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Stability Indicating RP-HPLC Method for Estimation of Cefquinome Sulphate in IV/IM Injection

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Abstract— *The aim of present study was to develop and validate a simple, isocratic, accurate, stable, roust, and economical Reversed Phase High-Performance Liquid Chromatography (RP-HPLC) method for the determination of Cefquinome Sulphate in the IV/IM dosage form. The chromatographic separation was achieved on Inert sustain C18 column (250mm x 4.6mm x 5µ). The mobile phase selected was 25mM KH_2PO_4 buffer (pH 6.5) and Acetonitrile in the ratio of 80:20 % v/v at flow rate of 1.0ml/min with column temperature maintained at 40°C and 5µl injection volume was used. The detection was conceded out at 265nm.The developed RP-HPLC method yielded a suitable retention time of 4.2min for Cefquinome Sulphate. The method was linear under the range of 20 to 160 µg/mL with a linear regression coefficient of 0.9991. The %RSD for the method precision and system precision was found to be less than 2.0%. The %assay of formulation is 99.28%. The %Mean recoveries were discovered to be 100.29%. The LOD and LOQ was found to be 0.44 µg/mL and 1.34 µg/mL respectively. The specificity was calculated by using forced degradation studies in which the drug is subjected to stress conditions such as thermal, acidic, basic, oxidative and photolytic degradation. The developed and validated RP-HPLC method for Cefquinome Sulphate takes short time and can be used for routine Quality analysis of marketed Cefquinome Sulphate pharmaceutical dosage forms.*

Keywords— *Cefquinome, Development, Forced degradation, Injection, Isocratic, RP-HPLC, Validation.*

I. INTRODUCTION

Cefquinome is a parenteral, veterinary, fourth generation cephalosporin. It has broad spectrum antibacterial activity against Gram positive & Gram-negative bacteria [5-7]. A beta-lactam group of cephalosporin is essential for the antibacterial activity. [1] They Inhibit the bacterial cell wall biosynthesis by blocking the –CH_2OH group of biocatalysts irreversibly [2].

The chemical name of Cefquinome Sulphate is Quinolinium, 1-[[(6R,7R)-7-[[(2Z)-(2-amino-4-thiazolyl) (mrthoxyimino) acetyl] amino]-2-carboxy-8-oxo-5-thia-1-azabicyclo [4.2.0]oct-2-en-3yl] methyl]-5,6,7,8-tetrahydro-,sulfate; and molecular weight is 626.68 with the molecular formula $C_{23}H_{24}N_6O_5S_2.H_2SO_4$.[11] Cefquinome is highly stable to beta-lactamases, which is used in the treatment of infections of urinary tract, lungs, skin, and soft tissues also in postoperative prophylaxis.[8] A quaternary quinoline group at 3rd position in the Cefem ring & their zwitterionic structure facilitate the rapid penetration of Cefquinome across the biological membrane of bacteria & animals, showing its fast bactericidal action after injection.[3]

According to the guidelines of the International Conference on Harmonization (ICH) for the determination of drugs after stability analysis require the development of Stability indicating assay methods (SIAMs) appropriately [13].

The literature survey reveals that calorimetric & HPLC method for the determination of Cefquinome Sulphate in bulk & dosage form were developed [9, 4]. In that stability indicating HPLC method was described but not given the results of SST parameters, Hence trials were made to develop RP-HPLC method with short run time for the estimation of Cefquinome Sulphate in injection (IV/IM) dosage form as per ICH guidelines.

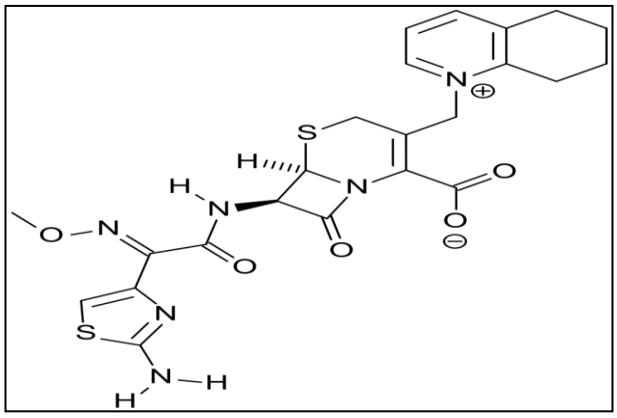

Fig. 1. Chemical structure of Cefquinome

II. MATERIALS AND METHODS

Chemicals and Reagents:

Cefquinome Sulphate working standard was procured from Central Drug Testing Laboratory, Mumbai with claimed potency [80.9 per cent as is basis]. BACTIVON (500 mg) Injection (Cefquinome Sulphate) was received from the local market. HPLC grade acetonitrile from Rankem, Potassium Dihydrogen Phosphate from Avra Synthesis LTD, Triethylamine from SRL chem, 0.45 µm high flow nylon membrane filter purchased from Axiva Sichem Pvt. Ltd and ultra-purified HPLC grade water from Milli-Q system (Millipore, MA, USA) water purification unit were used.

Twinkle Tarole, Pratibha Daroi, Vijaya Kumar Munipalli, Sayali Warde, Raman Mohan Singh, Anindita Nandi, and Vaidhun Bhaskar, "Stability Indicating RP-HPLC Method for Estimation of Cefquinome Sulphate in IV/IM Injection," *International Research Journal of Pharmacy and Medical Sciences (IRJPMS)*, Volume 5, Issue 3, pp. 51-56, 2022.

Instrumentation:

Lab India UV/VIS spectrometer connected to a computer loaded with UV WinLab ES software/version 6.0.4.0738 was used for all the spectrophotometric measurements. Thermo scientific Dionex ultimate 3000 using Chrome Leon 7.2.6 software with LC instrument control was used for chromatography. All weighing's were done with the Sartorius Analytical Balance. HPLC equipped with a Waters 2996 PDA (photodiode array) Detector was used for Degradation studies. The column used was Inert sustain 25cm × 4.6 mm & 5 µ particle size.

Selection of solvent (Diluents):

Based on the solubility and chemical nature of Cefquinome Sulphate, the HPLC grade water was selected as a diluent for the preparation of standard and sample solutions.

Selection of wavelemgth:

10.0 mg of Cefquinome was transferred to the 100ml volumetric flask and the volume was made up to the mark with diluent (100µg/mL) and from that stock solution further dilutions were made to make the concentration of 10 µg/ml. The solution was scanned in the range of 200 – 400 nm of the maximum absorbance was observed was at 266nm.

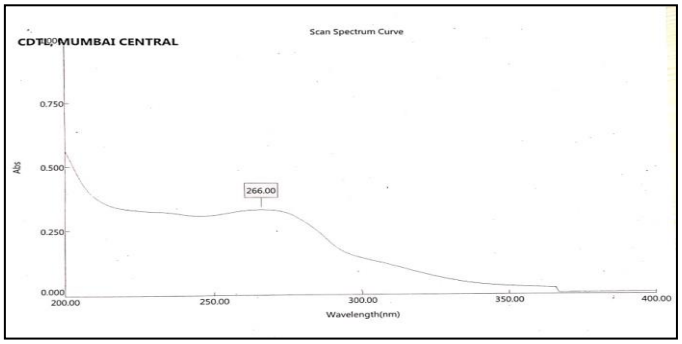

Fig. 2. Cefquinome UV Spectrum

Preparation of standard solution:

Transferred accurately 20 mg of Cefquinome Sulphate standard transferred in 20ml of volumetric flask and dissolved it by sonication with sufficient amount of diluent and made up the volume up to Merck (1000 µg/mL). Then further dilutions were made to make the concentration of 100µg/ml.

Analysis of marketed formulation:

Transferred the components 1 Vial equivalent (500 mg) to 100ml flask and volume was made with 100 mL diluent (5000µg/ mL) and filtered through 0.45µ nylon filter. Further dilutions were made to make the concentration of 100µg/ml.

Preparation of mobile phase:

25mM Potassium Dihydrogen Phosphate (KH_2PO_4) was prepared and adjusted with Triethylamine to 6.5 and Acetonitrile in the ratio of 80:20 v/v was used as a mobile phase. The mobile phase was vacuum filtered through 0.45 µm nylon membrane filter and sonicated using ultra sonicator.

Method Optimization:

The chemical structure of the Cefquinome Sulphate shows that the drug is an acidic and polar molecule therefore the mobile phase is selected according to nature and its affinity. The Peak symmetry, Retention and separation was highly dependent on pH and concentration of buffer. The trials were done by using different concentration of KH_2PO_4 buffer and acetonitrile (70:30 v/v) using Inertsustain C18 column, but peak was not eluted in reasonable time and the final method optimize after some trials by using mobile phase as KH_2PO_4 buffer (25mM) adjusting pH 6.5 with TEA and acetonitrile at the ratio of 80:20 with column Inert sustain 25cm × 4.6 mm & 5µ, the Column oven temperature was kept at 40°C, the flow rate is 1.0ml/min which gives a good peak shape at the retention time of 4.2 min at 265nm. Table I shows the selected method conditions.

Parameters were applied to SST (System Suitability Test) of standard solution and results were obtained as shown in Table II.

Method Validation:

Validation of developed method on HPLC was done as per ICH Q2 (R1) guidelines with respect to various parameters such as precision, linearity, accuracy, assay and robustness. Results of different tests were compared with the standard guidelines of ICH Q2 (R1) to get accurate results. [12]

Specificity:

The specificity of the method was established by demonstrating no interference from degradation products. This was demonstrated by carrying out forced degradation of the sample by exposing solid & liquid state degradation. The samples were prepared and injected into HPLC equipped with a Waters 2996 PDA (Photodiode array) detector as per developed chromatographic and instrumental conditions.

Linearity:

From the standard solution of Cefquinome Sulphate aliquots were prepared in the concentration range of 20-160ppm. By constructing the graph by plotting concentration verses area obtained from the response. The linear calibration plot was constructed by analyzing the concentrations over the selected range. The response for the drug was linear in the concentration range between 20-160 µg/ml. The analysis was shown in the Table III.

Precision:

Precision expresses the degree of reproducibility of responses of repeated measurements. The more responses give better precision & the smaller the error will be.

The sample and standard solution were injected 6 times to check their preciseness of method and the results are depicted in Table IV, V, VI.

System Precision:

Those six injections of standard solution (100 µg/mL) were injected with the developed method then %RSD values were calculated and the results are showed in Table IV.

Twinkle Tarole, Pratibha Daroi, Vijaya Kumar Munipalli, Sayali Warde, Raman Mohan Singh, Anindita Nandi, and Vaidhun Bhaskar, "Stability Indicating RP-HPLC Method for Estimation of Cefquinome Sulphate in IV/IM Injection," *International Research Journal of Pharmacy and Medical Sciences (IRJPMS)*, Volume 5, Issue 3, pp. 51-56, 2022.

Method Precision(Assay):

Sample solution of 100µg/mL of 6 different vials prepared and 6 injections of the sample were injected with the developed method then % RSD values were calculated and the results are shown in Table V.

Intraday Precision:

Study was carried out by injecting standard and sample solution at different time intervals i.e., 10.AM, 1.00PM & 4.00PM. In that %RSD is evaluated, which is shown in Table VI.

Intermediate (Interday) Precision:

Freshly prepared standard and sample solution injecting on two different days. To check their reproducibility on two different days the %RSD is calculated as shown in Table VII.

Accuracy (Standard addition method):

Accuracy refers to the closeness of the measured value of a quantity corresponds to its "true" value. In that accepted either true value or an accepted reference value and the estimated value.

Accuracy studies was carried out by standard addition method where known concentration of standard solution was added to pre analyzed sample and check the % mean recovery at 110%, 120% & 130% and mean % recoveries were calculated which is given in Table VIII.

Robustness:

The terms robustness and ruggedness demote to the ability of an analytical method to remain unaffected by small variations in the method parameters (mobile phase content, column temperature, etc.) and influential environmental factors (room temperature, air humidity, etc.) and characterize its reliability during normal usage. Deliberate changes were made in temperature, flow, wavelength, and mobile phase in the estimation of Cefquinome solution which shows no significant deviations in the results with indicating the reliability and results are shown in Table IX.

LOD and LOQ:

Limit of detection (LOD) & Limit of Quantification (LOQ) were calculated based on the standard deviation of the y-intercept and slope of the calibration curve. LOD = 3.3 δ/S, LOQ = 10 δ/S. The results were shown in Table X.

Forced degradation studies:

Stability of Active Pharmaceutical Ingredient and formulated product can be carried out by forced degradation studies. It helps in packaging development and storage conditions by studying the chemical activities of the drug molecule.

PDA Detector wad used to evaluate the peak purity of the Cefquinome Sulphate in different conditions to confirm the stability indicating nature of the proposed method. Forced degradation of the Cefquinome Sulphate was carried out under acidic, basic, thermal, oxidative, hydrolytic and photolytic conditions.

Acid degradation:

Cefquinome (250µg/ml) was refluxed & evaporated for 1 hour on water bath with 10 ml hydrochloric acid (1N) and the same concentration was left in HCL for different time intervals at room temperature. After this period, each solution was neutralized, filtered, and had the volume reconstituted with diluent to produce concentration equivalent to 100 µg/ml

Base degradation:

Cefquinome (250µg/ml) was refluxed & evaporated for 1 hour on water bath with 10 ml Sodium hydroxide (1N) and the same concentration was left in NaOH for different time intervals at room temperature. After this period, each solution was neutralized, filtered, and had the volume reconstituted with diluent to produce concentration equivalent to (100 µg/ml).

Oxidative degradation:

250µg/ml of Cefquinome was refluxed & evaporated with 10 ml of 10% hydrogen peroxide for 1 hour on water bath. After that filtered and completed to volume with diluent (100µg/ml)

Thermal degradation:

10mg of Cefquinome in solid state was spread to 1 mm thickness in Petri dish and kept in the oven at 40°C for 1 hour. This sample was taken into 100ml volumetric flask, dissolved and diluted with diluent (100µg/ml).

Photolytic degradation:

10ml of 250ppm solution of Cefquinome is kept under the UV-light for 24 hours. After that the solution completed to volume with diluent (100 µg/ml).

Hydrolytic degradation:

10ml of 250ppm solution of Cefquinome is evaporated on water bath at 70°C for 1 hour. After cooling of solution completed to volume with diluent (100 µg/ml).

III. RESULTS AND DISCUSSION

TABLE I. Optimized chromatographic condition

Program	Isocratic
HPLC System	Thermo ultimate 3000
Column	Inert sustain 25cm × 4.6 mm &5 µ
Mobile phase	25mM KH_2PO_4 buffer (pH 6.5): Acetonitrile (80:20v/v)
Diluent	Water
Standard solution concentration	Cefquinome stock solution (100ppm)
Flow rate	1.0 mL/min.
Run time	7 min.
Wavelength	265nm
Injection volume	5 µL
Column oven temperature	40^0C
Retention time	4.2 min.
Detector	UV-VIS

System suitability studies:

As system suitability test was an integral part of chromatographic methods development and it was carried under ICH (Q2) guidelines [7]. When HPLC method is optimized then to check their suitability and stability of the optimized method, the injections of blank (1injection) and standard Cefquinome Sulphate (6 injection replicates) were

Twinkle Tarole, Pratibha Daroi, Vijaya Kumar Munipalli, Sayali Warde, Raman Mohan Singh, Anindita Nandi, and Vaidhun Bhaskar, "Stability Indicating RP-HPLC Method for Estimation of Cefquinome Sulphate in IV/IM Injection," *International Research Journal of Pharmacy and Medical Sciences (IRJPMS)*, Volume 5, Issue 3, pp. 51-56, 2022.

given at a working concentration of 100 µg/ml. The chromatograms obtained by which peak area, retention time, theoretical plates and tailing factor of standard solution were determined and mentioned in the Table II.

TABLE II. System suitability parameter

INJ No	Ret. Time Min	Area uAU*min	Tailing Factor	Plates EP
1	4.25	15389.1	1.34	8427
2	4.253	15169	1.36	8421
3	4.257	15293.4	1.36	8488
4	4.258	15273.1	1.35	8377
5	4.253	15211.3	1.35	8415
6	4.25	15177.3	1.35	8341
Mean	4.2535	15252.2	1.35	8412
SD	0.0034	83.76	0.0075	49.71
% RSD	0.08	0.549	0.557	0.591

The typical chromatogram of Standard, Sample and Blank solution with optimized method is shown in Fig. 3, 4 and 5.

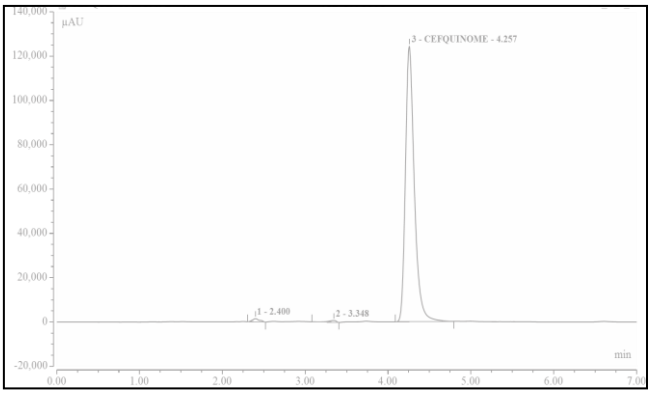

Fig. 3. Chromatogram of Cefquinome standard solution of 100 µg/ml

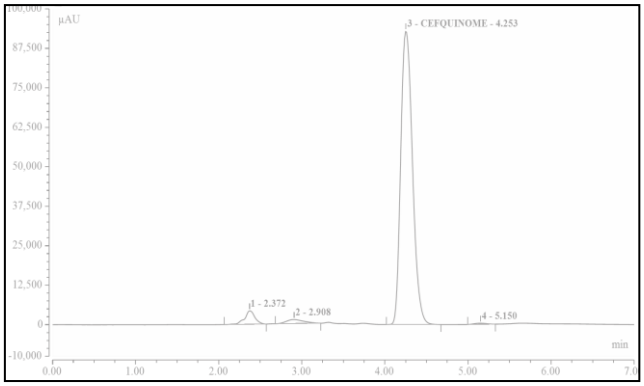

Fig. 4. Chromatogram of Cefquinome sample solution of 100 µg/ml

Method validation:

Linearity:

Linearity tests were performed in which different concentration sample vs. area performed in which results obtained it as y =156.92x-540.71 R2=0.9991 which is within specifications as in fig.6

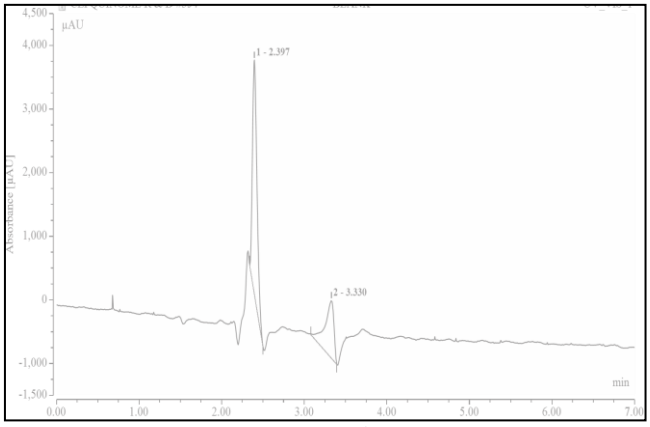

Fig. 5. Chromatogram of Blank solution

TABLE III: Cefquinome Linearity study in the range of 20-160 µg/ml

Linearity Level	Concentration	Area
1	20	6679.82
2	40	13553.85
3	60	20498.66
4	80	28602.03
5	100	37262.82
6	120	44220.04
7	160	58407.91

Precision:

The precision tests were performed in which interday, intraday, system precision, and method precision is performed in which any of the test R.S.D. was not more than 2.00%.

TABLE IV: System precision of standard solution (100 µg/ml)

System Precision	
Injection No.	**Area at 265 nm**
1	13365.74
2	13337.53
3	13325.93
4	13343.14
5	13302.81
6	13325.33
Mean	13333.41
SD	21.04506
% RSD	0.158

SD= Standard Deviation
%RSD= Percent relative standard deviation

TABLE V: Method precision of standard solution (100 µg/ml)

Method Precision	
Injection No.	**Assay %**
1	97.3
2	97.45
3	97.58
4	99.24
5	99.44
6	97.75
Mean	98.13
SD	0.95355
% RSD	0.972

SD= Standard Deviation
%RSD= Percent relative standard deviation

Twinkle Tarole, Pratibha Daroi, Vijaya Kumar Munipalli, Sayali Warde, Raman Mohan Singh, Anindita Nandi, and Vaidhun Bhaskar, "Stability Indicating RP-HPLC Method for Estimation of Cefquinome Sulphate in IV/IM Injection," *International Research Journal of Pharmacy and Medical Sciences (IRJPMS)*, Volume 5, Issue 3, pp. 51-56, 2022.

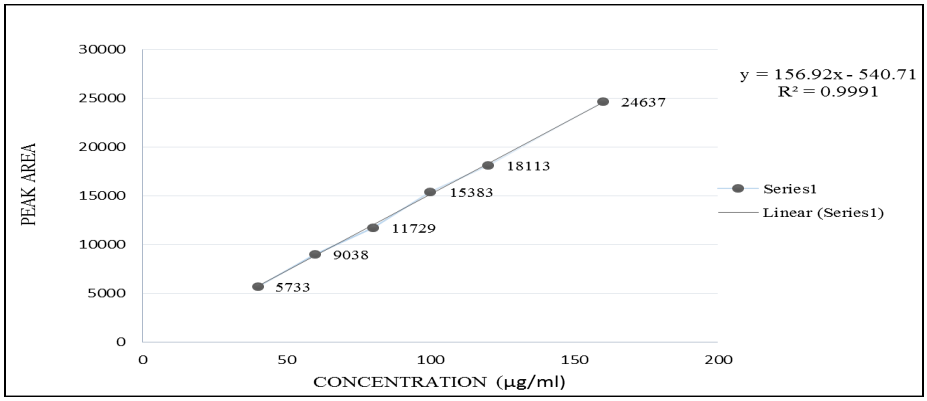

Fig. 6: Linearity Curve of Cefquinome in the range of 20-200 µg/ml

TABLE VI: Intraday precision of sample and standard solution

Intraday Precision			
Sr no.	**10:00 AM**	**1:00AM**	**4:00AM**
1	97.30	99.20	97.188
2	97.45	99.49	97.44
3	97.58	98.76	97.27
4	99.24	99.52	97.53
5	97.75	99.31	96.94
Mean	97.86	99.26	97.2736
SD	0.787	0.3068061	0.23024943
% RSD	0.804	0.3091059	0.236702898

SD= Standard Deviation
%RSD= Percent relative standard deviation

Accuracy:

Accuracy tests were performed in which closeness of the value and per cent mean recovery test performed in which %mean recovery is 100.29 and %R.S.D. NMT 2.00%. Assay tests were performed in which the content of the sample of Cefquinome Sulphate is determined, in that per cent assay is 98% to 105% & %R.S.D. is NMT 2.00%.

TABLE VII: Interday precision of sample and standard solution

Interday Precision		
Sr. no.	**Day 1**	**Day 2**
	Analyst A	**Analyst B**
1	97.3	99
2	97.45	98
3	97.58	100
4	99.24	102
5	97.75	103
MEAN	97.86	100
SD	0.787	2
%RSD	0.804	2

SD= Standard Deviation
%RSD= Percent relative standard deviation

TABLE VIII: Accuracy data of Cefquinome Sulphate

Accuracy						
%LEVEL	**STD Spiked (ml)**	**Recovery(mg)**	**%Recovery**	**%Mean Recovery**	**SD**	**% RSD**
110	1	544.14	98.88	98.79	0.1447	0.146
	1	542.69	98.62			
	1	543.35	98.86			
120	2	609.94	101.6	101.64	0.0781	0.077
	2	609.88	101.59			
	2	610.7	101.73			
130	3	651.09	100.11	100.45	0.7814	0.778
	3	649.66	99.89			
	3	659.08	101.34			

SD= Standard Deviation
%RSD= Percent relative standard deviation

TABLE IX: Robustness study of Cefquinome Sulphate

Robustness					
Parameter	**Change in parameter**		**% Estimation**	**Mean**	**SD**	**RSD**
Wavelength (± 2nm)	263		100.26	100.0	0.60357	0.60357
	265		99.31			
	267		100.43			
Temperature (± 2°C)	38		100.36	99.99	0.58705	0.58713
	40		99.31			
	42		100.29			
Flow rate (±0.5)	0.8		99.63	100.0	1.20578	1.20385
	1		99.31			
	1.2		101.54			
Mobile phase ratio (±5ml) Buffer: ACN A: B	A	B		99.21	0.14142	0.14255
	75	25	99.11			
	80	20	99.31			
	85	15	99.61			

SD= Standard Deviation
%RSD= Percent relative standard deviation

Twinkle Tarole, Pratibha Daroi, Vijaya Kumar Munipalli, Sayali Warde, Raman Mohan Singh, Anindita Nandi, and Vaidhun Bhaskar, "Stability Indicating RP-HPLC Method for Estimation of Cefquinome Sulphate in IV/IM Injection," *International Research Journal of Pharmacy and Medical Sciences (IRJPMS)*, Volume 5, Issue 3, pp. 51-56, 2022.

Robustness:

By deliberately changing the parameters which are wavelength, flow & temperature robustness test is performed in which reliability of the method was detected and %RSD is NMT 2.00%.

LOD and LOQ:

The LOD & LOQ found with the linearity curve are within limits.

TABLE X: Robustness study of Cefquinome Sulphate

Regression equation	y = 156.925x - 540.71
SLOPE	156.925
LOD	0.442559827 µg/ml
LOQ	1.341090385 µg/ml

Forced degradation studies:

The degradation studies of the Cefquinome Sulphate were performed with different degraded products for different time intervals. The results of these studies in Table XI shows that the peak purity of the Cefquinome Sulphate is within limits.

Chromatograms of oxidative and acidic degradation displayed extra peaks which indicates the slight degradation

TABLE XI: Robustness study of Cefquinome Sulphate

Forced degradation studies				
Product	**Normality & time**	**% Rel area**	**% Degradation**	**% Peak purity**
Acidic (HCL)	1N for 1 hr.	89.93	10.07	100
Basic (NaOH)	1N for 1 hr.	4.94	95.06	99.99
Oxidative (H_2O_2)	1 hr.	76.55	23.45	100
Thermal	1 hr.	86.86	13.14	100
Photolytic (UV)	24 hrs.	97.13	2.87	100

The HPLC method is an analytical procedure which is capable of determining the major active pharmaceutical ingredients from different dosage forms. The forced degradation studies help in understanding the stability of the drug during storage conditions. In the present developed method, the drug is eluted at retention time of 4.2 min with good resolution. This developed RP-HPLC method was validated and all validation parameters were found to be within the allowable limit according to ICH guidelines. Although methods have been reported for estimation of Cefquinome Sulphate in bulk and dosage forms, no work has been reported on its estimation by RP-HPLC followed by methods with stability indicators in IM/IV injection. Therefore, in present study we have developed and validated the stability indicating RP-HPLC method.

IV. CONCLUSION

The developed HPLC method is simple, specific, accurate, and precise Cefquinome Sulphate in an IV/IM dosage form. The method was successfully validated in terms of linearity, accuracy, precision, specificity, robustness and stability in accordance with ICH guidelines. The Degradation studies were performed with the developed method. Here we conclude that the developed method is accurate, sensitive, stabilized and superior with better system suitability parameter such as Theoretical plates, tailing factor. In basic hydrolysis and oxidation the Cefquinome Sulphate is vulnerable. Thus, the described method is suitable for routine analysis and quality control of Cefquinome Sulphate in IV/IM dosage forms.

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