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STABILITY TESTING IN THE FORMULATION OF CEFTRIAXONE TAZOBACTAM INJECTION

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ABSTRACT

Injections are liquid dosage forms which are designed to be injected, that have quicker action. They do not undergo first-pass metabolism. Stability is a crucial and important facet of pharmaceutical dosage forms. Determination of storage conditions, packaging materials and labelling requirements is desirable through stability studies. At different conditions, the accelerated stability study and reconstituted stability study can be performed in order to determine the stability. In accelerated stability studies, by increasing the Temperature (40^0C) and relative humidity (75%), we accelerate the degradation of the product. At various time intervals such as initial, 1, 2, 3 and 6 months, the samples were withdrawn from the chamber. The evaluation tests were then executed. From the results of the test, it was concluded that the injection is stable for 6 months under accelerated conditions. In the reconstitution stability study, we reconstituted the drug with different diluents and then it was kept under room temperature (NMT 25°C) and refrigerated conditions (2-8°C). The samples are then withdrawn at various time intervals such as initial, 6 hours, 12 hours, 24 hours, 72 hours, 7^{th} day and 10^{th} day, and evaluation tests are executed. From the result of the tests, it was concluded that the injection is stable for 24 hours at room temperature and stable for 10 days under refrigerated conditions.

KEYWORDS: Stability, Injections, Ceftriaxone, Tazobactam, Membrane Filtration.

1. INTRODUCTION

In order to increase the quality, safety, and effectiveness of a formulation, stability testing is an extensive and sophisticated series of procedures that incorporates scientific expertise. Pharmaceutical analysis and stability studies are two vital and crucial developmental stages steps that must be determined. They confirm the identity, strength, and purity of substances. The degree to which a product retains, within the predetermined limits, can be used to describe a pharmaceutical product's stability.[1] Physical, chemical, and microbiological changes might affect a product's stability. The purpose of stability testing is to confirm how the quality of the medication product changes over time while being influenced by numerous elements including temperature, humidity, and light. In addition to the unstable substance degrading into poisonous decomposition products, there is a loss of activity up to 85% of what is claimed on the label, which causes therapy to fail and cause death.[2] The advantages of stability studies at the developmental stage are to provide a database that may be useful in choosing appropriate formulations, excipients, and container closure systems for the development of a new product, shelf life determination, storage conditions, and preparation of registration dossier, to substantiate the claimed shelf life for the registration dossier, and as a result, they confirm that no changes have been made to the formulation or manufacturing process. Otherwise, it adversely impacts the product's stability.

2. MATERIALS AND METHODS

2.1 Materials

Ceftriaxone sodium was purchased from Shijiazhuang G-House Trading Co., Ltd. Hebei, China. Tazobactam sodium was purchased from Teenalabs Malkajgiri (Dist.), Hyderabad, Telangana. Normal Saline was purchased from Fresenius Kabi India Pvt. Limited, Goa, India. 1% Lidocaine was purchased from Pharmafabricon, Sivagangai Road, Vilathur, Madurai, Tamilnadu, India. 5% dextrose was purchased from Baxter (India), Private Limited, Chennai, India. Water for Injection was purchased from American Remedies Healthcare Private Limited, Mumbai, India.

2.2 Methods

2.2.1 Formulation by Membrane Filtration

PVDF filters and a filtration assembly are part of the membrane filtration. It uses PVDF filters with a 47mm diameter and 0.45. The three-place manifold and stainless steel filtration vessels that make up the membrane filtration unit need to be adequately sterilised at 121^0 30 minutes. Together with the filtering assembly,

the non-sterile membrane filter is sterilised. Furthermore suggested is a sterile filter membrane. Each vial is wiped with filtered 70% IPA. Then, the flip-off seal is removed. The contents of each vial are combined with 10ml dilution fluid A and mixed well. From each container, 3ml of the reconstituted sample, equivalent to 300 mg of solid is transferred into 200 ml of Dilution fluid A and mixed well. Shortly within time, they are filtered through a sterile 0.45µm pre-wetted membrane filter. With the aid of a vacuum, the liquid is drawn rapidly through the filter. The membrane is then washed five times with 100ml (100×5) of sterile Diluting fluid A. Add 0.5ml sterile penicillinase solution to the final rinsing portion of sterile diluting fluid A. The membrane is cut into two equal pieces after filtration. One half of the membrane is transferred to 100ml of Fluid Thioglycollate medium aseptically and another half of the membrane is transferred to 100ml of Soyabean casein digest medium. The bottle of Fluid Thioglycollate medium is incubated at 30 to 35°C and the Soyabean casein digest medium at 20 to 25°C for 14 days.[3] Negative control is also taken.

2.2.2 Growth promotion test: Inoculate 1ml of the diluted culture suspensions (Not more than 100CFU) and incubate as per the below table.[4]

Table No.1 Microorganisms and their incubation conditions.

Name of media	Microorganisms	Incubation condition
Fluid thioglycollate medium	Staphylococcus aureus ATC 6538	30 to 35°C
	Pseudomonas aeruginosa ATCC 9027	
	Clostridium sporogens, ATCC 19404	
Soyabean casein digest medium	Bacillus subtilis, ATCC 6633	20 to 25°C
	Candida albicans ATCC 10231	
	Aspergillus niger ATCC 16404	

If there is clear evidence of growth within 3 days for bacteria and within 5 days for yeast and mold, then the test medium is expected to be satisfactory.

2.2.3 Evaluation Test

2.2.3.1 Uniformity of dosage units

10 vials are randomly selected and uniformity is determined by the weight variation method. The acceptance value is not more than 15.0 (L1%).

2.2.3.2 Water

0.3 g of the sample is taken and using KF method the water content is resolved(Not more than10.0%w/w).

2.2.3.3 pH

10 ml of water is reconstituted in a vial and the pH is determined using a digital pH meter Limit- 5.00 - 7.00).

2.2.3.4 Particulate matter

Determine a pooled sample of 10 vials by LOPC method using a Digital Liquid particle counter.[5]
Particles ≥ 10-micron size – NMT 6000/vial.
Particles ≥ 25-micron size – NMT 600/vial.

2.2.3.5 Assay

pH 7.0 buffer—13.6g of dibasic potassium phosphate and 4.0 g of monobasic potassium phosphate is dissolved in water to obtain 1000 mL of solution. This solution is adjusted with phosphoric acid or 10 N potassium hydroxide to a pH of 7.0 ± 0.1.

pH 5.0 buffer— 25.8g of sodium citrate is dissolved in 500 mL of water and adjusted with citric acid solution (1 in 5) to a pH of 5.0 ± 0.1, and diluted with water to a volume of 1000 mL.

Mobile phase— 3.2g of tetraheptylammonium bromide is dissolved in 400 mL of acetonitrile. Add 44 mL of pH 7.0 buffer and 4 mL of pH 5.0 buffer, and water to make 1000mL. Filter through a membrane filter of 0.5 µm or finer porosity, and degas.

Standard solution

10 mg of USP Tazobactam RS was weighed accurately and about 80 mg of USP Ceftriaxone Sodium RS is weighed accurately into a 100 mL volumetric flask. Then, add 30 mL of mobile phase and shake it to dissolve completely. Finally, make up the volume to 100 mL with mobile phase and sonicate.[6]

Assay preparation

The contents of 10 vials of Ceftriaxone Tazobactam for injection are transferred into clean, dry glass mortar and pestle and grind well. Accurately measuring 100 mg of the sample into a volumetric flask, it is then dissolved, well mixed, and made up the volume with a mobile phase before being sonicated. Chromatographing the standard preparation must be done, and peak responses must be recorded as directed under the procedure.[7]

Procedure: Separately inject equal amounts (about 20 L) of the assay preparation, the standard preparation, and the blank into the chromatograph. Record the chromatograms and quantify the responses for the main peaks.

Calculate the quantity in µg of ceftriaxone and Tazobactam per mg of the Ceftriaxone and Tazobactam for injection by the formula:

- **For Tazobactam**

(Area of Sample / Area of Standard) × (Weight of Standard / Standard Dilution) × (Sample of Dilution /

weight of sample) × Average weight × Potency of standard = 'X'
% of label claim = 'X' × 100 / label claim

- **For Ceftriaxone**

(Area of Sample / Area of Standard) × (Weight of Standard / Standard Dilution) × (Sample of Dilution / weight of sample) × Average weight × Potency of standard = 'X'
% of label claim = 'X' × 100 / label claim

2.2.4 Reconstitution stability study

The purpose of the study was to establish documentary evidence for the stability of Ceftriaxone and Tazobactam after reconstitution with specified diluents, under specified conditions, up to the specified time.

2.2.4.1 Procedure for reconstitution

Initially, the cap is removed from the diluent. The top of the diluent vial is wiped with alcohol. The cap is removed from the syringe needle and then, the plunger is pulled back on the syringe to the volume of diluent, we decide to withdraw. Therefore, it prevents the vacuum from forming and injects air into the diluent vial. The amount of diluent required is withdrawn and the cap is removed from the medication vial. Using an alcohol wipe, the top of the medication vial is cleaned. The mixture is then agitated by shaking, inverting or rolling the vial. Rolling the vial prevents air bubble formation in the medication. Now, the mixed contents form into a concentration. Finally, after the reconstitution, the samples are stored in an inverted position under some conditions and analyzed at specific time intervals[8]. The storage conditions and time intervals are given in Table No.2.

Table No. 2: Storage conditions and testing intervals.

Condition	Temperature	Humidity	Testing interval
Room temperature	Not more than 25°C	40-75%RH	Initial, 6hours, 12hours, 24 hours
Refrigeration	2-8°C	NA	Initial, 6hours, 12hours, 24 hours, 7th day & 10th day

The various diluents used are sterile water for injection, Normal Saline, 5% Dextrose, and 1 % Lidocaine.

2.2.4.2 Evaluation of Test

2.2.4.2.1 pH

Reconstitute 10 ml of water in a vial and pH is determined using a digital pH meter (Limit- 5.00 - 7.00)

2.2.4.2.2Assay

pH 7.0 buffer— 13.6g of dibasic potassium phosphate and 4.0 g of monobasic potassium phosphate is dissolved in water to obtain 1000 mL of solution. Adjust this solution with phosphoric acid or 10 N potassium hydroxide to a pH of 7.0 ± 0.1.

pH 5.0 buffer— 25.8g of sodium citrate is dissolved in 500 mL of water and thereafter, adjust with a citric acid solution (1 in 5) to a pH of 5.0 ± 0.1, and dilute with water to a volume of 1000 mL.

Mobile phase— 3.2g of tetraheptylammonium bromide is dissolved in 400 mL of acetonitrile. Add 44 mL of pH 7.0 buffer and 4 mL of pH 5.0 buffer, and add water to make 1000 mL. Filter through a membrane filter of 0.5 µm or finer porosity, and degas. If necessary, adjustments can be made.

Standard solution

80.84mg of Ceftriaxone and 10.41mg of tazobactam are weighed accurately and transferred into a 100 mL volumetric flask. Made up the volume to 100 mL with diluent.

Sample Preparation

The reconstituted solution is transferred to a 100 mL volumetric flask. Made up the volume to 100 mL with diluent and further diluted 2 mL of this solution to 25 mL with diluent.

Table No. 3: Acceptance criteria.

Test	Limits
Appearance of solution	Clear particle-free solution
pH	5.0 – 7.0
Assay	Ceftriaxone and Tazobactam for injection contain the equivalent of not less than 90.0% and not more than 120.0% of the labelled amount of Ceftriaxone, and the equivalent of not less than 90.0% and not more than 120.0% of the 291labelled amount of Tazobactam [10]

3 RESULTS AND DISCUSSIONS

3.1 Graphical Data of Accelerated Stability Study

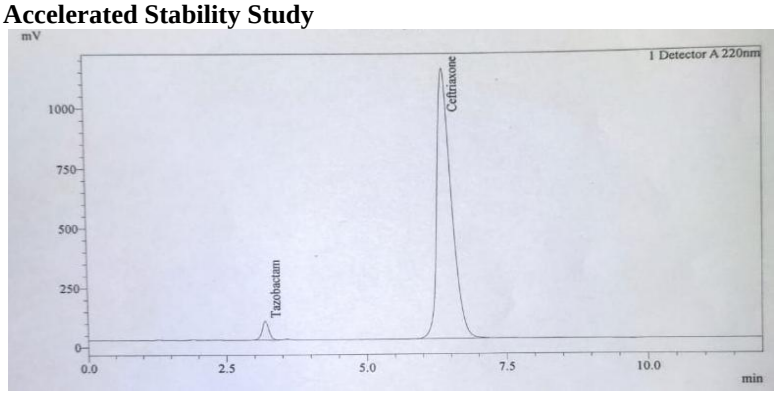
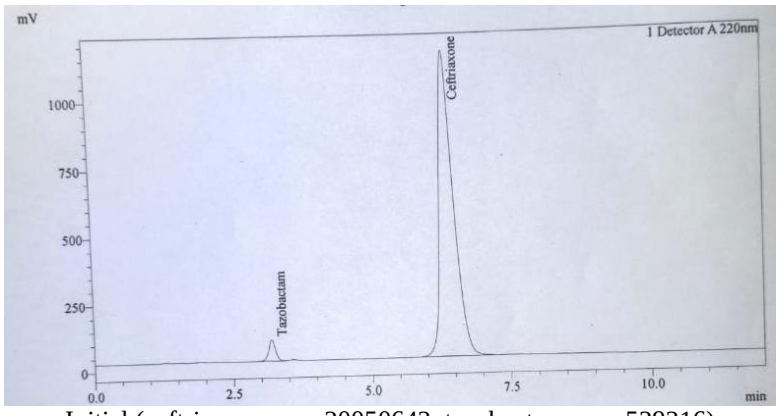
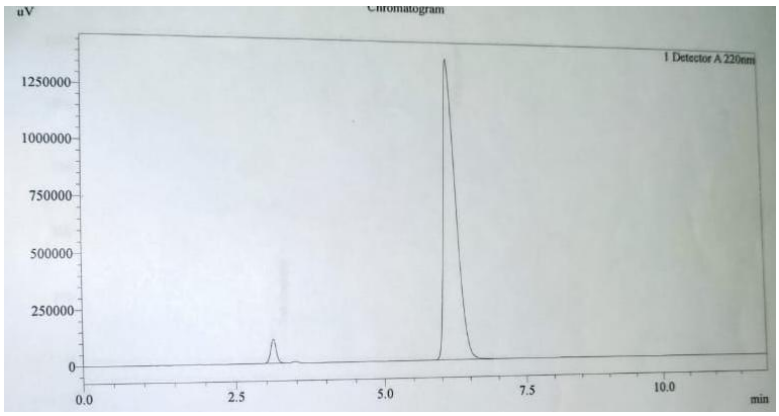


Fig No. 1 Chromatogram of Standard preparation of ceftriaxone and Tazobactam injection.

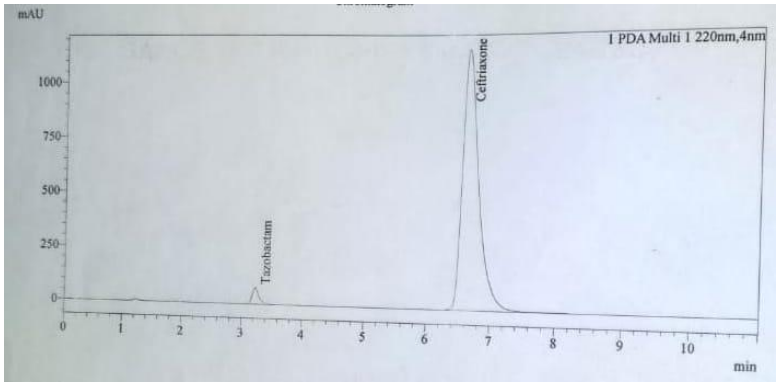


Initial (ceftriaxone area-20050642, tazobactam area-529216)

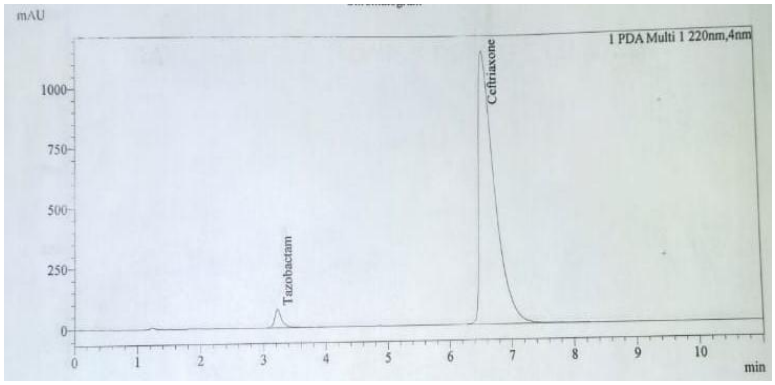


Initial (ceftriaxone area-19844964, tazobactam area-527130)

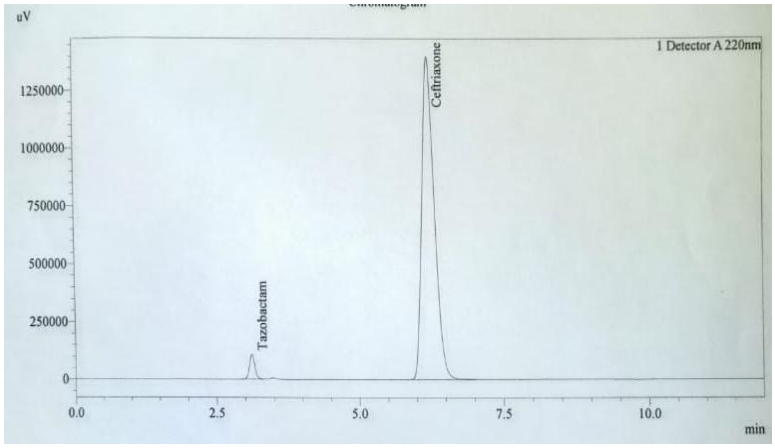
Figure No. 2: Chromatogram of Initial results of the sample.



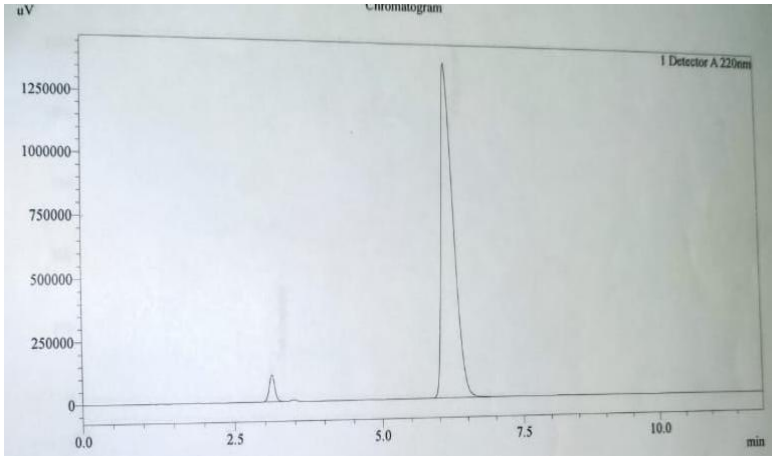
One month A1S1 (ceftriaxone area-20199642, tazobactam area-589227)



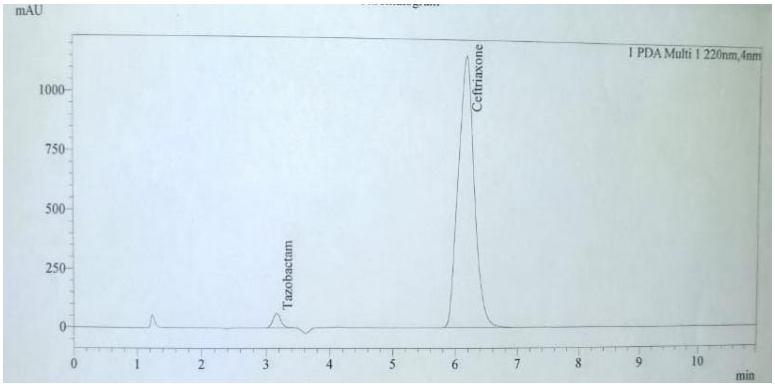
One month A1S2 (ceftriaxone area-20171849, tazobactam area-589280)



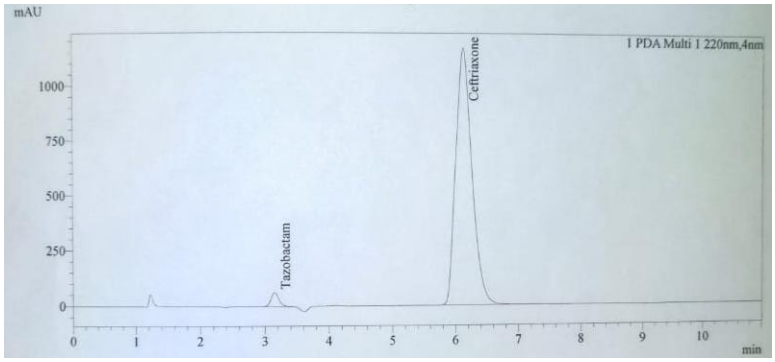
Two month A2S1 1(ceftriaxone area-20842647, tazobactam area-709666)



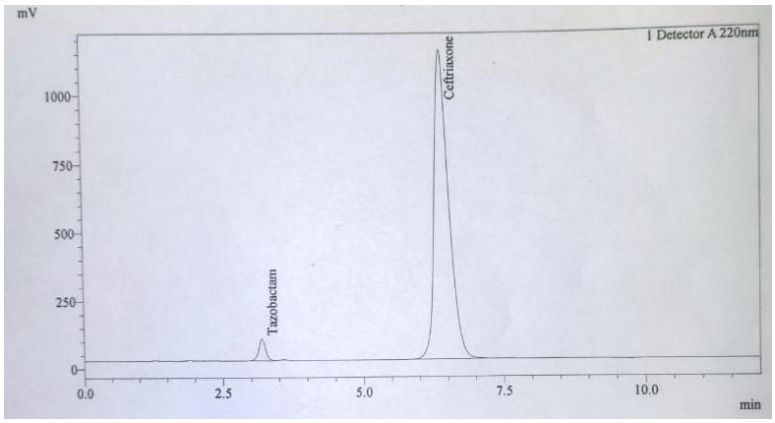
Two month A2S2 (ceftriaxone area-20725264, tazobactam area-704666)



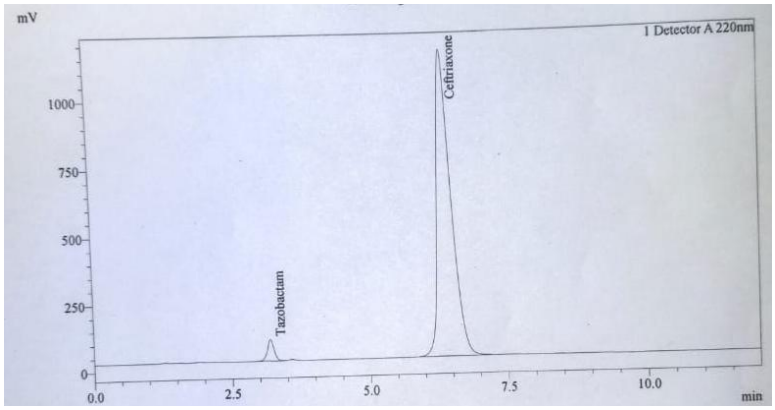
Three month A3S1(ceftriaxone area-20687027, tazobactam area-546140)



Three month A3S2(ceftriaxone area-20673832, tazobactam area-555223)



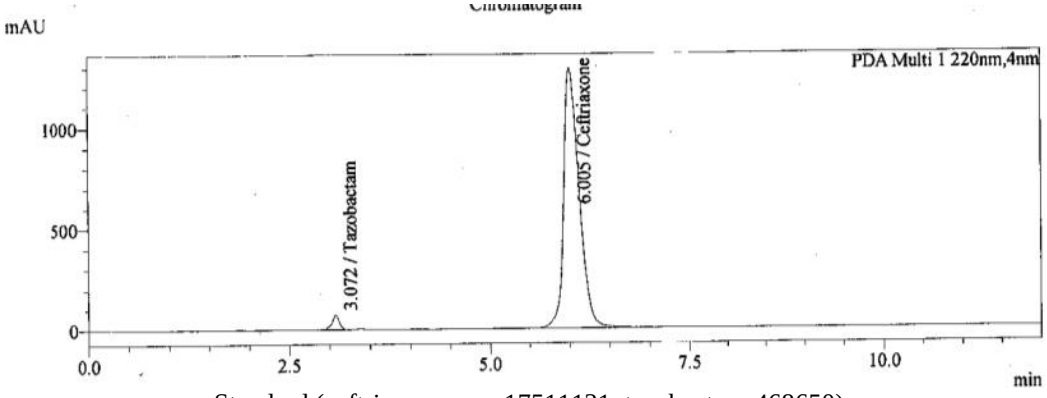
Six month A6S1 (ceftriaxone area-20305477, tazobactam area-669319)



Six month A6S1 (ceftriaxone area-20319308, tazobactam area-669095)

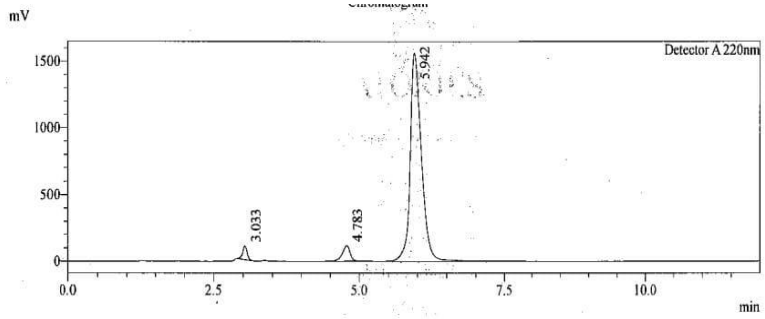
Fig. No. 3: Chromatogram of 1st month, 2nd month, 3rd month, 6th month results of samples.

GRAPHICAL DATA OF RECONSTITUTION STABILITY STUDY

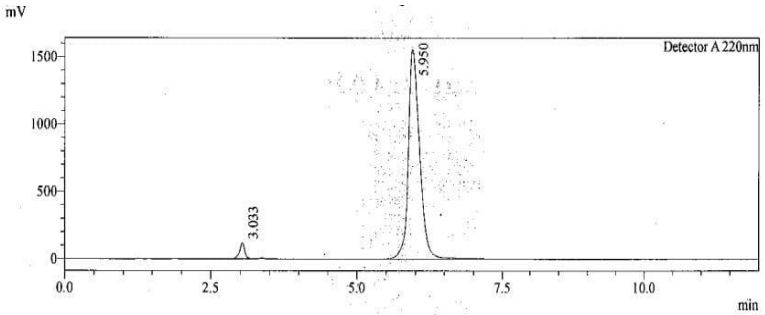


Standard (ceftriaxone area-17511131, tazobactam-468650)

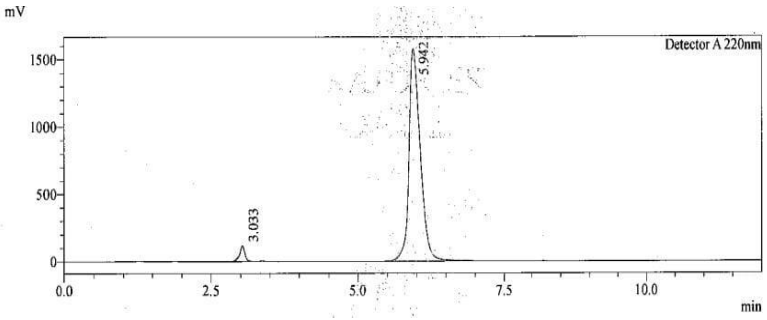
Fig.No. 4 - Chromatogram of Standard preparation of ceftriaxone and Tazobactam.



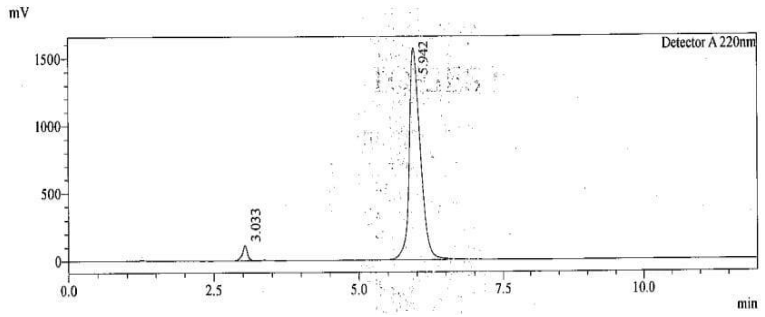
Lidocaine initial (ceftriaxone area-20951338, tazobactam area-542200



Normal saline initial (ceftriaxone area-21118578, tazobactam area-685191)

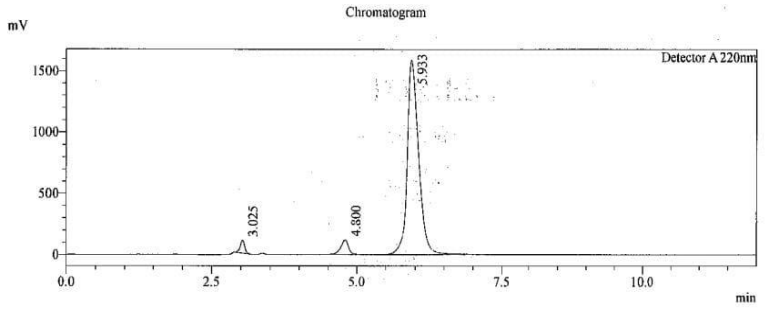


Dextrose initial (ceftriaxone area-20820931, tazobactam area-721968)

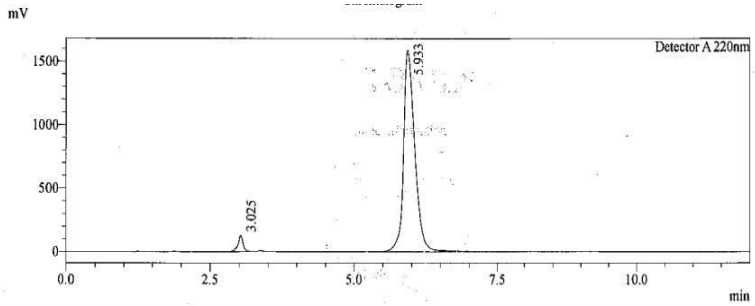


Water for injection initial (ceftriaxone area-21252669, tazobactam area-718128)

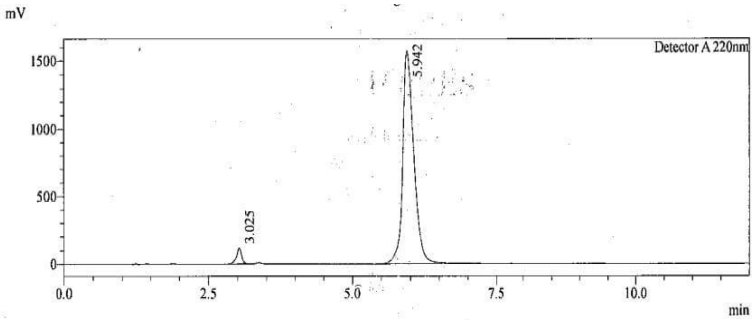
Fig.No. 5: Chromatogram of initial results.



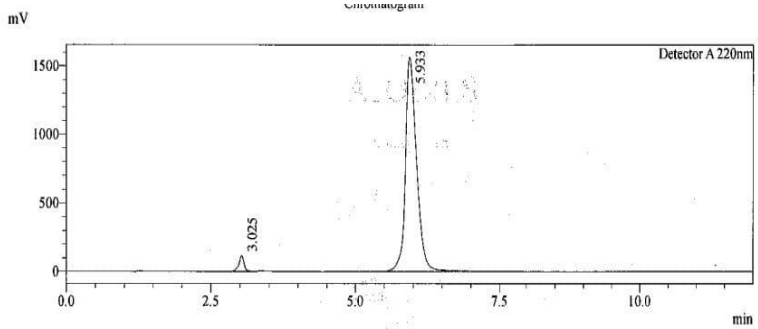
Lidocaine 6hr(ceftriaxone area-21473003, tazobactam area-548580



Normal saline 6hr (ceftriaxone area-21026767, tazobactam area-710083)

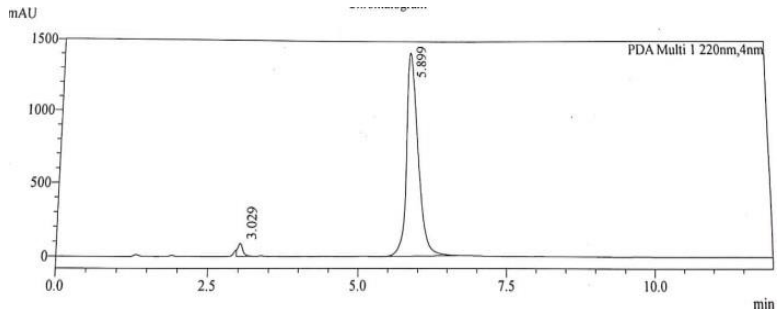


Dextrose 6hr(ceftriaxone area-21508025, tazobactam area-764044)

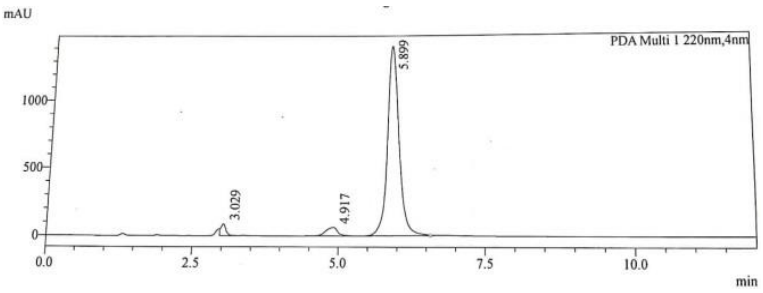


Water for injection 6hr(ceftriaxone area-21013381, tazobactam area-730665)

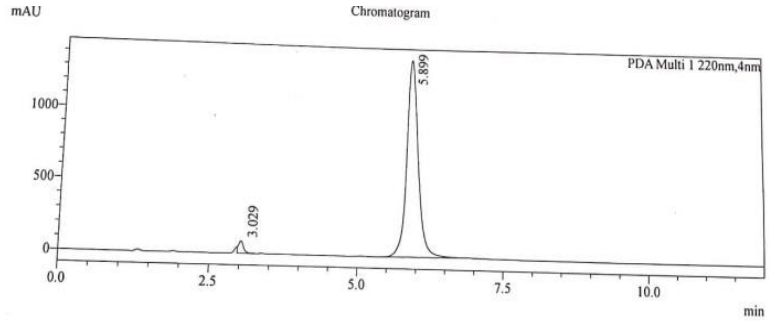
Fig. No. 6: Chromatogram of sample kept in the refrigerator for 6hr.



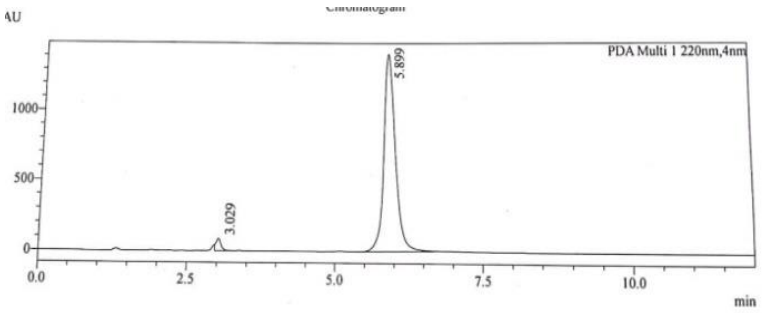
12hr R normal saline (ceftriaxone area-20167346, tazobactam area-493294)



12hr R lidocaine(ceftriaxone area-19691610, tazobactam area-534009)

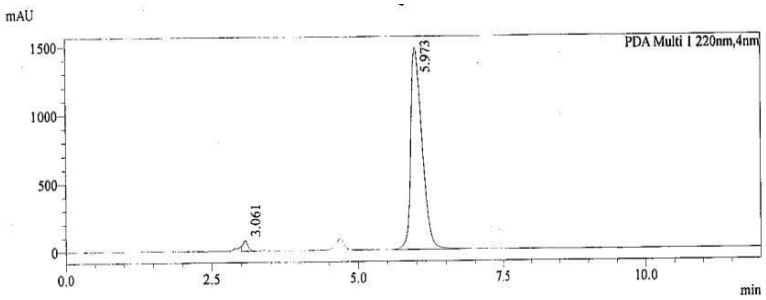


12hr R dextrose(ceftriaxone area-20229706, tazobactam area-477401)

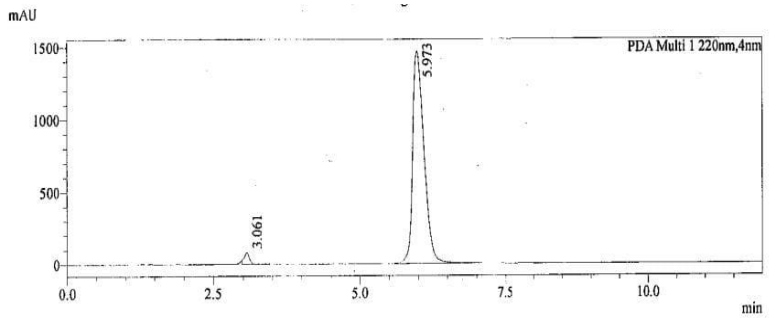


12hr R water for injection(ceftriaxone area-19965623, tazobactam area-502894)

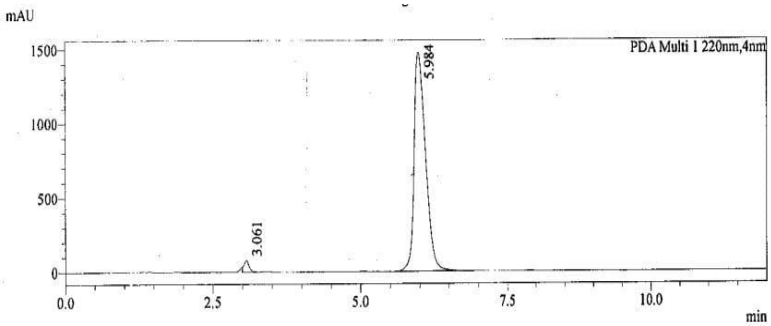
Fig. No. 7: Chromatogram of sample kept at refrigerator for 12hr.



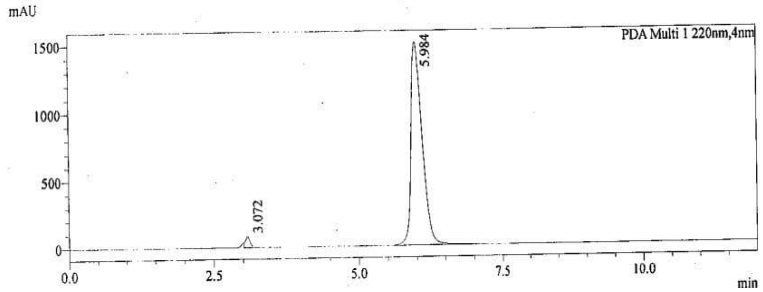
24hr R lidocaine(ceftriaxone area-20170067, tazobactam area-473142)



24hr R normal saline(ceftriaxone area-20521904, tazobactam area-480668)

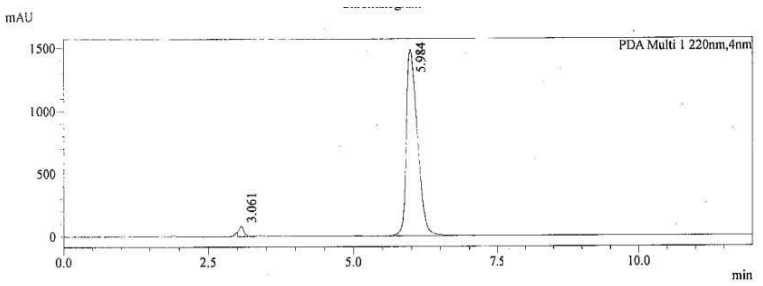


24hr R water for injection(ceftriaxone area-19989544, tazobactam area-526113

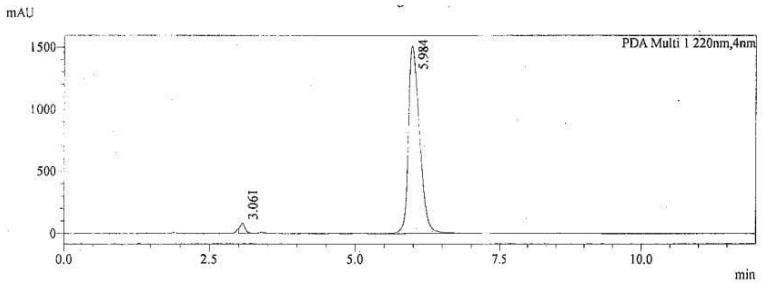


24hr R dextrose(ceftriaxone area- 20100703, tazobactam area-484423

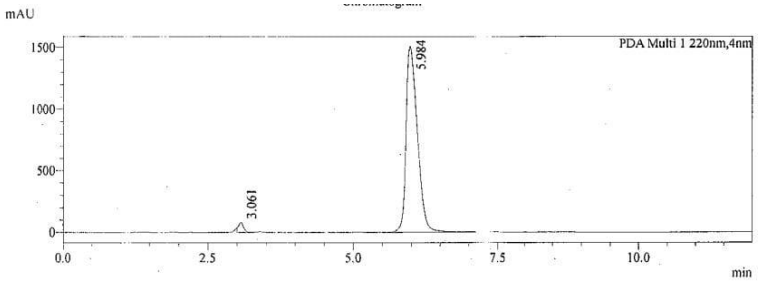
Fig. No. 8: Chromatogram of sample kept at refrigerator for 24hr.



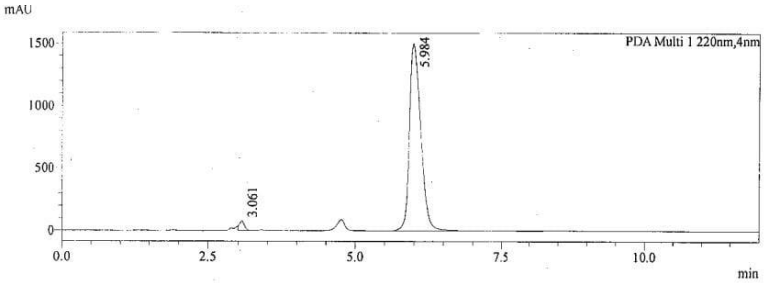
72hr R normal saline(ceftriaxone area-20011477, tazobactam area-499729)



72hr R dextrose(ceftriaxone area-20471041, tazobactam area-511558

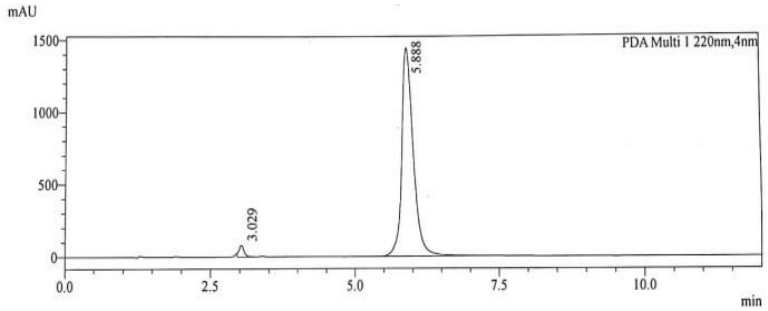


72hr R water for injection(ceftriaxone area-20504133, tazobactam area-494121

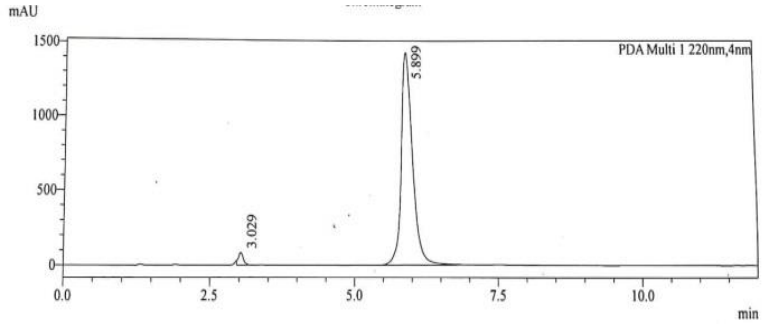


72hr R lidocaine(ceftriaxone area-20367010, tazobactam area-478274)

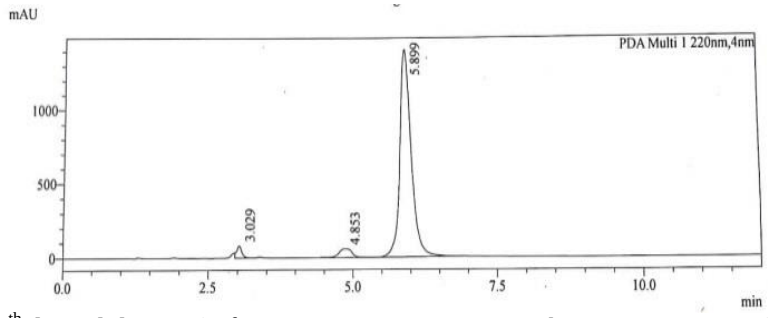
Fig.No. 9: Chromatogram of sample kept at refrigerator for 72hr.



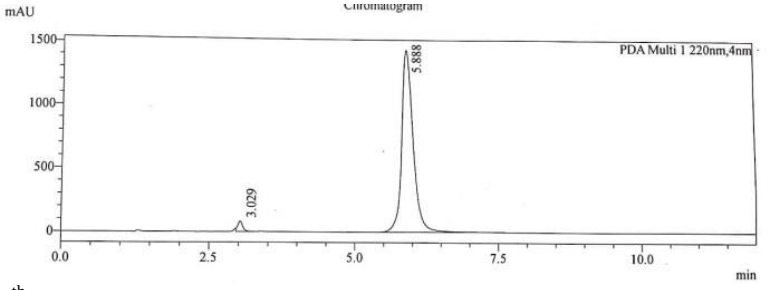
7th day R water for injection(ceftriaxone area-19884355, tazobactam area-509357



7th day R normal saline(ceftriaxone area-20276474, tazobactam area-489984)

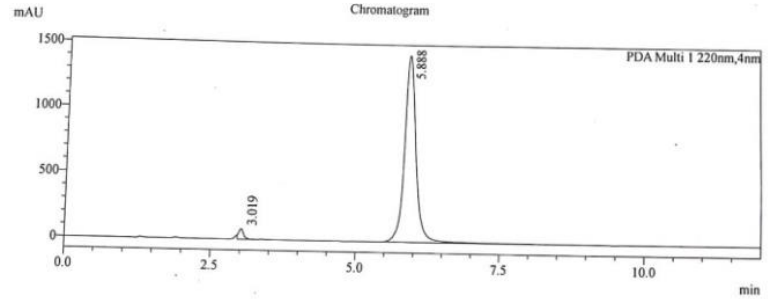


7th day R lidocaine(ceftriaxone area-19381569, tazobactam area-505669)

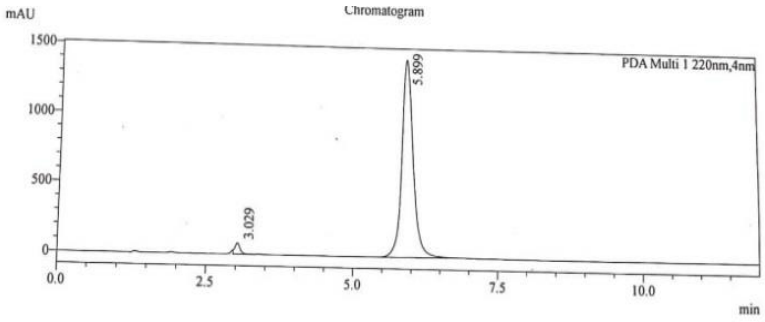


7th day R dextrose(ceftriaxone area-20319038, tazobactam area-488938)

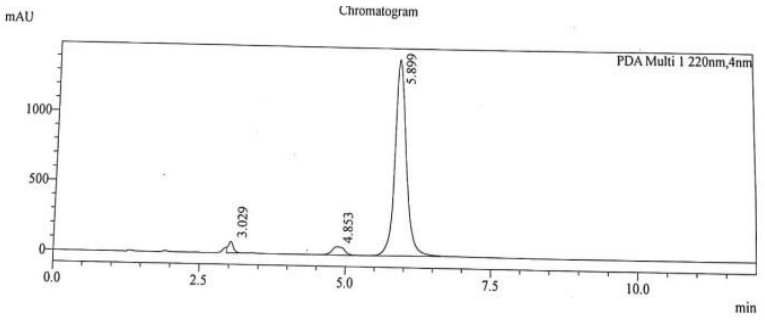
Fig.No.10: Chromatogram of sample kept at refrigerator for 7 days.



10th day R water for injection(ceftriaxone area-20201760, tazobactam area-468372)

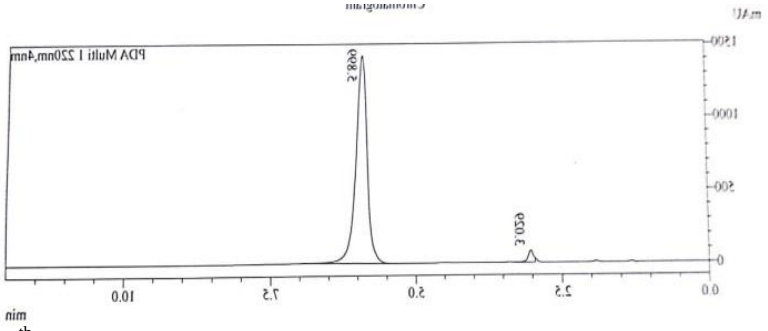


10th day R normal saline(ceftriaxone area-19450099, tazobactam area-491906)



Q

10th day R lidocaine(ceftriaxone area-19339396, tazobactam area-517673)



10th day R dextrose(ceftriaxone area-19493911, tazobactam area-508762)

Fig.No. 11: Chromatogram of sample kept at the refrigerator for 10 days.

3.3 ACCELERATED STABILITY STUDY DATA OF CEFTRIAXONE TAZOBACTAM INJECTION

Table No. 4 Results of initial study before stability study, two months, three months and six months of accelerated stability study.

1. Description	**Results of initial study before stability studies:** Conforms: Sterile off-white coloured free-flowing powder	**Results of two months of accelerated stability studies:** Conforms: Sterile off-white coloured free-flowing powder	**Results of three months of accelerated stability studies :** Conforms: Sterile off-white coloured free-flowing powder	**Results of six accelerated stability studies:** Conforms: Sterile off-white coloured free-flowing powder
2. Identification	A) The retention times of the major peaks are comparable. B) Gives the reaction of sodium	A) The retention times of the major peaks are comparable. B) Gives the reaction of sodium	A) The retention times of the major peaks are comparable. B) Gives the reaction of sodium	A) The retention times of the major peaks are comparable. B) Gives the reaction of sodium
3. pH	6.378	6.434	6.425	6.166
4. Water	9.4%	8.6%	8.9%	8.6%
5. Bacterial Endotoxins Test	Less than 0.20 USP EU/mg	NA	NA	NA
6. Sterility tests-	Sterile	NA	NA	NA

7. Particulate matter	Particles ≥10micron=1257/vial; Particles ≥25micron=101/vial;	NA	NA	NA
8. Uniformity of dosage units	Average fill weight = 1318.25 mg L%= ceftriaxone-2.48 Tazobactam=2.40	NA	NA	NA
9. Assay	Ceftriaxone = 98.4% of LA Tazobactam = 99.6% of LA	Ceftriaxone = 99.7% of LA Tazobactam = 94.2% of LA	Ceftriaxone = 103.0 % of LA Tazobactam = 94.2 % of LA	Ceftriaxone = 99.8% of LA Tazobactam = 92.3% of LA
10. Constituted solution (Completeness and Clarity of Solution	Complies: A) The solid dissolves completely leaving no visible residue B) The constituted solution is as clear as purified water. C)The solution is free from particles of foreign visible matters	A) The solid dissolves completely leaving no visible residue B) The constituted solution is as clear as purified water. C)The solution is free from particles of foreign visible matters	A) The solid dissolves completely leaving no visible residue B) The constituted solution is as clear as purified water. C)The solution is free from particles of foreign visible matters -	A) The solid dissolves completely leaving no visible residue B) The constituted solution is as clear as purified water. C)The solution is free from particles of foreign visible matters

3.4 RECONSTITUTION STABILITY STUDY DATA OF CEFTRIAXONE TAZOBACTAM

Table No. 5: Results of reconstitution stability study data and pH of 5% Dextrose and lidocaine.

	5% Dextrose	5% Dextrose	5% Dextrose	Lidocaine	Lidocaine	Lidocaine
Time	**Ceftriaxone**	**Tazobactam**	**pH**	**Ceftriaxone**	**Tazobactam**	**pH**
Initial	97.0	105.2	6.15	97.6	105.4	6.14
6hr RT	96.6	112.5	6.17	96.1	110.8	6.15
12hr RT	94.2	107.9	6.41	95.2	111.1	6.40
24hr RT	91.8	100.4	6.36	92.7	107.4	6.26
72hr RT	85.0	85.2	6.46	87.7	101.3	6.42
6hr 2-8°C	100.2	111.4	6.16	100.0	105.8	6.15
12hr 2-8°C	99.2	99.8	6.18	96.5	111.7	6.29
24hr 2-8°C	95.2	99.4	6.13	95.5	97.1	6.13
72hr 2-8°C	96.9	105.0	6.31	96.4	98.1	6.11
7th day	99.6	102.2	6.21	95.0	105.7	6.17
10th day	95.6	106.4	6.46	94.8	108.3	6.41

4. SUMMARY

The stability of a product provides proof of how the quality of the drug is maintained within its shelf-life without degradation. Visual changes appear eventually as time passes. Variations in the composition of the product can take place. It is required to fix an expiry date for the products. The pharmaceutical products are kept under accelerated conditions.

Initially, samples were withdrawn from production, which were divided into different categories for evaluation at different time intervals, in different conditions. First, the evaluation tests were carried out at the sample withdrawn time itself (Initial tests). In this different parameters were evaluated, like the description of the product, identification, pH, water content, bacterial endotoxin test, sterility test, particulate matter, and uniformity of dosage unit, assay, constituted solution (completeness and clarity of solution). The next part of the withdrawn samples from the production was loaded in the stability chamber (40ºC & 75%RH) for different time intervals (1 month, 2 months, 3 months, 6 months). After each time interval, samples were withdrawn from the stability chamber and the evaluation tests were carried out. From the results, it was concluded that all the evaluation results were within the limit. So, it states that Ceftriaxone and tazobactam injection is stable for six months under accelerated 40°C/75% RH condition.

Reconstitution studies were also simultaneously carried out with specified diluents like sterile water for injection, normal saline, 5% dextrose, and 1% lidocaine, in specified conditions like room temperature (NMT 25ºC, 40-75 % RH; refrigerated 2-8°C), up to the specified time(initial, 6hr, 12hr, 24hr, 72hr, 7th day, 10th day). In the reconstitution study, different parameters like the appearance of the solution, pH, and assay were performed. The result of the study indicates that the product, ceftriaxone and tazobactam injection is stable for 10 days under refrigerated conditions and for 24 hours at room temperature when reconstituted with the

diluents like sterile water for injection, normal saline, 5% dextrose, 1% lidocaine.

5. ACKNOWLEDGMENTS
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