceftriaxone and placed into tubes. After the addition of different volume of water and mobile phase as diluting solvent, the tubes were sonified for different times (3.5 and 10 min) and the solutions were analyzed by HPLC after filtration with Millipore millex – HV-PVDF 0.45 μm. The optimum conditions were achieved with 50% water and 50% mobile phase as the extracting solvent and sonification time of 5 min. This technique was applied in the subsequent work.

3.4. Validation of the method

Once the chromatographic conditions had been selected, the method was validated, whereby attention was paid to the selectivity, linearity, limit of detection, limit of quantification, precision, accuracy and sample, standard and mobile phase stability.

3.4.1. System suitability

During performing the system suitability test, in all cases relative standard deviation (RSD) of the peak areas was <2.0%, the average number of theoretical plates per column was >3600, the USP tailing Factor <1.2 and the resolution >2.0.

3.4.2. Specificity

Specificity is the ability of the method to accurately measure the analyte response in the presence of all potential sample components (excipients). The specificity of the method was checked by injecting ceftriaxone standard, ceftriaxone sample, the background control sample, the negative swab control, swabbed un-spiked stainless steel 10 cm × 10 cm plate as descried and four standard solutions after storage under destructive condition (80 °C for 24 h), (in acid for 24 h), (in base for 24 h) and (in H_2O_2 for 24 h). The samples have been chromatographed according to the experimental method to demonstrate the resolution of the ceftriaxone sodium from any unknown peaks. Ceftriaxone sodium has chromatographic resolution more than 1.5 from other peaks. The results are shown in Fig. 1a–f.

3.4.3. Linearity

Linearity of method was studied by analyzing standard solutions at seven different concentration levels ranging from 1.153 to 6.92 μg ml^{-1}, with triplicate determination at each level. The calibration curve was constructed by plotting mean response area against corresponding concentration injected, using the linear regression least square method. The calibration curve values of slope, intercept and correlation coefficient for ceftriaxone sodium are presented in Table 1 and indicate good linearity.

3.4.4. Limit of detection (LOD) and limit of quantification (LOQ)

LOD and LOQ were determined based on the standard deviation of the response (*y*-intercept) and the slope of the calibration curve at low concentration levels according to ICH guidelines [22,23]. The LOD and LOQ for ceftriaxone sodium were found to be 0.017 and 0.06 μg ml^{-1}, respectively.

3.4.5. Precision and accuracy

The precision and accuracy of the proposed cleaning validation procedure, reported as relative standard deviation (RSD) and the recovery (%), respectively, were assessed by comparing the amount of analyte determined versus the known amount spiked at three different concentration levels (0.93, 2.3 and 3.72 μg ml^{-1}) with 6 replicates ($n = 6$) for each investigated concentration level. The recovery and the RSD values (Table 2) for each level illustrated good precision and accuracy of the method. These precision and recovery results are excellent for the purpose of residue monitoring.

The intermediate precision of the method was investigated by performing five consecutive injections of standard solutions on two different days by different analysts and different reagents. The intermediate precision, expressed as the RSD was found to be 2.03% and 2.06% for the first and second days, respectively. The data obtained suggested that the method exhibited an excellent intermediate precision for ceftriaxone standard solution when analyzed on two different days by two different analysts.

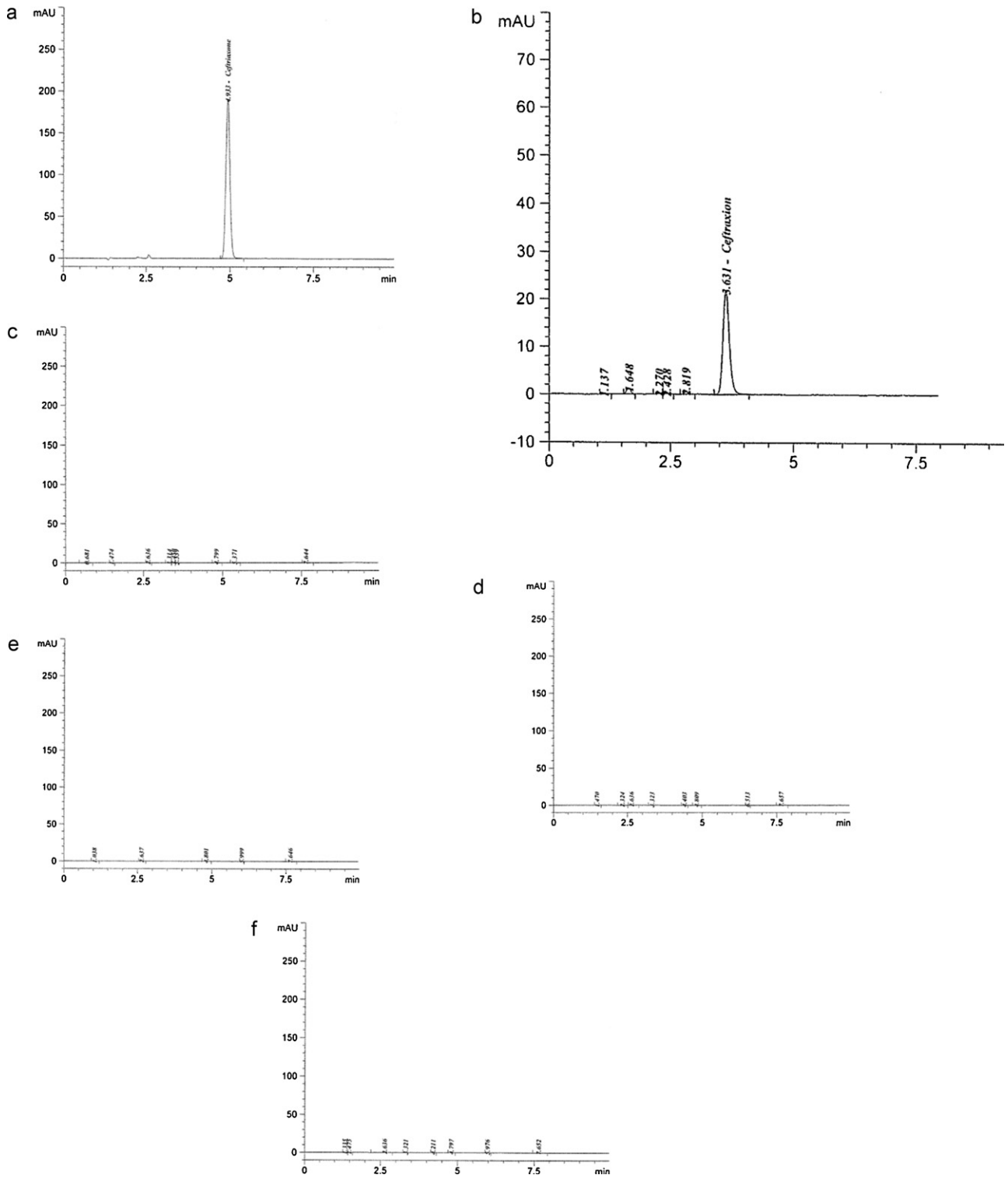

Fig. 1. Chromatograms obtained from (a) ceftriaxone standard solution, 45 ppm, (b) ceftriaxone sample, 10 ppm, (c) non-spiked stainless steel, (d) excipient mixture, (e) negative swab control and (f) background control sample.

Table 1
Linear regression data in the analysis of ceftriaxone sodium.

Statistical Parameters	Values
Concentration range ($\mu g\,ml^{-1}$)	1.153–6.92
Regression equation	$y = 17.763X - 1.665$
Coefficient of determination	$r^2 = 0.9998$
S(a)-error in intercept	1.71

Table 2
Precision and accuracy of the results obtained from swabbed plates spiked with ceftriaxone sodium.

Amount added ($\mu g\,ml^{-1}$)	Amount found ($\mu g\,ml^{-1}$)	95% confidence interval %	Recovery (%)	RSD % $n = 6$
0.93	0.85	91.2–93.04	91.12	1.2
2.33	2.18	93.67–94.02	93.8	0.24
3.72	3.67	98.07–99.42	98.7	0.85

3.4.6. Sample and standard stability

The stability of the ceftriaxone in the swab matrix and ceftriaxone standard solution, were tested. The spiked samples and standard solution were stored after analyses in the injector vial in auto-sampler tray at ambient temperature for 12 h. All samples and standard solutions were injected into appropriate HPLC system after 6 h, 12 h and 24 h against fresh standard solutions. The stability of the standard ceftriaxone solution (46.1 μg ml^{-1}) was also inspected after storage for 24 h at top bench condition with 2.13% difference in results. The stability of the samples solutions after storage for 24 h at top bench condition with 2.01% difference in results. In both cases, no change in the chromatography of the stored samples and standards were found and no additional peaks were registered when compared with the chromatograms of the freshly prepared samples.

3.5. Filter evaluation

Samples and standard solutions of ceftriaxone prepared as per analysis method, were filtered with Millipore millex – HV-PVDF 0.45 μm and millex – PTFE-0.45 μm, and then compared to the unfiltered samples. The Millipore millex – HV-PVDF 0.45 μm and millex – PTFE-0.45 μm pore size syringe filter were qualified for use with filter evaluation ratio 100.8% and 100.10 for ceftriaxone standard with PVDF and PTFE filter, respectively. For samples the filter evaluation ratio was 100.2% and 101.2% for PVDF and PTFE filter respectively.

3.6. Robustness

In order to test the robustness of the HPLC-UV method, the effect of different chromatographic parameters on the resolution and the concentration of cefriaxone from cleaning samples, was estimated. The amount of water in the mobile was varied from 50% to 59%, the flow rate was varied from 1.2 ml min^{-1} to 1.7 ml min^{-1}, column temperature was varied from 40 to 56 °C and the wavelength detector λ_{max} was varied from 250 to nm. The results obtained, Table 3, showed that only the % of water content of the mobile phase had a slight effect on the resolution (<1.5). On the other hand, the change in any of the estimated chromatographic parameters had no effect on the concentration of cefriaxone from cleaning samples.

Table 3
Effect of different chromatographic parameters.

Chromatographic parameter	RSD %	Resolution	Tailing factor	Plate count	Sample result (ppm)
(1) Wavelength (nm)					
250	0.13	2.07	1.20	3597	0.220
252	0.21	2.05	1.20	3595	0.220
254	1.13	2.06	1.20	3623	0.224
256	0.10	2.07	1.20	3641	0.224
258	0.27	2.09	1.20	3594	0.223
(2) Flow rate (ml min^{-1})					
1.2	0.58	2.17	1.21	3841	0.221
1.3	1.01	2.17	1.21	3841	0.221
1.5	1.13	2.07	1.21	3573	0.222
1.6	1.22	2.03	1.21	3447	0.224
1.7	1.40	1.99	1.20	3308	0.221
(3) Column temperature (°C)					
40	0.24	2.18	1.19	3478	0.220
45	0.31	2.13	1.20	3563	0.220
50	0.14	2.06	1.20	3623	0.224
53	0.94	2.04	1.20	3721	0.224
56	1.39	2.03	1.19	3754	0.220
(4) % of water content in the mobile phase					
50	0.52	1.39	1.18	3549	0.226
52.5	0.51	1.66	1.21	3606	0.227
55	0.14	2.06	1.20	3623	0.224
57.5	1.17	2.68	1.21	3814	0.224
59.5	0.44	3.39	1.22	3905	0.227

Table 4
Determination of ceftriaxone in actual swab samples collected from 100 cm^2 swabbed area from different locations of the equipment train (sterile powder filling machine).

Serial no.	Location description	Results (ppm)
1	Dosing disc	Less than detection limit
2	Lower hopper	0.21
3	Lower connecting sleeve	0.508
4	Upper connecting sleeve	0.161
5	Piston	0.244

3.7. Assay of swab samples collected from different locations within the equipment train

Swab samples from different locations within the manufacturing equipment train have been analyzed to determine the residues of ceftriaxone. These samples were prepared and analyzed by the proposed method. Some of the results obtained for these samples are presented in Table 4.

4. Conclusion

In conclusion, a simple to use HPLC-UV method to quantify residues of the active pharmaceutical ingredient ceftriaxone on swabs, in support of cleaning validation of pharmaceutical manufacturing equipment, was developed. Validation studies showed that the HPLC-UV method is selective, linear, precise and accurate. To extract the ceftriaxone residue from the surface, a wipe test procedure using a cotton swab is recommended. The recoveries obtained from the stainless steel surfaces were close to 94.5% or higher and there was no interference from the cotton swab. Stability studies show that the ceftriaxone samples are at least, stable over the investigated 24 h. The overall procedure can be used as part of a cleaning validation program in pharmaceutical manufacture of ceftriaxone.

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