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STABILITY INDICATING RP-HPLC METHOD FOR SIMULTANEOUS ESTIMATION OF CEFPIROME SULPHATE AND SULBACTAM SODIUM IN BULK AND COMBINED PHARMACEUTICAL DOSAGE FORM

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Abstract: A simple stability indicating high Performance Liquid Chromatographic method was developed and validated for simultaneous estimation of Cefpirome sulphate and Sulbactam sodium in bulk and combined pharmaceutical dosage form. Reverse phase High Performance Liquid Chromatography was performed on Shimadzu model SPD-20AT, using a mixture of phosphate buffer (pH-5): acetonitrile (40:60 v/v) as mobile phase with flow rate 1.0 ml/min. Detecting wavelength was selected 215nm. The retention time for Cefpirome sulphate and Sulbactam sodium was found to be 3.91 min. and 5.78 min, respectively. The linearity of Cefpirome sulphate and Sulbactam sodium were found in range of 10-30 µg/ml and 5-15 µg/ml, respectively. The Cefpirome sulphate and Sulbactam sodium were subjected to stress condition including acidic, alkaline, oxidation, thermal and sunlight degradation. The method was validated as per ICH guidelines.

Keywords: RP-HPLC, Stability indicating method, Cefpirome sulphate (CPS), Sulbactam sodium (SULS).

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INTRODUCTION

Cefpirome sulfate (CPS, Fig. 1) is a new, parenteral, fourth generation cephalosporin. CPS is effective against Gram-positive bacteria including Staphylococcus aureus and Gram-negative micro-organisms, such as Pseudomonas aeruginosa. The elements responsible for such spectrum of activity are 2-amino-thiazolylmethoxyimino group in a side-chain in position 7 and cyclopentapyridine in position 3. CPS is used in treatment of various infections such as pneumonia, sepsis, urinary tract infections, and intra-abdominal infections in adult patients. CPS like other cephalosporin's have surprisingly few serious side effects, which make it attractive for use in the treatment of a wide variety of serious infections. Simultaneously, most of the side effects of β-lactams are caused by their degradation products thus it is so important to estimate the stability and mechanism of the degradation of this group of drugs. Forced degradation or stress testing is undertaken to demonstrate specificity when developing stability-indicating methods, particularly when little information is available about potential degradation products [1]. The ICH guideline entitled "Stability Testing of New Drug Substances and Products" requires the stress testing to be carried out to elucidate the inherent stability characteristics of the active substances [2]. The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity, and light; it enables recommendation of storage conditions, retest periods, and shelf lives to be established. Regulatory agencies recommend the use of stability-indicating methods for the analysis of stability samples. Thus, stress studies are required in order to generate the stressed samples, method development and method validation [3]. Stability studies are an integral part of the drug development process and are widely recognized as one of the most important procedures in pharmaceutical products registration. Previous studies confirm that cephalosporin's are susceptible to degradation in aqueous solutions and in a solid state. CPS in solution is stable in pH 4-7, slightly unstable below pH 3 and promptly degraded at pH 9 and higher [1].

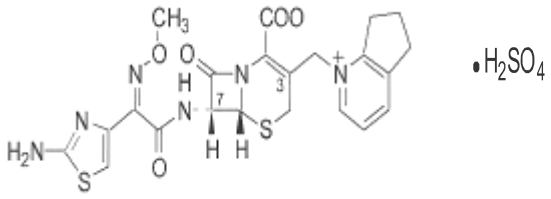

Fig.1 Chemical structure of Cefpirome sulphate

Sulbactam Sodium (SULS) is chemically Sodium (2S, 5R)-3, 3-dimethyl-7-oxo-4-thia-1-azabicyclo [3.2.0] heptane-2-carboxylate 4, 4-dioxide (Fig.2) is beta-lactamase inhibitor, enhance the activity of penicillin's and cephalosporin's against many resistant strains of bacteria. [6, 7]

It is official in British Pharmacopoeia (BP) and United States Pharmacopoeia (USP), BP describe High Performance Liquid Chromatography (HPLC) and USP also describe HPLC method. Literature survey also reveals Spectrophotometric Methods and RP-HPLC [5] for determination of SULS with other drugs. The combined dosage form of CPS and SULS is also available in the market for systemic system infection. The combination of these two drugs is not official in any pharmacopoeia; hence no official method is available for simultaneous estimation of CPS and SULS in their combined dosage form. Literature survey does not reveal any simple Spectrophotometric or other method for simultaneous estimation of CPS and SULS in combined dosage form.

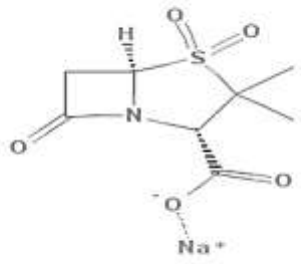

Fig.2 chemical structure of Sulbactam sodium

Cefpirome is frequently used for empirical therapy in severely ill patient in intensive care, oncology and transplantation unite but emergency of resistance in range of bacteria limit future therapeutic choices and is associated with increased rates of mortality and morbidity and higher cost. Many micro-organism initially susceptible to Cefpirome have become resistance due to the production of β-lactamases. It was concluded from available emerging resistance that a mechanistic combination at least two antibiotics may provide better result in order to reduce resistance.

However, there is no work was reported for the simultaneous estimation of these drugs by RP-HPLC method. Hence, in the present study an attempt has been made to develop simple, accurate, sensitive, precise and repeatable RP-HPLC method, for the simultaneous estimation of both drugs in dry powder for injection dosage form.

METHOD AND MATERIALS

Chemicals and Reagents

CPS and SULS were kindly given as a gratis sample by Gitar laboratory, Ahmedabad and Oasis laboratory, Ahmedabad, respectively. The market formulation PIROTUM (CPS 1000 mg and SULS 500 mg) was procured from local market which is manufactured by Venus remedies Ltd, India. Acetonitrile (HPLC Grade) were obtained from Finar Ltd. and Water (HPLC Grade) and O-phosphoric acid were obtained from Merck specialties pvt, Ltd., Mumbai.

RP-HPLC Instrumentation and Conditions:

The chromatographic separation achieved by using BDS Hypersil C_{18} (25cm x 0.46 cm) column and phosphate buffer (pH-5): acetonitrile (40:60 v/v) as mobile phase at flow rate of 1.0 ml/min with detection wavelength 215 nm.

Preparation of mobile phase

Mobile phase was prepared by mixing 600ml of acetonitrile and 400ml of phosphate buffer (pH-5.0), filtered through 0.45µm Whatmann filter and sonicated for 10 min.

Preparation of Stock and Standard Solution

For Cefpirome Sulphate:

Cefpirome Sulphate stock solution (1000 µg/ml): Accurately weighed 10mg of Cefpirome Sulphate was taken in 10ml volumetric flask and diluted with methanol up to the mark.

Cefpirome Sulphate standard solution (200µg/ml): prepared by transferring 2 ml from stock solution, and diluted up to the mark with methanol in 10ml volumetric flask.

For Sulbactam Sodium:

Sulbactam Sodium standard stock solution (1000 µg/ml): Accurately weighed 10 mg of Sulbactam Sodium was taken in 10ml volumetric flask and diluted with methanol up to the mark.

Sulbactam Sodium working standard stock solution (100µg/ml): prepared by transferring 1 ml from stock solution, and diluted up to the mark with methanol in 10ml volumetric flask.

Preparation of standard solution of binary mixtures of Cefpirome Sulphate (20 µg/mL) and Sulbactam sodium (10 µg/mL)

Take 1 mL from the Cefpirome Sulphate stock solution and 1mL from Sulbactam stock solution and transferred to 10 mL volumetric flask and volume made up to the mark by mobile phase which was used in particular trials.

Preparation Sample solution

Sample Stock Solution (Cefpirome sulphate 200 µg/mL, and Sulbactam sodium 100 µg/mL):

Take powdered dosage form 30mg (equivalent to 20 mg of Cefpirome sulphate, and 10 mg of Sulbactam sodium) was transferred to a 100 ml volumetric flask containing 60 ml methanol and Shake for 15 min and make up volume with Mobile phase. The solution was filtered through Whatman filter paper no. 42.

Standard Sample Preparation (Cefpirome sulphate 20 µg/mL, and Sulbactam sodium 10 µg/mL):

Take 1 mL from standard stock solution and transferred to 10 ml volumetric flask and made up volume up to the mark with the mobile phase.

Optimization of RP-HPLC method:

The pure drug solution of Cefpirome sulphate (20µg/ml) and Sulbactam sodium (10µg/ml) were injected individually in to HPLC system and allow to run in different mobile phase like Methanol, Water: Methanol, Water: Acetonitrile, Phosphate Buffer: Methanol, Phosphate Buffer: Acetonitrile were tried in order to find the optimum condition for the separation of Cefpirome sulphate and Sulbactam sodium. It was found that mobile phase containing Phosphate Buffer (pH=5): Acetonitrile(40:60 v/v) at a flow rate of 1 ml/min with detecting wavelength 215nm gave satisfactory result with sharp, well defined and resolving peak with minimum tailing as compared to other mobile phases. Under these condition the retention time were typically 3.87 min. for Cefpirome sulphate and 5.683 min. for Sulbactam sodium and optimized chromatographic condition.

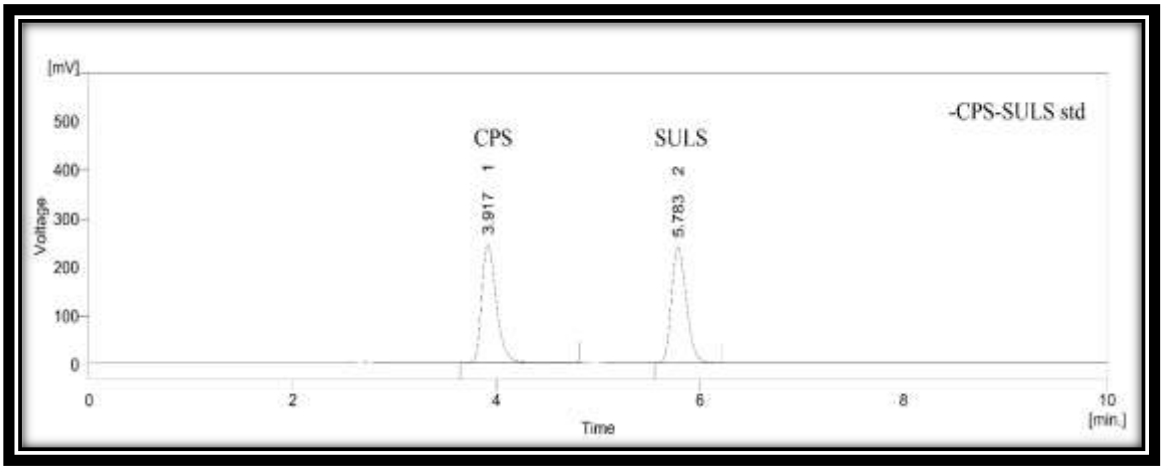

Fig. 3 Chromatogram of standard solution containing 20µg/ml of Cefpirome sulphate and 10µg/ml of Sulbactam sodium using phosphate buffer (pH-5.0): Acetonitrile (40-60 v/v) as mobile phase.

Table: 1 Optimized chromatographic conditions for simultaneous estimation of CPS and SULS.

Parameters	Chromatographic Condition
Mode of elution	Isocratic
Mobile Phase	Buffer(pH 5.0) : Acetonitrile (40:60)
column	C18 (25cm x 0.46 cm) Hypersil BDS
Flow rate	1ml/min
Runtime	8 min
Injection volume	20 µL
Detection wavelength	215 nm

HPLC method validation

The developed HPLC method was validated as per ICH guidelines for following parameters Linearity, Limit of Detection, Limit of Quantification, accuracy, Precision, Robustness.

Forced degradation studies

The study was intended to ensure the effective separation of CPS, SULS and its degradation peaks of formulation ingredients at the retention time of CPS and SULS. Forced degradation study was performed to evaluate the stability indicating properties and specificity of the method.

Acid degradation

1 ml standard stock solution of CPS, SULS and mixture of standard solution were taken. 2 ml of 0.1N HCL was added and kept for 3hr at room temperature in 10 ml volumetric flask. After 3 hour the solution was neutralized with 2 ml 0.1 N NaOH to stop the degradation further. Now make up volume with mobile phase [Buffer (pH-5.0)-Acetonitrile 40:60 v/v]. The forced degradation was performed in the dark to exclude the possible degradation effect of light and control the respective solution was made at each stage of degradation study to eliminate possible changes due to heat and light. The resulting solution (20µg/ml of CPS and 10µg/ml of SULS and combined standard mixture of 20µg/ml of CPS and 10µg/ml of SULS) were injected in HPLC system and the chromatograms were recorded. Chromatograms are shown in figure 4.

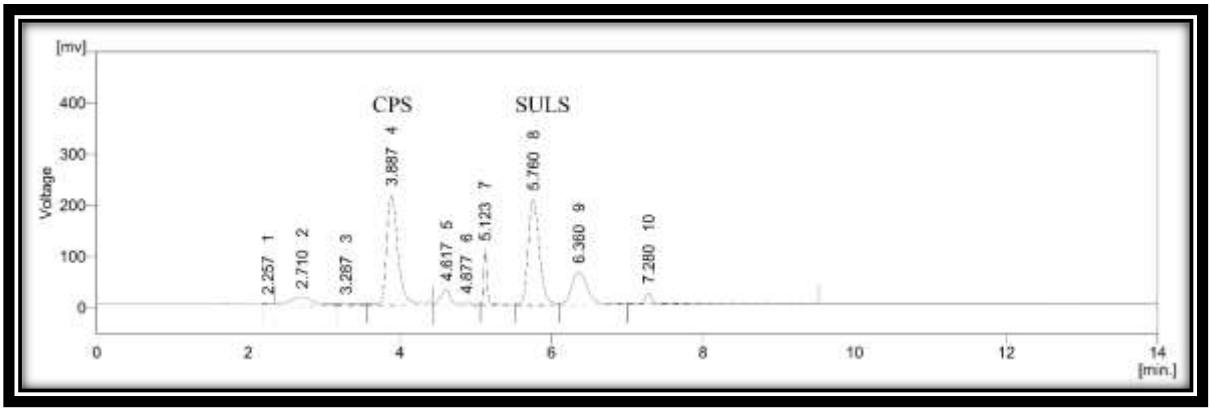

Fig.4 Chromatogram of combined CPS and SULS in acid degradation (0.1 N HCL, 3 hour).

Basic degradation

1 ml standard stock solution of CPS, SULS and mixture of standard solution were taken. 2 ml of 0.1 N NaOH was added and kept for 3hr at room temperature in 10 ml volumetric flask. After 3 hour the solution was neutralized with 2 ml 0.1 N HCL to stop the degradation further. Now make up volume with mobile phase [Buffer (pH-5.0)-Acetonitrile 40:60 v/v]. The forced degradation was performed in the dark to exclude the possible degradation effect of light and control the respective solution was made at each stage of degradation study to eliminate possible changes due to heat and light. The resulting solution (20µg/ml of CPS and 10µg/ml of SULS and combined standard mixture of 20µg/ml of CPS and 10µg/ml of SULS) were injected in HPLC system and the chromatograms were recorded. Chromatograms are shown in figure 5.

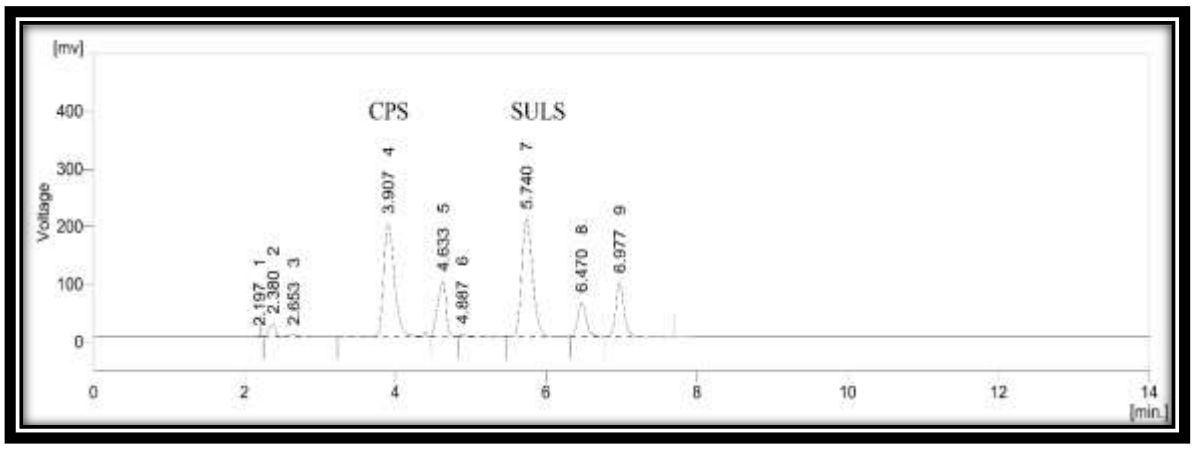

Fig. 5 Chromatogram of combined CPS and SULS in basic degradation (0.1 N NaOH, 3 hour).

Oxidation degradation

1 ml standard stock solution of CPS, SULS and mixture of standard solution were taken in 10 ml volumetric flask, respectively. 2 ml of Hydrogen peroxide (3%) was added in 10 ml volumetric flask, respectively and kept for 3 hour in room temperature. After 3 hour the solution was make up with mobile phase [Buffer (pH-5.0)-Acetonitrile 40:60 v/v]. The forced degradation was performed in the dark to exclude the possible degradation effect of light and control the respective solution was made at each stage of degradation study to eliminate possible changes due to heat and light. The resulting solution (20µg/ml of CPS and 10µg/ml of SULS and combined standard mixture of 20µg/ml of CPS and 10µg/ml of SULS) were injected in HPLC system and the chromatograms were recorded. Chromatograms are shown in figure 6.

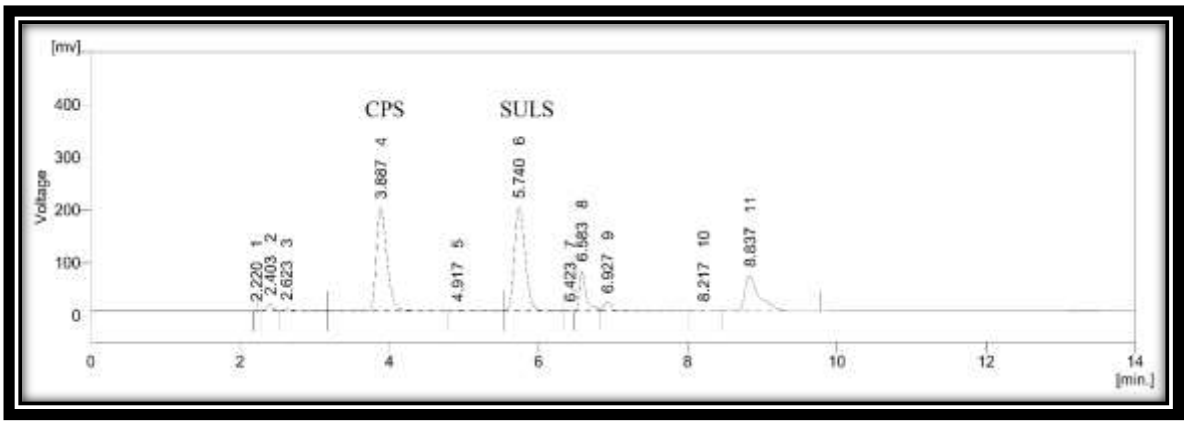

Fig.6 Chromatogram of combined CPS and SULS in oxidative degradation (3% H_2O_2, 3 hour).

Thermal degradation

1 ml standard stock solution of CPS, SULS and mixture sample solution were taken. Solutions were exposed to temperature of 105 ^{0}C for 2 hour in oven. After 2 hour, solution were diluted with mobile phase [Buffer (pH-5.0)-Acetonitrile 40:60 v/v] up to 10 ml. The resulting solution (20µg/ml of CPS and 10µg/ml of SULS and combined standard mixture of 20µg/ml of CPS and 10µg/ml of SULS) were injected in HPLC system and the chromatograms were recorded. Chromatograms are shown in figure 7.

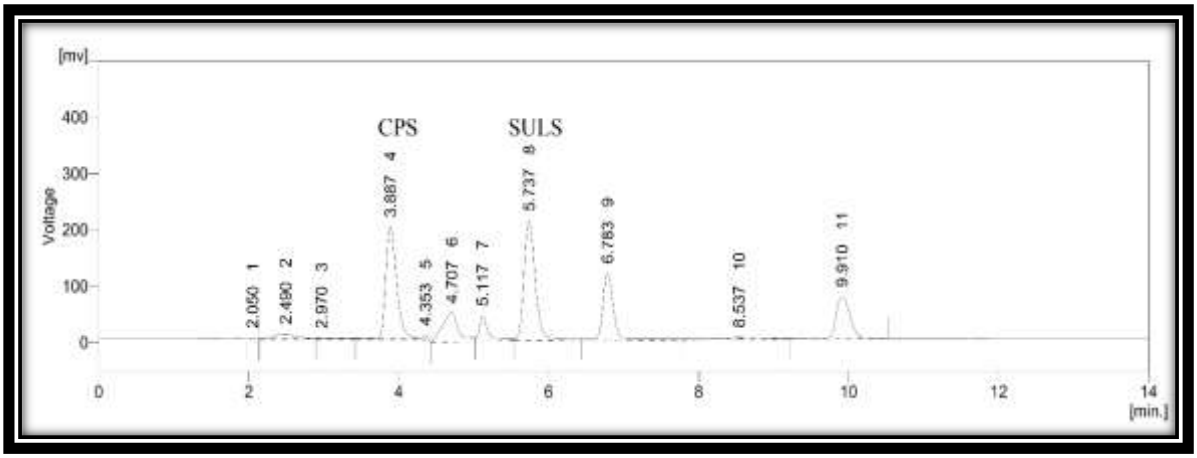

Fig.7 Chromatogram of combined CPS and SULS in thermal degradation (105°C, 2 min.).

Sunlight degradation

1 ml standard stock solution of CPS, SULS and mixture sample solution were taken and exposed to sun light for 6 hour. After 6 hour solution were diluted with mobile phase [Buffer (pH-5.0)-Acetonitrile 40:60 v/v] up to 10 ml. The resulting solution (20µg/ml of CPS and 10µg/ml of SULS and combined standard mixture of 20µg/ml of CPS and 10µg/ml of SULS) were injected in HPLC system and the chromatograms were recorded. Chromatograms are shown in figure 8.

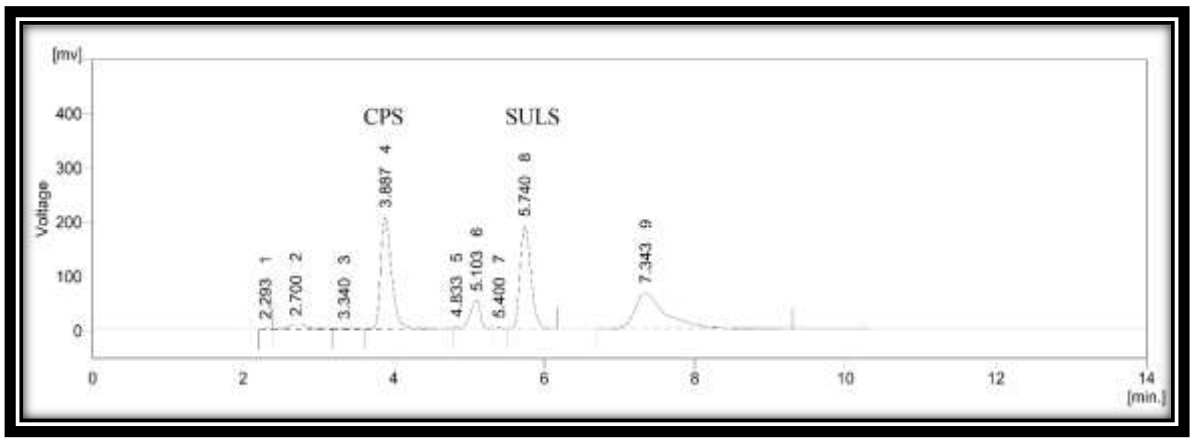

Fig. 8 Chromatogram of combined CPS and SULS in photo degradation (6 hr.).

RESULTS AND DISCUSSION

Linearity:

The linearity of analytical procedure is it ability (within given range) to obtain test result which are directly proportional to concentration of analyte in sample. The drug response was linear (R^2 = 0.9995 for Cefpirome sulphate and 0.9996 for Sulbactam sodium) over the concentration range between 10-30 µg/ml for Cefpirome sulphate and 5-15 µm/ml for Sulbactam sodium. The linear equation for the calibration plots were y=121.32x-25.822 for Cefpirome sulphate and y=239.34x-28.363 for Sulbactam sodium.

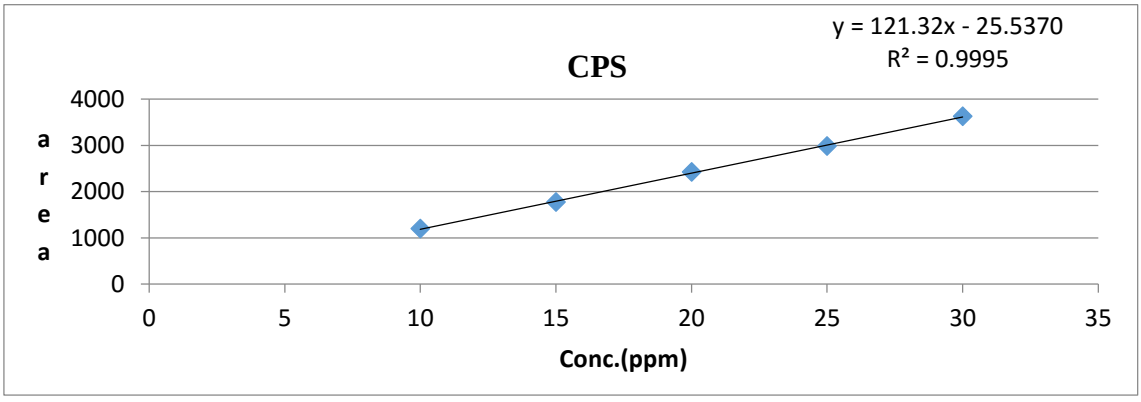

Fig.9 calibration curve of Cefpirome sulphate

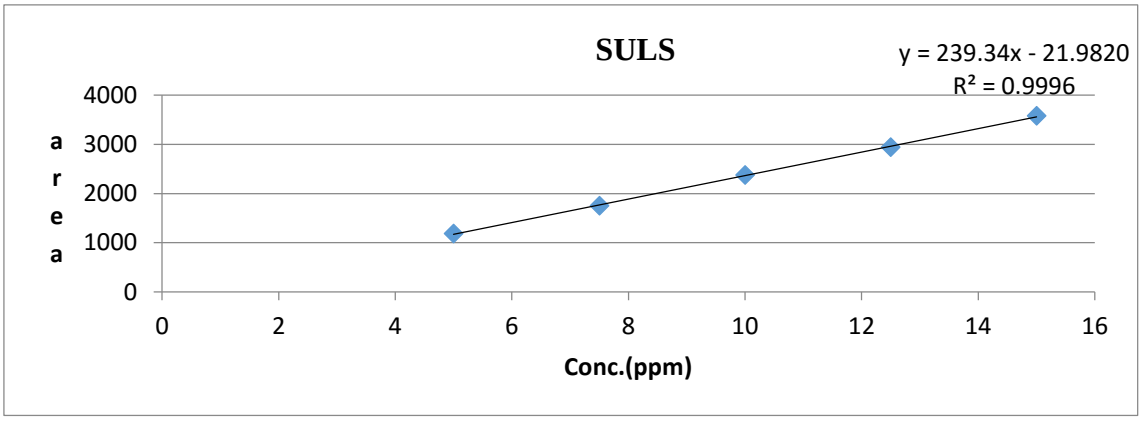

Fig.10 calibration curve of Sulbactam sodium

Table: 2 Calibration curve data for Cefpirome sulphate and Sulbactam sodium.

CPS		**SULS**	
Concentration(µm/ml)	**Mean Peak Area(n=3)**	**Concentration (µg/ml)**	**Mean Peak Area (n=3)**
10	1199.97	5	1183.831
15	1771.384	7.5	1747.64
20	2421.719	10	2373.567
25	2981.746	12.5	2941.34
30	3627.695	15	3578.706
Correlation coefficient	0.999734244	**Correlation coefficient**	0.99979760
Intercept	25.5370	**Intercept**	21.9820
Slope	121.3	**Slope**	239.3
Regression equation	Y=121.3x-25.5370	**Regression equation**	Y=239.3x-21.9820
LOD (µg/ml)	0.69474	**LOD (µg/ml)**	0.30313
LOQ (µg/ml)	2.10528	**LOQ (µg/ml)**	0.91859

Sensitivity:

The detection limit of an individual analytical procedure is the lowest amount of analyte in sample which can be detected but not necessarily quantitated as an exact value. The quantitation limit of an individual analyte procedure is the lowest amount of analyte in the sample which can be quantitatively determined with suitable precision and accuracy. The LOD

and LOQ were calculated by respective equations. The LOD value were found to be 0.694 µg/ml and 0.3031µg/ml for Cefpirome sulphate and Sulbactam sodium respectively. The LOQ value were found to be 2.1052 µg/ml and 0.9185 µg/ml for Cefpirome sulphate and Sulbactam sodium respectively.

Precision:

The precision of analytical procedure expresses the closeness of agreement (degree of scatter) between a series of measurement obtained from multiple sampling of same homogenous sample under the reproducibility. Precision may be considered at three level: repeatability, intermediate precision and reproducibility [7]. The results of the repeatability, intra-day precision and inter-day precision experiments are shown respectively as given in (Table: 3) and (Table: 4).the developed method was found to be precise as the RSD values for repeatability of intra-day and inter-day precision study were < 2%.

Table: 3 Repeatability study of Cefpirome sulphate and Sulbactam sodium.

concentration	CPS (20µg/ml)	SULS (10µg/ml)
Area	2412.022	2379.345
	2329.939	2384.207
	2421.761	2328.047
	2426.55	2393.783
	2414.442	2381.731
	2419.234	2386.596
Mean	2403.991333	2375.618
±SD	36.64546219	23.82651
%RSD	1.524359164	1.002961

Table: 4 intra-day and inter-day precision of CPS and SULS.

Drug	Intra-day precision			Inter-day precision		
	Conc. (µg/ml)	Area Mean ± S.D. (n=3)	% R.S.D	Conc. (µg/ml)	Area Mean ± S.D. (n=3)	% R.S.D
CPS	10	1185.55±14.617	1.2329	10	1183.554±14.880	1.2572
	20	2389.965±40.372	1.6892	20	2389.953±38.162	1.5967
	30	3583.186±55.302	1.5433	30	3588.262±43.177	1.2033

SULS	5	1175.902±5.196	0.4418	10	1183.554±14.880	1.2572
	10	2369.065±16.923	0.7143	20	2389.953±38.162	1.5967
	15	3552.438±19.793	0.5571	30	3588.262±43.177	1.2033

Accuracy:

The accuracy of an analytical procedure express the closeness of agreement between the value which is accepted either as a conventional true value or an accepted reference value and the value found. As show in (table: 5) and (table: 6), good recovery of the Cefpirome sulphate and sulbactam sodium in the range from 99.4 to 99.8 were obtained at various added concentrations.

For Cefpirome sulphate

10 µg/ml drug solution was taken in three different flask label A, B and C. Spiked 80%, 100%, 120% of standard solution in it and diluted up to 10ml. The area of each solution peak was measured at 215 nm. The amount of Cefpirome sulphate was calculated at each level and % recoveries were computed.

Table: 5 Recovery data for Cefpirome sulphate.

SR. NO.	Conc. Level (%)	Sample Amount	Amount Added	Amount recovered (µg/ml)	% Recovery	% Mean Recovery ± S.D
1	80 %	10	8	7.8958	98.697	99.412 ± 0.722
2		10	8	7.9521	99.401	
3		10	8	8.0114	100.142	
4	100 %	10	10	9.8901	98.901	99.436± 0.475
5		10	10	9.9812	99.812	
6		10	10	9.9593	99.593	
7	120 %	10	12	11.9334	99.445	99.406± 0.258
8		10	12	11.8957	99.130	
9		10	12	11.9572	99.643	

For Sulbactam sodium

5 µg/ml drug solution was taken in three different flask label A, B and C. Spiked 80%, 100%, 120% of standard solution in it and diluted up to 10ml. The area of each solution peak was measured at 215 nm. The amount of Sulbactam sodium was calculated at each level and % recoveries were computed.

Table: 6 Recovery data for Sulbactam sodium.

Sr. NO.	Conc. Level (%)	Sample Amount	Amount Added	Amount recovered (µg/ml)	% Recovery	% Mean Recovery ± S.D
1	80 %	5	4	3.9465	98.663	99.885 ±1.126
2		5	4	4.0353	100.882	
3		5	4	4.0044	100.111	
4	100 %	5	5	4.9483	98.966	99.598± 0.649
5		5	5	5.0131	100.263	
6		5	5	4.9783	99.566	
7	120 %	5	6	6.0049	100.082	99.601± 0.490
8		5	6	5.9461	99.102	
9		5	6	5.9771	99.619	

Robustness:

The standard deviation of the area was calculated for each parameter and the %RSD was found to be less than 2%. Result show low value of %RSD as show in (table: 7) and signify the robustness of the method**.**

Table: 7 Robustness data of Cefpirome sulphate and Sulbactam sodium.

Parameter	Normal condition	Change in condition	Drug	Conc.(µg/ml)	Mean area (n=3)±SD	%RSD
		42:59	**CPS**	20	2343.43±46.08	1.9666
			SULS	10	2322.86±20.25	0.8718
		38:62	**CPS**	20	2467.28±34.99	1.4184

Mobile phase ratio (Phosphate Buffer: Acetonitrile)	40:60 V/V		**SULS**	10	2443.51±16.21	0.6636
Change in flow rate	1 ml/min	1.2 ml/min	**CPS**	20	2345.75±43.60	1.8588
			SULS	10	2328.12±13.35	0.5737
		0.8 ml/min	**CPS**	20	2494.74±37.64	1.5090
			SULS	10	2470.81±14.94	0.6050
Change in pH	5.0	5.2	**CPS**	20	2301.42±40.78	1.7721
			SULS	10	2276.59±21.72	0.9541
		4.8	**CPS**	20	2473.95±31.68	1.2807
			SULS	10	2447.59±14.04	0.573

Forced degradation study

The results of the forced degradation study of CPS and SULS combined dosage form are summarized in table 8 & 9.

Table 8: Results of forced degradation study of CPS in combined dosage form

Stress condition	Time (hr.)	Retention time (min)	Area	% degradants
Acidic (0.1N HCL)	3	3.88	2263.83	10.55
Basic (0.1 N NaOH)	3	3.90	1955.20	22.75
Oxidative (3% H_2O_2)	3	3.88	1940.15	23.34
Thermal	2	3.88	2015.93	20.35

(105 °C)				
Sunlight exposure	6	3.88	2069.19	18.24

Table 9: Results of forced degradation study of SULS in combined dosage form

Stress condition	Time (hr.)	Retention time (min)	Area	% degradants
Acidic (0.1N HCL)	3	5.76	2119.42	11.72
Basic (0.1 N NaOH)	3	5.74	2039.83	15.04
Oxidative (3% H_2O_2)	3	5.74	1973.49	17.8
Thermal (105 °C)	2	5.73	2011.78	16.2
Sunlight exposure	6	5.74	1892.86	21.17

CONCLUSION

The proposed stability-indicating HPLC method was validated as per ICH guideline and applied for the determination of Cefpirome sulphate and Sulbactam sodium in combined pharmaceutical dosage forms. It can also be successfully applied to perform long-term and accelerated stability studies of combined dosage formulation of Cefpirome sulphate and Sulbactam sodium.

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