Journal of Applied Pharmaceutical Science Vol. 12(06), pp 215-223, June, 2022
Available online at http://www.japsonline.com
DOI: 10.7324/JAPS.2022.120621
ISSN 2231-3354

Newly validated stability-indicating ultra-performance liquid chromatography-tandem mass spectrometry method for the estimation of Ceftaroline Fosamil by using a quadrupole mass detector

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ARTICLE INFO

Received on: 10/02/2022
Accepted on: 25/04/2022
Available Online: 05/06/2022

Key words:
Antibiotic, Ceftaroline Fosamil, cephalosporin, stability studies, UPLC-MS/MS, ICH guidelines.

ABSTRACT

The present study aims to develop and validate a stability-indicating assay method to determine Ceftaroline Fosamil by using a hyphenated technique ultra-performance liquid chromatography-tandem mass spectrometry (UPLC-MS/MS) in Active Pharmaceutical Ingredient (API) and dosage form. An Acquity C18 UPLC Bridged Ethyl Hybrid (BEH) (50 × 2.1 mm, 1.7 µm) analytical column coupled to a triple quadrupole mass detector was used. The isocratic elution was employed with acetonitrile and 0.1% formic acid in water in a 70:30 v/v ratio as the mobile phase. Mobile phase flow rate and column temperature were maintained at 0.35 ml/minute and 30°C, respectively, with an injection volume of 5 µl and runtime of 3 minutes. Positive electrospray ionization in Multiple reaction monitoring (MRM) mode was maintained. Ceftaroline Fosamil showed good resolution with a retention time of 0.91 ± 0.04 minute and was quantified at the transition pair *m/z* 685.30 → 208.10. The Limit of Detection (LOD) and Limit of Quantification (LOQ) were found to be 30 and 100 ng/ml, respectively. In the forced degradation studies, it was observed that Ceftaroline Fosamil was stable in all the stress conditions except in the basic medium. A UPLC-MS/MS analytical method was developed and validated along with stability studies in accordance with the International Council for Harmonisation (of Technical Requirements for Pharmaceuticals for Human Use) (ICH) guidelines to determine Ceftaroline Fosamil in the parental dosage form and API.

INTRODUCTION

A novel, advanced, fifth-generation, broad-spectrum cephalosporin parental antibiotic, namely Ceftaroline Fosamil (Fig.1) ((6R,7R)-7-[[(2Z)-2-ethoxyimino-2-[5-(phosphonoamino)-1,2,4-thiadiazol-3yl]acetyl]amino]-3-[[4-(1-methylpyridin-1-ium-4-yl)-1,3-thiazol-2-yl]sulfanyl]-8-oxo-5-thia-1azabicyclo[4.2.0]oct-2-ene-2-carboxylate), is a potent bactericidal. It has potent activity against a broad range of bacteria, especially methicillin-resistant *Staphylococcus aureus* and penicillin-resistant *Streptococcus pneumonia* (Gram-positive), *Moraxella catarrhalis* (Gram-negative), including positive lactamase strains, such as *Haemophilus influenza*, and bacteria with various resistance phenotypes (Kaushik *et al*., 2011).

A hyphenated methodology is a valuable tool for assessing drugs in various biological samples (Junza *et al*., 2011; Junza *et al*., 2014; Van den Meersche *et al*., 2016). The hyphenated technique, such as liquid chromatography-tandem mass spectrometry (LC-MS/MS), couples a chromatographic system to a spectroscopic system with the appropriate interface. It is well known that the performance features of ultra-performance liquid chromatography (UPLC) benefit detection significantly. By optimizing sample pretreatment and minimizing analysis time, LC-MS/MS can detect over 300 compounds of different classes with a minimal injection volume. On the other hand, MS/MS measures the compound's *m/z* with its intermediates (by-products) (Glish and Burinsky, 2008).

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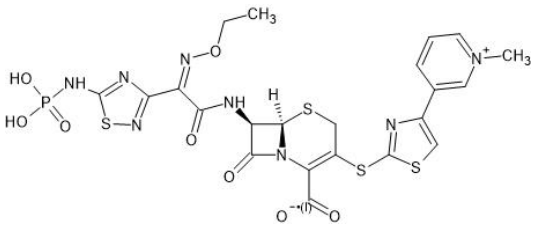

Figure 1. Chemical structure of Ceftaroline Fosamil.

Various chromatography-based assays were published to estimate Ceftaroline Fosamil (Alarcia lacalle *et al*., 2021; Gregoire *et al*., 2016; Izabela *et al*., 2017; Reddy Govardhan *et al*., 2018; Suneetha and Venkanna, 2013). But none of the current analytical methods have reported measurements of Ceftaroline Fosamil on hyphenated techniques, such as UPLC-MS/MS. The proposed methodology is simple, with easy sample pretreatment and fast analysis by optimizing all chromatographic and mass detection parameters at various stages of drug analysis. The purpose is to develop a sensitive, selective, and accurate method for analyzing Ceftaroline Fosamil on the UPLC column coupled to MS/MS by using triple quadrupole (QQQ) mass detection. Acetonitrile (ACN) and 0.1% formic acid in water, in a proportion of 70:30 v/v, were used as the mobile phase. The proposed UPLC-MS/MS method was validated, and the forced degradation studies were conducted for Ceftaroline Fosamil.

MATERIALS AND METHODS

Chemicals and reagents

All the chemicals were analytical grade with 99.0% purity. Ceftaroline Fosamil standard (99.8%) was obtained from Clear Synth (Hyderabad). The LC-grade water, ACN, and methanol were procured from Merck (Mumbai, India). Formic acid and all other reagents were purchased from SD Fine Chemicals Ltd. The Zinforo injection (Ceftaroline Fosamil 600 mg) was purchased from Apollo Pharmacy (Hyderabad).

Instrumentation and chromatographic conditions

All chromatographic separations were achieved on a hyphenated UPLC system coupled to MS/MS (UPLC-MS/MS-All Waters, USA). Acquity C18 UPLC BEH (50 × 2.1 mm, 1.7 µm) was used as the analytical column with a QQQ mass detector using MassLynx software. ACN and 0.1% formic acid in water, in a proportion of 70:30 v/v, were used as the mobile phase. The mobile phase flow rate was 0.35 ml/minute with isocratic elution mode. The column temperature was maintained at 30°C with an injection volume of 5 µl and the runtime was 3 minutes. The mass spectrophotometer operated in MRM mode with positive electrospray ionization (+ESI). The typical optimized MS/MS parameters included are capillary voltages of 3.00 and 2.94 kV, cone voltages of 40 and 43 V, source temperatures of 120°C and 119°C, desolvation gas flow of 850 l/hour, cone gas flow of 102 l/hour, nebulizer gas flow of 7 bars, ion energy of 2 1.0, syringe pump flow of 100 l/minute, pressure of 6.54e-3, collision gas flow of 0.15 ml/minute, collision energy of 40–41 eV, and with dwell seconds of 0.20.

Preparation of diluent solution

The diluent used was a 50:50 v/v mixture of methanol and water. The diluent was used to obtain blank mass spectra.

Preparations of standard stock solution

A standard stock solution (stock solution A) of Ceftaroline Fosamil was prepared using a diluent solvent with a concentration of 1,000 µg/ml. Stock solution A was diluted to get standard solutions of Ceftaroline Fosamil with concentrations of 1,000 and 100 ng/ml, respectively.

Preparation of sample solution (marketed formulation)

Each ampoule has 600 mg of Ceftaroline Fosamil (Zinforo) and 10.66 mg of injection powder was dissolved in 10 ml of diluent to give a 1,000 µg/ml solution. It was diluted further to a concentration of 1,000 ng/ml.

Preparation of the mobile phase

ACN and 0.1% formic acid in water, in a 70:30 v/v ratio, were prepared and used as the mobile phase. Mixed solvents were sonicated and employed as the mobile phase.

VALIDATION PROCEDURE

Parameters like precision, linearity, specificity, accuracy, LOQ, system suitability, and LOD were determined to evaluate the validation for the proposed Ceftaroline Fosamil UPLC-MS/MS method.

System suitability

Many analytical methods, include system suitability testing as an intrinsic and essential part of the procedure, analytical procedures with tailing factor < 2, Relative Standard Deviation (RSD) < 1%, and theoretical plates > 2,000, will show the appropriateness of the method (Shabir, 2003). The system compatibility of the proposed analytical method was determined by analyzing six samples of Ceftaroline Fosamil of 1,000 ng/ml.

Specificity

To evaluate the specificity, a blank sample (methanol: water of 50:50 v/v) and working standard (1,000 ng/ml) were prepared as per the developed method and injected into the UPLC-MS/MS system.

Linearity and range

Seven linear concentration solutions were prepared from the standard stock solution by dilution to obtain calibration standards ranging from 100 to 1,500 ng/ml and to evaluate the linearity of the method proposed. The calibration curve is plotted against the area using the above range of solutions. Slope, intercept, and correlation coefficient (r^2) was used to evaluate linearity.

Sensitivity

By injecting the range of diluted solutions of known concentration, the LOD and LOQ were determined using signal-to-noise (S/N) ratios of 3:1 and 10:1, respectively.

Precision (%repeatability)

Precision was measured by injecting (n = 6) 100 ng/ml of Ceftaroline Fosamil. Intraday and interday precisions were measured using Ceftaroline Fosamil standard solutions with concentrations of 1,000, 500, and 100 ng/ml, six times on the same day and six times on other days, respectively. The results were expressed as %RSD.

Accuracy

Accuracy was measured at three concentration levels, 50%, 100%, and 150%, of the standard solutions. A preanalyzed sample solution (1,000 ng/ml) was spiked with 50%, 100%, and 150% standard solutions prior to analysis, and the results were reported as a percentage recovery.

Robustness

Robustness was measured by altering the experimental parameters, such as injection volume, column temperature, and flow rate. Flow rate was modified to 0.32 ml/minute and 0.37 ml/minute, respectively. The effect of temperature on the column was studied at 27°C and 32°C. The mobile phase composition was not altered in any of these experiments.

Solution stability

A solution containing 1,000 ng/ml Ceftaroline Fosamil standard was kept at room temperature over 24 hours to check its stability. Ceftaroline Fosamil (1,000 ng/ml) was injected thrice to evaluate solution stability. The percentage RSD was used to express the results.

Assay procedure

5 µl standard and sample solutions (1,000 ng/ml) were injected separately into the chromatographic system. The assay of the sample solution was determined using the peak area.

Forced degradation studies of Ceftaroline Fosamil

UPLC-MS/MS was used to conduct the forced degradation studies for Ceftaroline Fosamil. The forced degradation of Ceftaroline Fosamil was accelerated by using 0.5 ml of 1N HCl, 0.5 ml of 1N NaOH, 0.5 ml of water, and 0.5 ml of 3% peroxide solution for forced acidic, basic, neutral, and oxidation stress studies, respectively. The standard solution was kept in a hot air oven at 70°C for 60 minutes to accelerate thermal degradation. Accurately 0.5 ml of standard Ceftaroline Fosamil (10 µg/ml) was added to the stress-specific reagent, and the final volume was made to 5 ml by adding the diluent. The final solution injected into the UPLC-MS/MS system of Ceftaroline Fosamil was 1,000 ng/ml. All the solutions were analyzed at regular intervals for 1 week, every 6, 12, and 24 hours.

RESULTS AND DISCUSSION

Chromatographic conditions

MS analysis confirmed that the molecule is Ceftaroline Fosamil and found that the mass spectrum of $[M+H]^+$ peak (parent ion peak) is at *m/z* 685.33. $[M+H]^+$ fragmented peak (daughter ion peak) after ionization was found at *m/z* 208.1. Ceftaroline Fosamil was quantified using +ESI in positive MRM mode at the transition pair *m/z* 685.30 → 208.10. The compound Ceftaroline Fosamil showed good resolution with a retention time of 0.91 ± 0.04 minute when a C18 column (Aquity UPLC BEH) was used

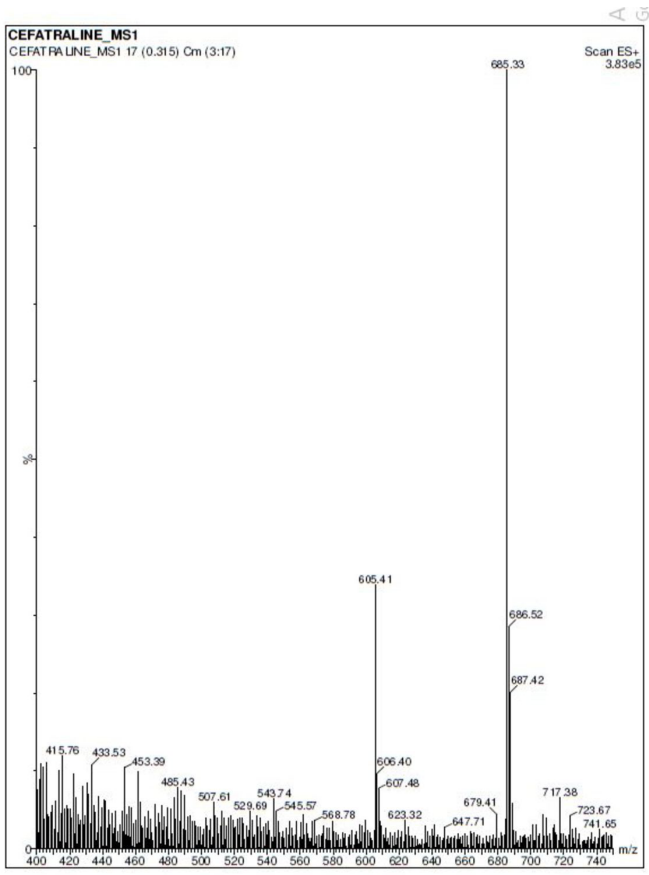

Figure 2. Mass spectrum of the parent ion of Ceftaroline Fosamil.

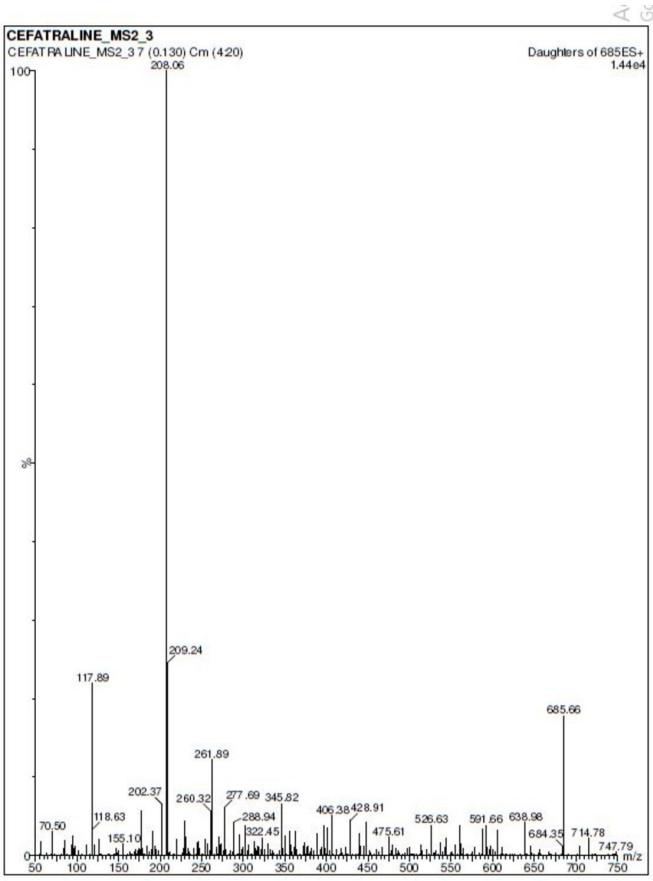

Figure 3. Mass spectrum of the daughter ion of Ceftaroline Fosamil.

Table 1. System suitable parameters for Ceftaroline Fosamil by UPLC-MS/MS.

Trail no:	Concentration taken (ng/ml)	Area	Retention time (Rt)	Concentration obtained (ng/ml)
1.	1,000	11,218.129	0.91	951.7
2.	1,000	10,869.244	0.91	920.9
3.	1,000	11,265.263	0.91	955.8
4.	1,000	11,265.574	0.91	950.3
5.	1,000	111.58.431	0.91	946.4
6.	1,000	11,280.145	0.91	957.1
	Mean	11,165.631	0.91	947.0
	Standard deviation	151.695	-	13.3
	% R.S.D	1.35	-	1.4

with 0.1% formic acid and ACN (30:70 v/v) as the mobile phase at 0.35 ml/minute flow rate and 100 ng/ml concentration. The $[M+H]^+$ spectra of Ceftaroline Fosamil parent ion and fragmented daughter ion are shown in Figures 2 and 3, respectively.

Validation

For system suitability parameters, peak area and concentration were determined with %RSD of 1.35 and 1.4, respectively. The tailing factor was equal to 1.16. Table 1 presents the results. The retention time, peak area, and peak symmetry are all within acceptable limits, indicating the suitability of the proposed method. The specificity was evaluated using a blank sample (methanol: water of 50:50 v/v) and working standard (1,000 ng/ml). The result found was that Ceftaroline Fosamil $[M+H]^+$ had a retention time of 0.91 minute with a 685.3 *m/e* ratio with respect to the blank sample. Figure 4 shows specific chromatograms of blank and standard Ceftaroline Fosamil peaks. The linearity of the proposed method was measured by constructing a calibration curve in a range of 100–1,500 ng/ml. The findings reveal that the peak area and analyte concentration have an excellent correlation with linearity in the investigated concentration range with $Y = 11.3263 * \times + 439.292$ ($R^2 = 0.99$) as the linear regression equation. Figure 5 shows the calibration curve. Table 2 presents the linearity results. The sensitivity was measured for LOD at 30 ng/ml and LOQ at 100 ng/ml, using signal-to-noise (S/N) ratios of 3:1 and 10:1, respectively. Figure 6 shows the chromatograms at LOD and LOQ levels. The precision was measured as intraday and interday precisions at three concentrations. The %RSD for intraday results at 1,000, 500, and 100 ng/ml was found to be 1.40, 1.09, and 2.01, respectively. The %RSD for interday results at 1,000, 500, and 100 ng/ml were found to be 1.1, 1.3, and 2.5 respectively. Table 3 presents the precision results. Percentage recovery at 50%, 100%, and 150% were 106.98%, 95.48%, and 95.48%, respectively. Table 4 shows the accuracy results for the proposed method. Method robustness was measured by modifying flow rate, column temperature, and %RSD of the same was within 2%. Table 5 presents the method robustness results. %RSD of solutions stability was <2%. Table 6 shows solution stability results.

The percentage assay of marketed Zinforo (600 mg) was found to be 99.63 ± 0.58 with the amount obtained as 598.53 mg.

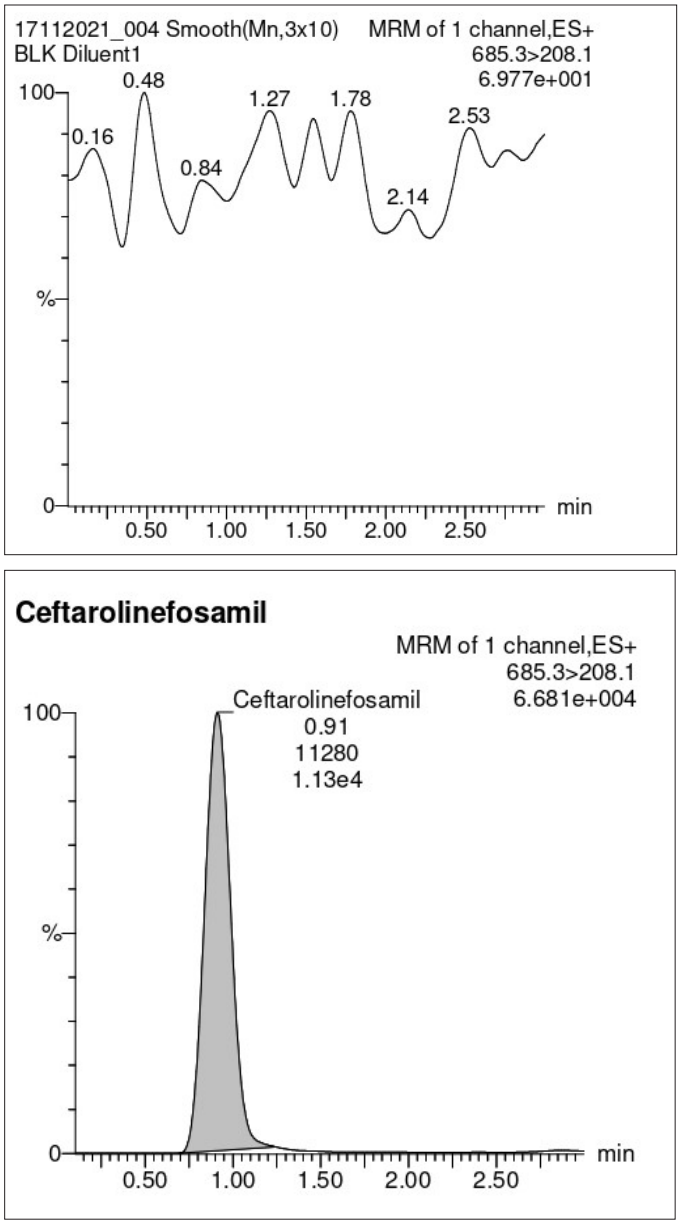

Figure 4. Specificity. (A) Blank. (B) Working standard of Ceftaroline Fosamil.

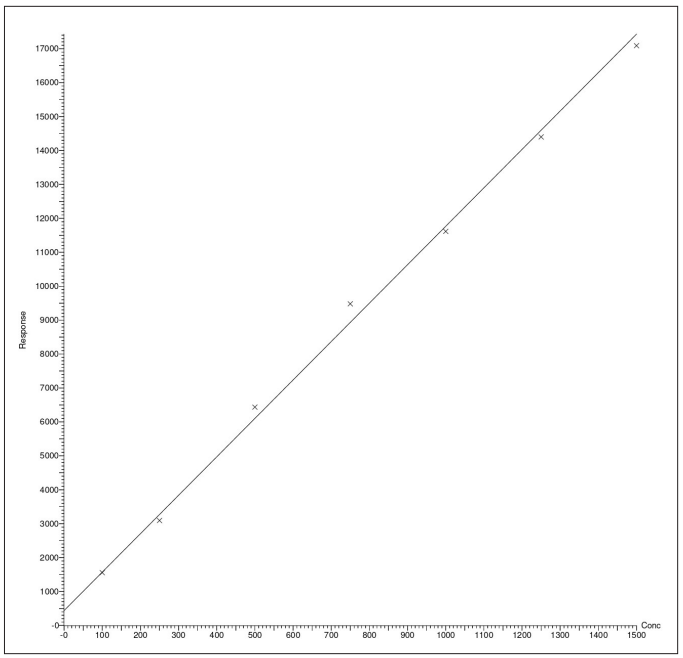

Figure 5. Linear calibration curve for Ceftaroline Fosamil.

Table 2. Linearity of Ceftaroline Fosamil by UPLC-MS/MS.

S.No	Concentration (ng/ml)	Area[a]	Relative standard deviation
1.	100	1,557.240	0.86
2.	250	3,092.145	0.09
3.	500	6,435.636	0.08
4.	750	9,481.938	0.07
5.	1,000	11,614.535	0.07
6.	1,250	14,399.315	0.36
7.	1,500	17,089.996	0.29
Correlation coefficient (r)		0.998805	
Squared correlation coefficient (r2)		0.99	
Slope		11.3263	
Intercept		439.292	

[a] Number of determinations (n) = 6.

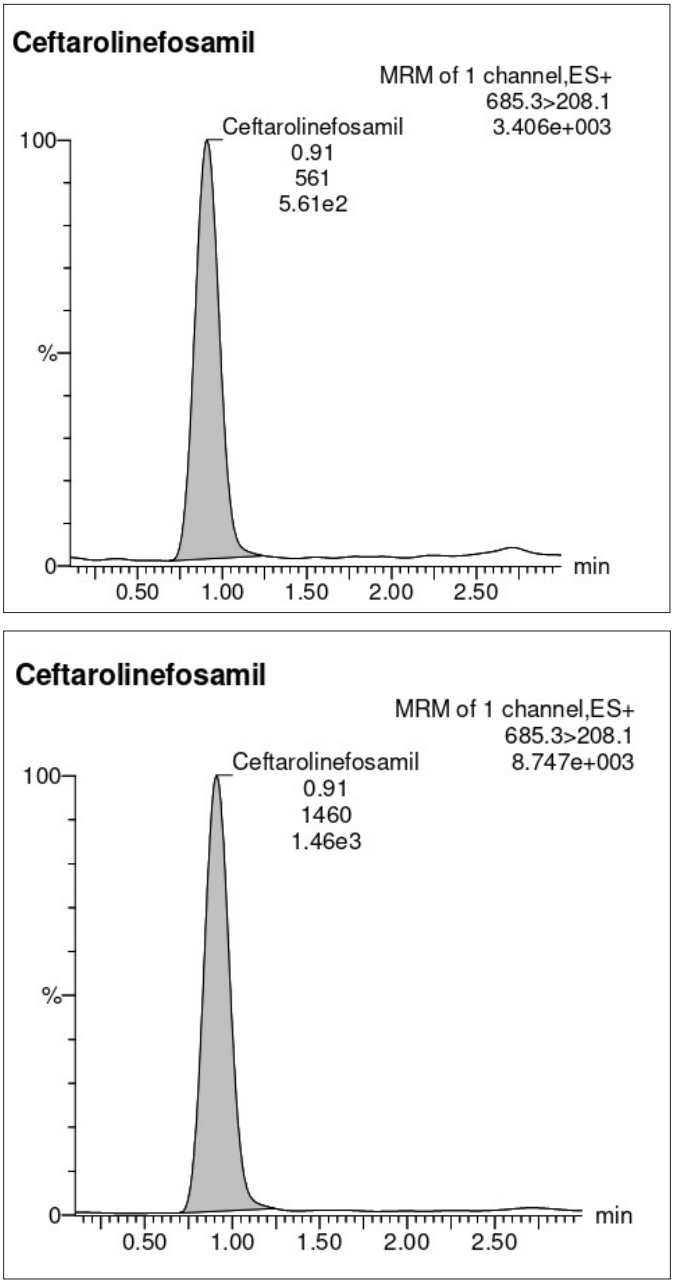

Figure 6. Sensitivity. (A) LOD. (B) LOQ.

Forced degradation studies

In acidic conditions, the retention time of forced degradation acidic solution was found to be 0.87 minute with no degradation of Ceftaroline Fosamil, indicating its stability in acidic solution. In basic conditions, the retention time of forced basic solution of Ceftaroline Fosamil was at 1.39 minutes with a degradant fragment at an m/z ratio of 263.08, indicating its instability in basic medium and that it has degraded completely with no Ceftaroline Fosamil parent peak (Niessen, 2010). Figure 7 shows the degradant fragmentation of Ceftaroline Fosamil in the basic medium. Figure 8 shows the MS spectra of Ceftaroline Fosamil in forced basic condition. In neutral oxidation and thermal conditions, the retention time of forced degradation solutions was found to be 0.87 minute with no degradation of Ceftaroline Fosamil, indicating its stability in water, 3% hydrogen peroxide solution, and heat. In thermal conditions, it was observed that the peak area obtained has slightly deviated. Table 7 shows a brief summary of the Stability Indicating Assay Method (SIAM) method for Ceftaroline Fosamil using UPLC-MS/MS.

DISCUSSION

Although many methods for estimating Ceftaroline Fosamil using various chromatography techniques, such as HPLC or LC-MS are available, the current method was found to be more accurate, precise, and faster by utilizing an advanced hyphenated UPLC-MS/MS technology. A comparison of the published LC-

Table 3. Intraday and interday precision of Ceftaroline Fosamil by UPLC-MS/MS.

Conc. of Ceftaroline Fosamil (API) (ng/ml)	Observed Conc. of Ceftaroline Fosamil (ng/ml)) by the proposed method					
	Intraday			Interday		
	Mean (n = 6)	Standard deviation	% RSD	Mean (n = 6)	Standard deviation	% RSD
100	87.5	3.72	1.40	86.0	3.06	**1.1**
500	533.3	5.85	1.09	502	7.54	**1.3**
1,000	98.5	19.8	2.019	85.2	25.6	**2.5**

Table 4. Accuracy and %recovery of the spiked samples of Ceftaroline Fosamil by UPLC-MS/MS.

Spiked level	Theoretical Conc. of pure drug (ng/ml) added	Area	Conc. of pure Found (ng/ml)	Conc. Mean	Standard deviation	% RSD	% recovery
50%	500	6,477.5	533.1				
50%	500	6,457.8	531.4	534.9	5.121	0.9	106.98
50%	500	6,562.8	540.7				
100%	1,000	11,218	951.7				
100%	1,000	11,280	957.1	954.8	2.81	0.29	95.48
100%	1,000	11,265	955.8				
150%	1,500	16,913	1,454.5				
150%	1,500	17,162	1,476.5	1,477.6	23.77	1.06	95.48
150%	1,500	17,451	1,502.0				

Table 5. Robustness of the proposed method by UPLC-MS/MS for Ceftaroline Fosamil.

Change in parameter	% RSD
Flow rate (0.32 ml/minute)	0.9
Flow rate (0.34 ml/minute)	0.2
Temperature (27°C)	1.4
Temperature (32°C)	1.9
Retention time (Rt)	0.91 ± 0.04

Table 6. Solution stability of Ceftaroline Fosamil.

Time (hours)	Theoretical concentration (ng/ml)	Concentration found (ng/ml)	Mean value of three determinations			
			Mean	Standard deviation	% RSD	% recovery
0	1,000	1,000 1,000 998	999.9	0.05	0.01	99
12	1,000	995 998 998	997	1.73	0.17	99
24	1,000	955 955 955	968	23.09	2.38	96.8

MS/MS (Izabela *et al*., 2017) and the current proposed work is shown in Table 8. The main focus of the proposed work was to develop a UPLC-MS/MS method and apply this method to study the stability studies of Ceftaroline Fosamil. On the contrary, this method enables analysts to estimate Ceftaroline Fosamil samples using simple and uncomplicated methods involving no complex samples preparation or mobile phase, or use of buffer solution, resulting in an eco-friendly greenness method.

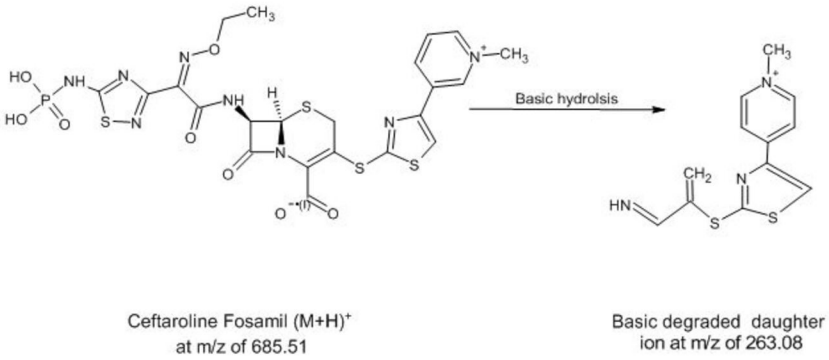

Figure 7. Fragmentation of Ceftaroline Fosamil in basic medium.

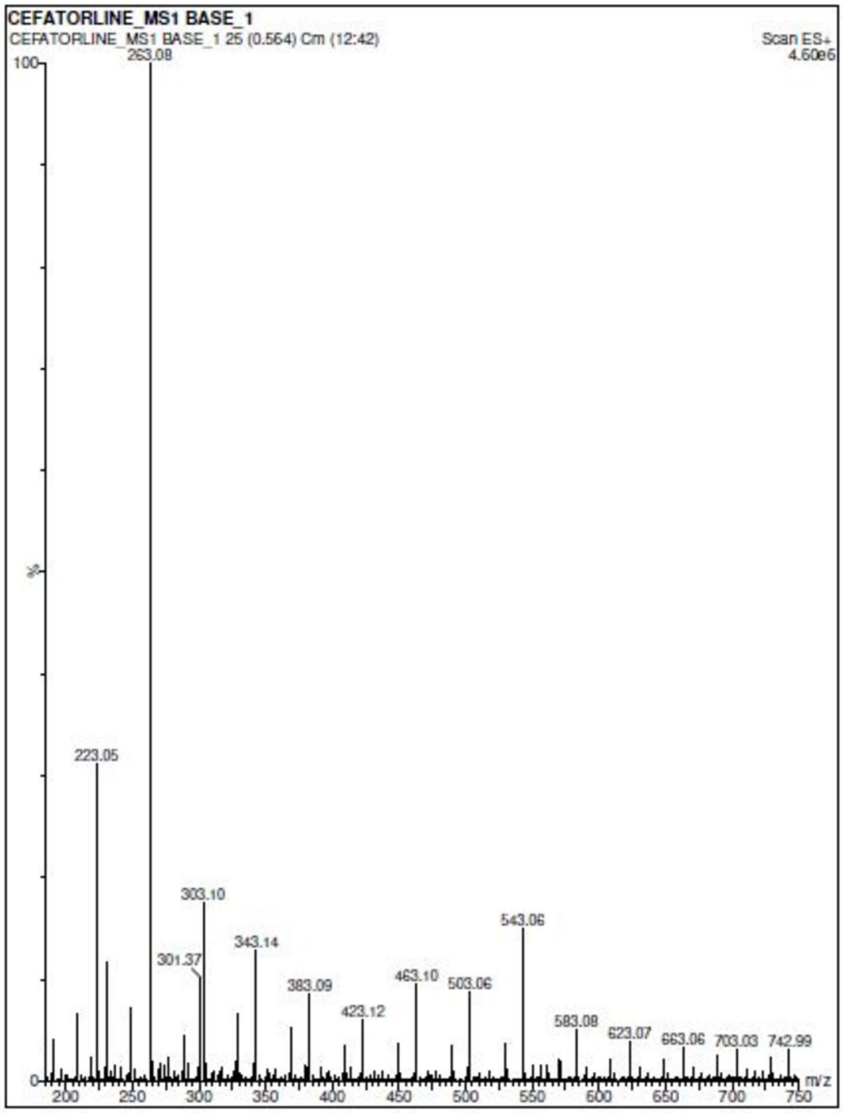

Figure 8. Mass spectra of Ceftaroline Fosamil in a forced basic condition.

Table 7. Summary of the SIAM method for Ceftaroline Fosamil.

Stress condition	Rt (minutes)	Peak area	Observation $[M+H]^+$ (*m*/*z*)	Concentration found after SIAM (%)
Control (standard)	0.87	1,418.95	685.51 (parent compound)	---
Acidic	0.87	1,418.95	685.31 (stable)	100.00
Basic	1.39	1,916.02	263.08 (unstable)	Completely degraded
Neutral	0.87	1,311.51	685.64 (stable)	92.43
Oxidative	0.87	1,322.82	685.44 (stable)	93.22
Thermal	0.87	1,203.14	685.51 (stable)	84.79

Table 8. Comparative study of the published LC-MS/MS work (Izabela *et al*., 2017) and proposed UPLC-MS/MS work.

Analytical parameter	Published method	Proposed method
Methodology or technique	HPLC (chromatographic separation) UPLC-MS/MS (for mass detection) LC-ESI-QTOF-MS is used	UPLC-MS/MS (for chromatographic separation as well as detection) UPLC-ESI-QQQ-MS is used
Stationary phase	HPLC: LiChrospher 100 RP (e) (250 × 4.6 mm; 5 µm)	Acquity C18 UPLC BEH (50 × 2.1 mm, 1.7 µm)
Mobile phase and its elution type	Gradient elution; Mobile phase A: ammonium acetate buffer (50 mM) pH 3.5 and Mobile phase B: ACN	Isocratic elution; ACN and 0.1% formic acid in water in 70:30 v/v
Diluent	Combination of mobile phase A and mobile phase B (same as mobile phase)	Methanol: water (50:50 v/v)
Internal standard	NA	NA
Flow rate	1 ml/minute	0.35 ml/minute
Injection volume	20 µl	5 µl
Working standard (taken as 100%)	1 mg/ml	100 ng/ml (for method development) 1,000 ng/ml (for validation)
MS/MS conditions	Capillary voltage: 4,500 V Nebulizer gas pressure: 1.6 bars Dry gas (Nitrogen) flow rate: 8 l/minute Collision energy: 20 to 35 eV Ionization Mode: + ESI	Capillary voltage:3.00 kV and 2.94 kV Nebulizer gas flow: 7 bars Cone gas flow: 102, 99 l/hour Collision energy: 40–41 eV Ionization Mode: + ESI (MRM)
m/z of degraded fragments[M+H]+	258.1, 209.0, 309.0, 605.1, 423.0	263.08
Application	Ceftaroline Fosamil and eight other structurally similar antibiotics were studied.	To analyze API and formulation of Ceftaroline Fosamil (assay and stability)
Retention time	Relative Rt is taken as 1	0.91 ± 0.04 minutes
Merits	In detail, the degradation studies of Ceftaroline Fosamil were illustrated. Fragmentation pattern was illustrated. Linearity: 0.8–1.2 mg/ml LOD: 0.15 µg/ml and LOQ:0.5µg/ml	Fast analysis: 54.6 seconds Sensitivity increased (in terms of ng level), low solvent consumption. Linearity: 100–1,500 ng/ml, LOD: 30 ng/ml & LOQ:100 ng/ml Particle size of stationary phase is 1.7 µm, which is ideal for UPLC analysis.
Method greenness	----	Reduction in analyzing time, use of solvents (volume) and energy; eco-friendly diluent used (methanol and water), method automation, less wastage, and no use of buffers.

CONCLUSION

A novel, stability-indicating, hyphenated tandem MS coupled to the UPLC method to determine stability in various stress conditions for Ceftaroline Fosamil has been developed. The proposed method is fast, precise, economical, and advanced to achieve higher and better specificity, and also allows for the isolation of API from its excipients and other impurities if they are present in the formulation. The proposed method can be used to analyze

Ceftaroline Fosamil parental powder regularly. The development of a fast and simpler MS/MS detection method was prioritized to obtain a retention time within 1 minute, i.e., 54.6 seconds. The parent ion has been protonated to get a daughter ion, therefore increasing the sensitivity toward detection and quantification. Forced degradation studies and all the validation parameters were conducted according to ICH guidelines. The proposed UPLC-MS/MS process is simple (with easy sample preparation), accurate, consistent, linear, and precise, evidenced by high recoveries and an appropriate RSD. The assay findings show that the method can be used to analyze Ceftaroline Fosamil in formulations. All of the parameters are within acceptable ranges, so it can be concluded that the method was created and validated as per the ICH requirements (European Medicines Agency, 1995; Harron, 1994).

ACKNOWLEDGMENT

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

AUTHOR CONTRIBUTIONS

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work. All the authors are eligible to be an author as per the international committee of medical journal editors (ICMJE) requirements/guidelines.

FUNDING

There is no funding to report.

CONFLICTS OF INTEREST

The authors report no financial or any other conflicts of interest in this work.

ETHICAL APPROVALS

This study does not involve experiments on animals or human subjects.

DATA AVAILABILITY

All data generated and analyzed are included within this research article.

PUBLISHER'S NOTE

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FUTURE PLAN OF WORK

The developed method can be applied to determine Ceftaroline Fosamil in blood, CSF, and urine samples by using this automated UPLC-MS/MS technique.

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How to cite this article:
Jabeen, Suma BV. Newly validated stability-indicating ultra-performance liquid chromatography-tandem mass spectrometry method for the estimation of Ceftaroline Fosamil by using a quadrupole mass detector. J Appl Pharm Sci, 2022; 12(06):215–223.