



Research Article

SIMULTANEOUS ESTIMATION OF IMIPENEM, CILASTATIN, AND RELEBACTUM IN PHARMACEUTICAL LYOPHILIZED POWDER FOR INJECTION BY APPLYING STABILITY INDICATING LC-PDA METHOD

*¹Gollu Gowri, ²Madhavi karimajji, ²Lekhya Gurijala, ¹Polipalli Venkata Navya, ³Sivanaga Tejaswini Naredla

¹*Department of Pharmaceutical Analysis, Raghu College of Pharmacy, Dakamarri, Visakhapatnam-531162, Andhra Pradesh, India.

²Department of Pharmaceutical Analysis, Maharajah's College of Pharmacy, Visakhapatnam, India

³Department of Pharmaceutical analysis, Chalapathi College of Pharmacy, Guntur, India

Article History: Received 9th September 2025; Accepted 13th November 2025; Published 30th November 2025

ABSTRACT

Triple combination of Imipenem, Cilastatin and Relebactam (RECARBRIO) was FDA approved in 2019 to treat various bacterial infections. For the simultaneous estimation of Imipenem, Cilastatin, and Relebactam in pharmaceutical dosage form, an accurate and precise method was established. The chromatographic separation was performed using a BDS C18 column (150x4.6mm, 5mm). At 1.0 ml/min flow rate and 248 nm detection wavelength, mobile phase containing 0.1% orthophosphoric acid and acetonitrile (60:40, v/v) was passed down the column over the run time of 4.5 min. 30°C was kept as the temperature. Cilastatin and Relebactam eluted with retention times of 2.328, 3.092, and 3.625 min., respectively. Linearity was observed with the concentration range of 12.5-75 µg/mL, 12.5-75 µg/mL and 6.25-37.5 µg/mL for, cilastatin the imipenem and relebactam respectively. The %RSD of method precision were determined to be 1.0, 1.2, and 0.5, respectively and %RSD of intermediate precision that was determined to be, respectively, 1.3, 0.7, and 1.1. Imipenem, Cilastatin, and Relebactam, respectively, showed 99.87%, 99.78%, and 99.84% recovery rates. Stability indicating nature of the method was assessed by conducting forced degradation studies and the percentage degradation of respective analytes were reported. Comparatively retention times of all respective analytes have reduced and all the three respective analytes eluted within 4 min., resulted in a simple and affordable method that can be used in routine quality control tests in pharmaceutical industries.

Keywords: Imipenem, Cilastatin, Relebactam, RP-HPLC, Forced degradation, ICH guideline.

INTRODUCTION

Imipenem is a carbapenem antibiotic that is typically given along with Cilastatin to treat different infections. Imipenem is a semisynthetic thienamycin with broad-spectrum antibacterial action against gram-positive and gram negative aerobic and anaerobic bacteria, as well as numerous multiresistant species (Buckley *et al.*, 1992; Nicolau *et al.*, 2008). Chemical name for imipenem is (5R,6S)-3-[(2S)-2-[(E-aminomethylidene) amino] ethyl] sulfanyl-6-[(1R)-1-hydroxyethyl]-7-oxoazabicyclo [3.2.0] hept-2-ene-2-carboxylic acid (Figure 1 a). Imipenem functions as an antibacterial by inhibiting the cell wall

production of certain gram-positive and gram-negative bacteria. This suppression of cell wall production in gram-negative bacteria is achieved by binding to penicillin-binding proteins (PBPs). This suppression of PBPs stops the bacterial cell from contributing to the peptidoglycan polymer that forms the bacterial cell wall, ultimately leading to cell death (Buckley *et al.*, 1992; Nicolau *et al.*, 2008). Chemical name for cilastatin is (2Z)-7-[[[(2R)-2-amino-2-carboxyethyl] sulfanyl] [(1S)-2,2-dimethylcyclopropyl] formamido-2-heptenoic acid (Figure 1b). Cilastatin, a renal dehydropeptidase inhibitor, prevents imipenem from being broken down. A number of infections are treated using a combination of both drugs. The enzyme renal

*Corresponding Author: Mrs. G. Gowri, Associate Professor, Raghu College of Pharmacy, Dakamarri, Visakhapatnam-531162, Andhra Pradesh, India. Email: gowri33rx@gmail.com.

dehydropeptidase, which is inhibited by cilastatin, facilitates the conversion of leukotriene D4 to leukotriene E4 and the metabolism of thienamycin beta-lactam antibiotics. Cilastatin is used in conjunction with imipenem to stop its metabolism since imipenem is one of these antibiotics that are hydrolyzed by dehydropeptidase (Lin *et al.*, 1989). For the treatment of bacterial infections in the respiratory, skin, bone, gynecological, urinary tract, intra-abdominal, septicemia, and endocarditis, cilastatin is appropriate in combination with imipenem, with or without relebactam (Richerson *et al.*, 1998). Chemical name for relebactam

is[(1R,2S,5R)7oxo-2-[(piperidin-4-yl)carbamoyl]-1,6-diazabicyclo[3.2.1]octan-6-yl]oxidanesulfonic acid (figure 1c). Beta-lactamase inhibitor relebactam is used to stop the breakdown of beta-lactam antibiotics, increasing their efficiency. Relebactam is a diazabicyclooctane beta-lactamase inhibitor with a piperidine ring that reduces the effort needed of bacterial cells by delivering a charge that is positive. The structure is similar to that of avibactam. To treat severe intra-abdominal infections, pyelonephritis, and UTI in adults, it

is currently available in a combination product with imipenem and cilastatin. (Papp-wallace *et al.*, 2018; Wong *et al.*, 2017; Zhanel *et al.*, 2018). Triple combination of Imipenem, Cilastatin and Relebactam (RECARBRIO) was FDA approved in 2019. Thorough literature survey revealed, RP-HPLC methods for the quantification of Imipenem, Cilastatin (Murali *et al.*, 2018; Santhosh *et al.*, 2019; Regena *et al.*, 2020; Thotla *et al.*, 2015; Meghana *et al.*, 2022) & along with its impurities (Venkatesh *et al.*, 2020), RP-HPLC method for the simultaneous quantification of Imipenem, Cilastatin and Relebactam (Krishnaphanisri *et al.*, 2021; Swapna *et al.*, 2021) an UPLC method for the determination of Imipenem and Relebactam (Meenakshi Sundari *et al.*, 2021). On keen study of reported above cited RP-HPLC methods, there are two drawbacks need to be corrected such as high retention time and high amount of organic phase, which made the method costly and time consuming. As a result, attempts were made to create a simple, cost-effective, and quick RP-HPLC technique for simultaneously quantifying Imipenem, Cilastatin, and Relebactam.

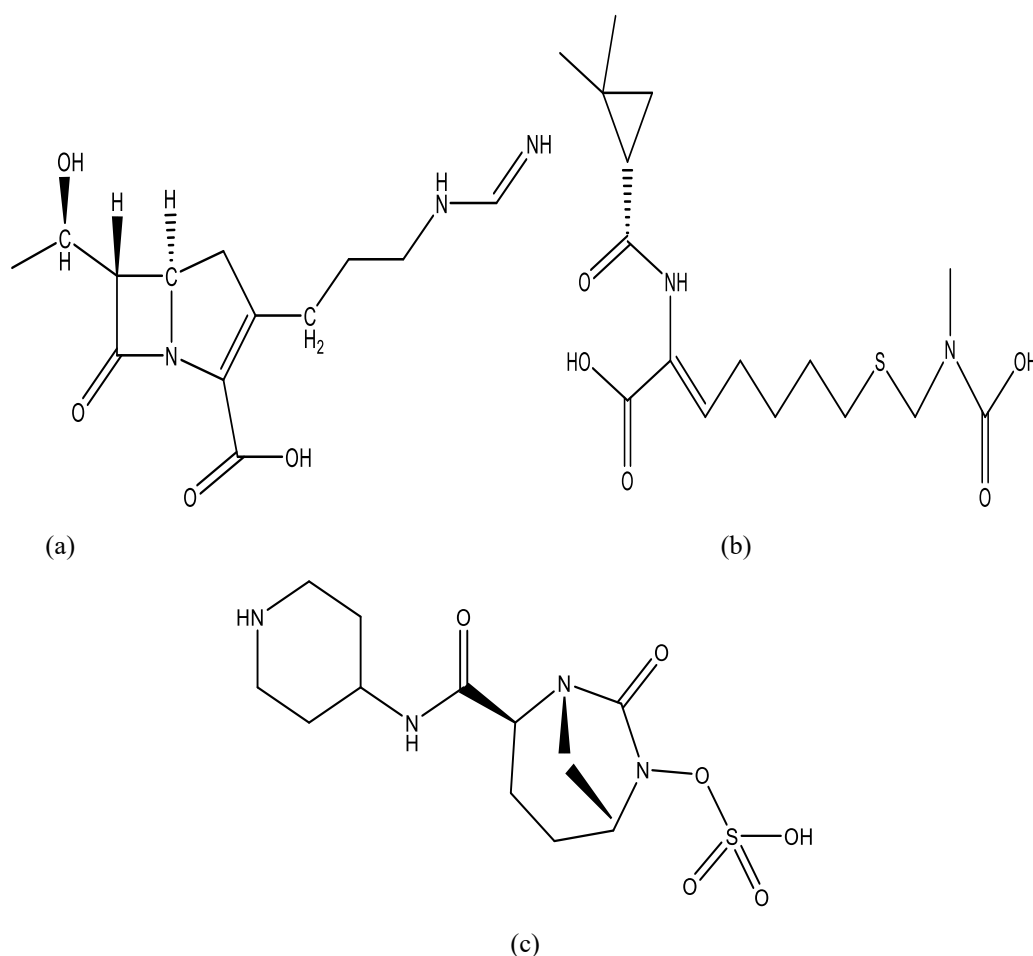


Figure 1.(a) Imipenem chemical structure, (b) Cilastatin chemical structure, (c) Relebactam chemical structure.

MATERIALS AND METHODS

Materials and techniques

Imipenem, Cilastatin, and Relebactam's active pharmaceutical ingredients were given as gift samples by Spectrum Pharma Research Solutions Pvt. Ltd. (Hyderabad, Telangana, India). Pharmaceutical dosage form (RECARBRIO; Merck Sharp and Dohme Corp) obtained from a nearby pharmacy store. All solvents utilized in this investigation are of HPLC grade and purchased from RANKEM (New Delhi, India).

Chromatographic conditions

Present analysis was performed on Waters HPLC 2695 system equipped with Quaternary pumps, a light diode array detector, and an autosampler. Empower 2 software was used for data compilation and analysis. BDS C18 column (150 x 4.6 mm, 5 μ m) with flow rate of 1 mL/min at 248nm was used for the separation. Combination of 0.1% Ortho phosphoric acid and acetonitrile (60:40 v/v), was used as mobile phase with injection volume of 10 μ L to attain resolution (>1.5) and adequate retention duration between Imipenem, Cilastatin, and Relebactum. Total run time was 5 minutes.

Buffer preparation

1mL of Orthophosphoric acid accurately pipetted in to a 1000 mL volumetric flask containing 900 mL of Milli-Q water. Finally fill the volume by adding water, results in 0.1% orthophosphoric acid.

Standard stock solution preparation

25 mg each of imipenem, cilastatin and 12.5 mg of relebactum pure standards were accurately weighed separately in to three different 50 mL clean, dry volumetric flasks. Each flask received 10 mL of diluent, and the solution was then subjected to sonication for 20 minutes. The diluent was added to make up the volume and results in solutions of 500 μ g/mL Imipenem, 500 μ g/mL cilastatin, and 250 μ g/mL Relebactum). 1 mL of each stock solution was pipetted into a 10 mL volumetric flask and make up to mark with diluent. (Imipenem 50 μ g/mL, Cilastatin 50 μ g/mL, and Relebactum 25 μ g/mL).

Preparation of sample stock solutions

5vials of recarbion (marketed dosage form) were unpacked and powder was mixed thoroughly for uniform mixing. Powder equivalent to 25 mg of Imipenem, 25 mg of Cilastatin, and 12.5 mg of Relebactum taken in 50 mL volumetric flask, dissolved with diluent and sonicated for 25 minutes. Final volume was made up to mark by adding diluent and 0.45 μ HPLC filters were used for filtering. A 10 mL volumetric flask was filled with diluent after 1 mL of the stock solution from the filtered sample was pipetted into it. (Imipenem 50 μ g/ mL, Cilastatin 5 μ g/mL, and Relebactum 25 μ g/mL) A Combination of water and acetonitrile at 50:50V/V are used as a diluent.

Method validation

In accordance with ICH (International Conference on Harmonization) standards, the optimized method was validated (Vibha *et al.*, 2012; Basant *et al.*, 2019, ICH 1996)

System suitability

To ensure System suitability of chromatographic system, six injections of standard solution of imipenem, cilastatin and relebactum were prepared and injected. Further characteristics, including resolution, peak tailing and theoretical plate count, were established for the resulting chromatograms. Relative standard deviation (%RSD) calculated from the six peak areas should not be more than 2%.

Specificity

The injection of the blank, placebo samples and test sample demonstrates the method's specificity. The retention time of analyte should not be hampered with any excipients and from any other components (degradants). Peak purity was also determined

Linearity

By making three separate series of solutions for imipenem (12.5-75 μ g/mL), cilastatin (12.5-75 μ g/mL), and relebactum (6.25-37.5 μ g/mL), the linearity of the approach was assessed. Calibration curve was plotted against concentration and obtained peak areas. Above respective series of solutions are prepared by diluting standard stock solution with diluent.

Precision

By making six replicates of sample solutions at 100% working standard concentration and administering them into the chromatographic system, the method's accuracy was demonstrated. From the obtained response, relative standard deviation of the assay was computed. Precision demonstrated on same day considered as method precision and performed on three consecutive days as intermediate precision.

Accuracy

The usual standard addition method was used to assess accuracy at three different levels: 50%, 100%, and 150%. In the pharmaceutical dose form, the percentage recoveries of imipenem, cilastatin, and relebactum were calculated.

Preparation of 50% spiked solution

1.0 mL of the standard stock solution was pipetted in to 10mL volumetric flask and 0.5 mL of a precisely weighed sample stock solution was added. Required volume of diluent was added to fill the volume before the mixture was administered into the chromatographic system.

Preparation of 100% spiked solution

1 mL of the sample stock solution, which had been precisely weighed, added to 1 mL of the standard stock solution in a 10-mL volumetric flask. The flask's remaining volume was filled by adding diluent before the solution was introduced into the chromatographic system.

Preparation of 150% spiked solution

1.5 mL of the sample stock solution was added to 1.0 mL of the standard stock solution in 10ml volumetric flask. The diluent was used to fill the flask's remaining volume before the solution introduced in to chromatographic system.

Limit of detection and limit of quantification

LOD and LOQ of respective analytes were determined based on signal to noise ratio at 3:1 and 10: 1 respectively

The LOD sample preparation

Three separate 10 mL volumetric flasks were filled with 0.25 mL each standard stock solution separately and made up to mark with diluent. From those solutions, 0.1ml from each flask was transferred into 10ml volumetric flask and required diluent was added to fill the remaining volume.

The LOQ sample preparation

Three separate 10 mL volumetric flasks were filled with 0.25 mL each standard stock solution separately and made up to mark with diluent. From those solutions, 0.3ml from each flask was transferred into 10ml volumetric flask and required diluent was added to fill the remaining volume.

Method robustness

By making intentional, minor modifications to the chromatographic parameters such as flow rate (± 0.2 mL/min), organic solvent in mobile phase (± 10 mL), column temperature (5%, or 27 C to +33 C), organic mobile phase ratio (10%), and optimized procedure, the robustness of the new method was assessed. The parameters for system suitability, assay, % SD were determined and should be within acceptable bounds.

Forced degradation studies

Oxidation

Each 1 mL stock solution of Imipenem, cilastatin, and relebactam were taken in 10ml volumetric flask with 1 mL of 20% hydrogen peroxide (H_2O_2). The solutions were held at 60°C for 30 min., and diluted to obtain 50 μ g/mL, 50 μ g/mL, and 25 μ g/mL of Imipenem, cilastatin, and relebactam. Resulting solution was administered and chromatograms were recorded.

Acid degradation studies

Each 1 mL stock solution of Imipenem, cilastatin, and relebactam were taken in 10ml volumetric flask with 1 mL

of 2N HCl. The solutions were refluxed at 60°C for 30 min. and diluted to obtain 50 μ g/mL, 50 μ g/mL, and 25 μ g/mL of Imipenem, cilastatin, and relebactam. Resulting solution was administered and chromatograms were recorded

Alkali degradation studies

1 mL of 2 N NaOH was pipetted to 10 mL volumetric flask containing each 1ml stock solution of imipenem, cilastatin, and relebactam, and refluxed for 30 min. at 60° C. Further solutions are diluted to 50 μ g/mL, 50 μ g/mL, and 25 μ g/mL for the HPLC investigation. Each of these solutions was fed into the system, and the chromatograms were recorded.

Dry heat degradation studies

To assess dry heat degradation, the sample powder equivalent to 25 mg of Imipenem, 25 mg of Cilastatin, and 12.5 mg of Relebactam was heated to 105°C for six hours in oven. The resulting solution was diluted to create solutions containing 50, 50, and 25 μ g/mL for the HPLC investigation. Each of these solutions was fed into the system, and the chromatograms were recorded to determine the sample's stability.

Photochemical stability studies

To assess the photochemical stability stock solution containing 500 μ g/mL Imipenem, 500 μ g/mL Cilastatin, and 250 μ g/mL Relebactam was placed in a photostability chamber (200-watt hours/m²). Resulting solution was diluted to get 50 μ g/mL, Imipenem, 50 μ g/mL Cilastatin, and 25 μ g/mL of 250 μ g/mL. Resulting solution was administered to the system, and the resulting chromatograms were integrated to determine the sample's stability.

RESULTS AND DISCUSSION

Creating a sensitive and economical RP-HPLC method for the concurrent measurement of imipenem, cilastatin, and relebactam in the marketed dosage form was the main goal of this work. Based on the solubility studies of three respective drugs, combination of water and acetonitrile at 1:1 ratio with respect to the pKa of the three respective drugs, various mobile phases including acetonitrile and potassium dihydrogen phosphate [KH_2PO_4] buffer, methanol and ortho phosphoric acid (OPA) buffer, and acetonitrile and OPA buffer were attempted. However, system suitability parameters such as tailing factor and theoretical plates for the first two combinations were unsatisfactory. So, 0.1% ortho-phosphoric acid (OPA) and acetonitrile at 80:20 v/v, 75:25 v/v and 70:30 v/v were tried. However, resolution was not satisfactory. Finally, all three respective drugs are eluted with satisfied resolution and theoretical plates using 0.1% ortho-phosphoric acid (OPA) and acetonitrile (60:40 v/v) as mobile phase on BDS C₁₈ (150 X 4.6 mm, 5 μ m) column at 248 nm, with run time of 5 min (Figure 2).

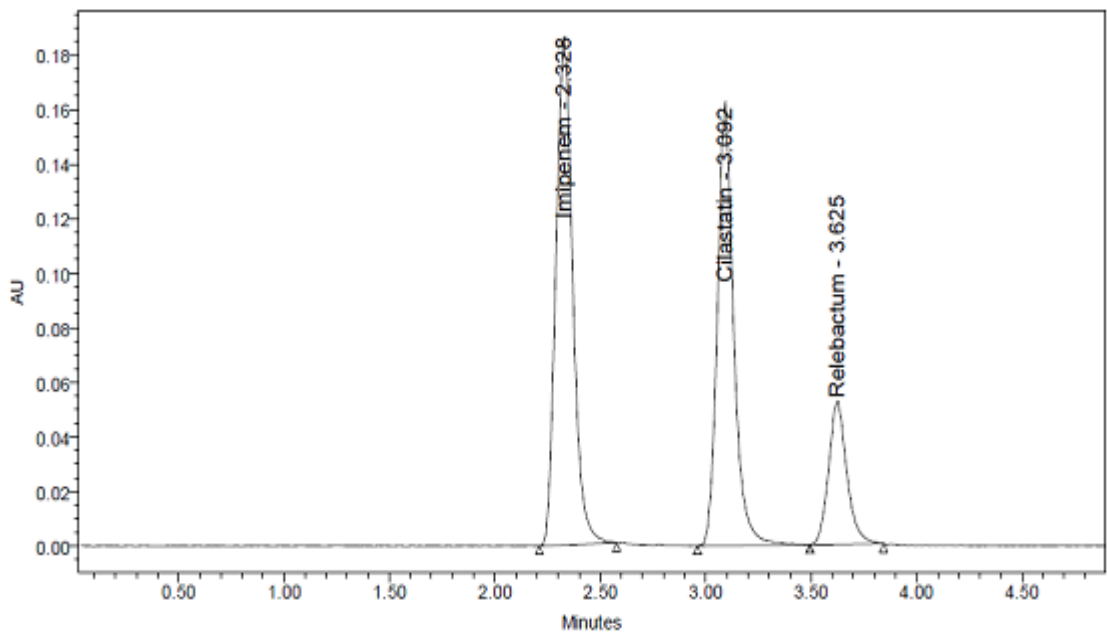


Figure 2. Optimized chromatogram of relebactam, cilastatin, and imipenem.

Table 1. Optimized chromatographic conditions with system suitability parameters for Cilastatin, Relebactam, and Imipenem.

Parameter		Value		
Column		Waters BDS C18 X-bridge phenyl (150x4.6mm, 5.6µm particle size) column.		
Mobile phase		Acetonitrile and Ortho phosphoric acid (0.1%v/v) (40:60, v/v)		
Elution mode		Isocratic		
Detection wavelength		248nm		
Column temperature		25°C		
Volume of injection		10µL		
Run time		5 min.		
Flow rate		1mL/min.		
	Retention time(min.)	Resolution	Theoretical plates	Tailing factor
Imipenem	2.32	-	3307	1.19
Cilastatin	3.09	4.9	6485	1.14
Relebactam	3.62	3.4	6986	1.11

Prior to performing the validation, the system suitability test was conducted by preparing and injecting 6 replicates of standard solution of imipenem, cilastatin and relebactam. The retention times for imipenem, cilastatin, and relebactam were 2.328, 3.092, and 3.625 min, respectively. All system suitability parameters including plate count, theoretical plates and tailing factor were found to be within acceptable limits (table 1). To ensure method the method acceptability, the optimized method was validated as per ICH guidelines. It was determined that the linearity ranges for the imipenem, cilastatin and relebactam were 12.5-75 µg/mL, 12.5-75 µg/mL and 6.25-37.5 µg/mL respectively. The following linear regression equations were used to describe them: y (imipenem) = 22000x + 2627 (r^2 = 0.999), y (cilastatin) = 19605x + 7344 (r^2 = 0.999), and y

(relebactam) = 9627x + 1261 (r^2 = 0.999). The least-squares method was used to build the regression line, and the results showed that imipenem, cilastatin, and relebactam were showed linearity at the respective concentration ranges with correlation coefficients (r^2) of 0.999. Calibration curves were depicted in figure 3. Six samples of working concentration were prepared in order to assess the method's accuracy. %RSD of imipenem, cilastatin, and relebactam were 1.3%, 0.7%, and 1.1% for, respectively. In a similar manner, intermediate precision was assessed by repeating same procedure in three consecutive days. % RSD were computed after calculating average peak area and standard deviation (SD), and the results were 1.0%, 1.2%, and 0.5%, respectively (Table 2).

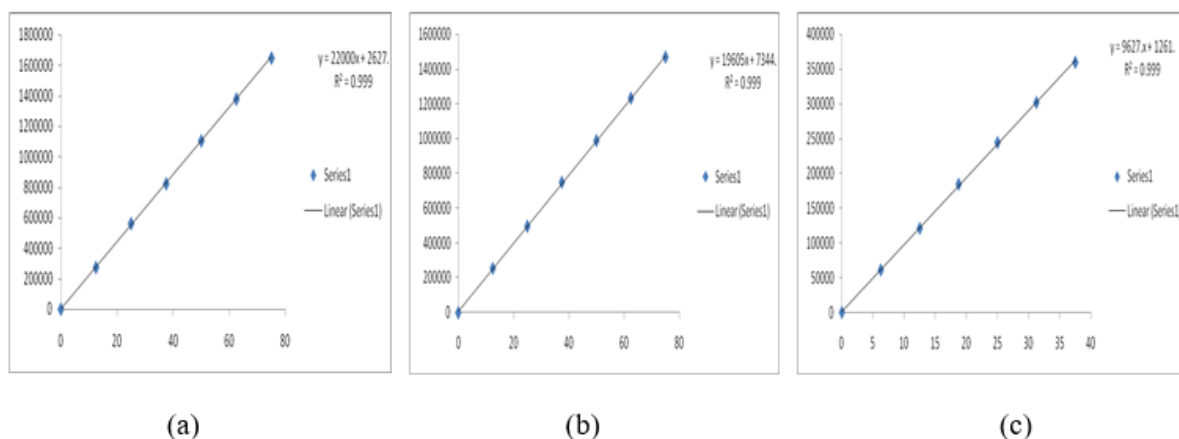


Figure 3. Calibration curves of Imipenem, Cilastatin, and Relebactam.

Table 2. Precision results of imipenem, cilastatin, and relebactam.

Method precision			Intermediate precision		
Imipenem	Cilastatin	Relebactam	Imipenem	Cilastatin Peak	Relebactam
Peak area*, ± SD,	Peak area*, ±	Peak area*, ±	Peak area*, ± SD,	area*, ± SD, %	Peak area*, ±
% RSD	SD, % RSD	SD, % RSD	% RSD	RSD	SD, % RSD
1101642±14109.7,	984190±6932.2,	363256±3863.3,	1092458±10485.8,	981466±11718.1,	361242±1974.3,
1.3	0.7	1.1	1.0	1.2	0.5

* Mean of six determinations

Accuracy of the method was assessed by standard addition method. Percentage recoveries of Imipenem, Cilastatin, and Relebactam were, 99.87%, 99.78%, and 99.84% respectively. The outcomes of the recovery studies conclusively show that the suggested method is accurate and results were shown in table 3. For imipenem, cilastatin, and relebactam, the LOD and LOQ values were 0.32 and 0.96 g/mL, 0.31 and 0.95 g/mL, and 0.15 and 0.44 g/ mL, respectively. Through the analysis of the sample and the reference imipenem, cilastatin, and relebactam solution, the proposed method's robustness was shown to have a nonsignificant variation (Table 4). Results were collected and then compared to those of the optimal method, which revealed that the deliberate modifications in the parameters had no appreciable impact on system suitability parameters. Optimized method applied to quantify the amount of three analytes in marketed formulation (RECARBRIO-Imipenem

500 mg, cilastatin 500 mg, and relebactam 250 mg). The aforementioned formulation was used to conduct the experiment. Purity percentage of Imipenem, cilastatin, and relebactam were 100.59%, 99.37%, and 99.86%, respectively (Table 5). The amount of degradation for imipenem, cilastatin, and relebactam were all within the acceptable ranges according to forced degradation studies. Significant degradation was observed for imipenem, cilastatin, and relebactam in the presence of acid, alkali, peroxide, and heat (Table 6). Peak purity test findings from the photodiode-array detector in the degradation investigations showed that the imipenem, cilastatin, and relebactam peaks were uniform and pure in all the examined stress samples observed. Under forced photolytic and neutral degradations, imipenem, cilastatin, and relebactam remained stable.

Table 3. Accuracy data for cilastatin, relebactam, and imipenem.

Name of the drug	Level%	Recovered amount	Mean recovery, %	Average
Imipenem	50	24.809	99.24	99.69
	100	49.946	99.89	
	150	74.973	99.96	
	50	24.904	99.61	
Cilastatin	100	49.787	99.57	99.45

	150	74.393	99.19	
	50	12.375	99.00	
Relebactum	100	24.789	99.16	99.15
	150	37.241	99.31	

Table 4. Robustness data for Imipenem, Cilastatin and Relebactum.

S. No	Condition	%RSD of Imipenem.	%RSD of Cilastatin	%RSD of Relebactum
1	Flow rate (-) 0.9ml/min	0.7	1.0	1.0
2	Flow rate (+) 1.1ml/min	1.5	0.4	1.3
3	Mobile phase (-) 65B:35A	1.0	0.3	1.1
4	Mobile phase (+) 55B:45A	1.9	0.5	0.6
5	Temperature (-) 27°C	1.1	0.5	1.4
6	Temperature (+) 37°C	0.5	0.7	0.2

Table 5. Assay results for Imipenem, cilastatin, and relebactam.

	Imipenem	Cilastatin	Relebactum
Assay*	100.59	99.37	99.86
Standard deviation	1.288	0.70	1.062
% RSD	1.3	0.7	1.1

*Mean of three determinations

Table 6. Forced degradation results for Imipenem, cilastatin, and relebactam.

S. No	Degradation parameter	Imipenem	Cilastatin	Relebactum
			% Degradation	
1	Acid	4.94	4.83	4.83
2	Alkali	4.51	4.42	4.28
3	Oxidation	5.64	6.07	5.98
4	Thermal	2.76	2.39	2.62
5	UV	1.47	1.70	1.08

In this research work, the development of an RP-HPLC stability-indicating method for the simultaneous estimation of Imipenem, Cilastatin, and Relebactam is meticulously validated to ensure its reliability and robustness. To design a simple, robust, and quick chromatographic process, several mobile phase combinations are studied. The selected column and mobile phase produced the best results, with well-defined peaks. To illustrate the validity of the devised approach, different characteristics such as linearity, precision, accuracy, robustness, system adaptability, specificity, and sensitivity were tested, and the statistical findings were within acceptable bounds. To investigate the method's stability indicating property, the dosage form was subjected to a variety of stress settings, and the degradation of all three medications was measured under stress. Optimized RP-HPLC method is more rapid, and economical when compared with reported RP-HPLC methods in literature as all the three analytes eluted within 4 min. As a result, our devised procedure is simple, inexpensive, and quick enough to be employed on a regular basis in a quality control laboratory.

CONCLUSION

A novel, simple, accurate, rapid, and exact HPLC method was developed and validated for simultaneously

quantifying imipenem, cilastatin, and relebactam in pharmaceutical dose form. As a result, this approach may be utilized in drug testing laboratories and the pharmaceutical sector to calculate imipenem, cilastatin, and relebactam.

ACKNOWLEDGMENT

The authors express sincere thanks to the head of the Department of Pharmaceutical Analysis, Raghu College of Pharmacy, Dakamarri, Visakhapatnam-531162, Andhra Pradesh, India for the facilities provided to carry out this research work.

CONFLICT OF INTERESTS

The authors declare no conflict of interest

ETHICS APPROVAL

Not applicable

FUNDING

This study received no specific funding from public, commercial, or not-for-profit funding agencies.

AI TOOL DECLARATION

The authors declares that no AI and related tools are used to write the scientific content of this manuscript.

DATA AVAILABILITY

Data will be available on request

REFERENCES

- Basant, L., Devesh, K., & Manish, J. (2019). A review on analytical method validation and its regulatory perspectives. *Journal of Drug Delivery and Therapeutics*, 9, 501–506. <https://doi.org/10.22270/jddt.v9i2.2403>
- Buckley, M. M., Brogden, R. N., Barradell, L. B., & Goa, K. L. (1992). Imipenem/cilastatin: A reappraisal of its antibacterial activity, pharmacokinetic properties and therapeutic efficacy. *Drugs*, 44(3), 408–444.
- ICH. (1996). *Validation of analytical procedures: Text and methodology*. International Conference on Harmonization.
- Krishnaphanisri, P., & Sunitha, K. (2021). Novel RP-HPLC-PDA approach for efficient simultaneous quantification of imipenem, cilastatin and relebactam in bulk drug and injection dose forms. *Asian Journal of Chemistry*, 33(4), 897–902.
- Lin, J. H., Chen, I. W., & Ulm, E. H. (1989). Dose-dependent kinetics of cilastatin in laboratory animals. *Drug Metabolism and Disposition*, 17(4), 426–432.
- Meghana, C. H., Rashmitha, P., Bhargavi, B., & Lalitha, M. C. H. (2022). The analytical method development and validation for the simultaneous estimation of imipenem and cilastatin by using RP-HPLC. *Indo American Journal of Pharmaceutical Sciences*, 9(4).
- Meenakshi Sundari, M., Lalitha, R., & Shruthi Teja, K. (2021). Method development and validation for the simultaneous estimation of imipenem and relebactam in bulk and pharmaceutical dosage form by UPLC. *International Journal of Advance Research and Innovative Ideas in Education*, 7(3), 2395–4396.
- Murali, D., & Purnachandra Rao, G. (2018). Stability indicating RP-HPLC method for the simultaneous estimation of imipenem and cilastatin in injection formulation. *World Journal of Pharmaceutical Sciences and Research*, 8(1), 898–913.
- Nicolau, D. P. (2008). Carbapenems: A potent class of antibiotics. *Expert Opinion on Pharmacotherapy*, 9(1), 23–37.
- Papp-Wallace, K. M., Barnes, M. D., Alsop, J., Taracila, M. A., Bethel, C. R., Becka, S. A., Van Duin, D., Kreiswirth, B. N., Kaye, K. S., & Bonomo, R. A. (2018). Relebactam is a potent inhibitor of the KPC-2 beta-lactamase and restores imipenem susceptibility in KPC-producing Enterobacteriaceae. *Antimicrobial Agents and Chemotherapy*, 62(6), Article e00174-18. <https://doi.org/10.1128/AAC.00174-18>.
- Richerson, M. A., Ambrose, P. G., Quintiliani, R., & Nightingale, C. H. (1998). Formulary review of the carbapenems: Comparison of imipenem/cilastatin and meropenem. *Connecticut Medicine*, 62(3), 165–169.
- Regena Angel, G. (2020). The analytical method development and validation for the simultaneous estimation of imipenem and cilastatin by using RP-HPLC. *International Institute of Justice & Police Sciences*, 7(5), 831–855.
- Santhosh, I., Pravlika, G., & Ashok Reddy, P. (2019). A new simple analytical development and validation of imipenem and cilastatin by simultaneous estimation of pharmaceutical dosage form by RP-HPLC. *International Journal of Pharma and Bio Sciences*, 9(3), 694–703.
- Swapna, K., Deepthi, K., & Padmini, T. A. (2021). RP-HPLC method development and validation for simultaneous estimation of imipenem, cilastatin and relebactam in API and pharmaceutical lyophilized powder for injection. *Research Journal of Pharmacy and Therapeutics*, 14(2), 925–930.
- Thotla, S., Vasanthi, R., Alagar Raja, M., Rao, K. N. V., & Banji, D. (2015). A novel method for the simultaneous estimation of imipenem and cilastatin by using RP-HPLC in its bulk and pharmaceutical dosage form. *International Journal of Medicine and Pharmaceutical Research*, 3(4), 1133–1138.
- Venkatesh, K., & Krishna Mohan, G. V. (2020). Simultaneous determination of imipenem and cilastatin impurities in combination product of imipenem and cilastatin injection by RP-HPLC. *Journal of Chemical and Pharmaceutical Research*, 12(12), 35–47.
- Vibha, G., Ajay Deep Kumar, J., Gill, N. S., & Kapil. (2012). Development and validation of HPLC method. *International Research Journal of Pharmaceutical and Applied Sciences*, 2(4).
- Wong, D., & van Duin, D. (2017). Novel beta-lactamase inhibitors: Unlocking their potential in therapy. *Drugs*, 77(6), 615–628. <https://doi.org/10.1007/s40265-017-0725-1>.
- Zhanel, G. G. (2018). Imipenem-relebactam and meropenem-vaborbactam: Two novel carbapenem-beta-lactamase inhibitor combinations. *Drugs*, 78(1), 65–98. <https://doi.org/10.1007/s40265-017-0851-9>.