World Journal of Pharmaceutical Sciences
ISSN (Print): 2321-3310; ISSN (Online): 2321-3086
Available online at: https://wjpsonline.com/
Research Article

SIMULTANEOUS ESTIMATION OF THE SULBACTAM AND DURLOBACTAM IN BULK AND TABLET DOSAGE FORM BY RP-HPLC

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Received: 22-01-2025 / Revised Accepted: 27-01-2025 / Published: 03-02-2025

ABSTRACT:

A simple, Accurate, precise method was developed for the simultaneous estimation of the Sulbactam and Durlobactam in bulk and Tablet dosage form. Chromatogram was run through phenomenexC18 250 x 4.6 mm, 5m. Mobile phase containing Buffer 0.1% OPA: Acetonotrile taken in the ratio 60:40 was pumped through column at a flow rate of 1 ml/min. Buffer used in this method was 0.1% OPA. Temperature was maintained at 30°C. Optimized wavelength selected was 270 nm. Retention of Sulbactam and Durlobactam were eluted at 2.206 min and 2.871 min. %RSD of the Sulbactam and Durlobactam were and found to be 0.8 and 0.9 respectively. %Recovery was obtained as 100.35% and 100.70% for Sulbactam and Durlobactam respectively. LOD, LOQ values obtained from regression equations of Sulbactam and Durlobactam were 0.63, 1.90 and 0.11, 0.34 respectively. Regression equation of Sulbactam is y = 15617x + 4696.6, and y = 18901x + 2971 of Durlobactam. Retention times were decreased and that run time was decreased, so the method developed was simple and economical that can be adopted in regular Quality control test in Industries.

Key Words: Sulbactam, Durlobactam, RP-HPLC

INTRODUCTION

Bacterial infections are any illness or condition caused by bacterial growth or poisons (toxins). You can get sick from getting harmful bacteria in your skin, gut (GI tract), lungs, heart, brain, blood or anywhere else in your body. Harmful bacteria from the environment, an infected person or animal, a bug bite or something contaminated (like food, water or surfaces) can cause infections. Bacteria that's not normally harmful but that gets into a place in your body where it shouldn't be can also cause infections.[1]

The risk of getting a bacterial infection increases when you are in contact with flood water. Flood water can come from storms or cyclones. Touching items affected by flooding can also increase your risk of bacterial infection. You should avoid contact with flood water and practice good hand hygiene. Wash your hands with soap and clean water. If clean water isn't available, use hand sanitiser.[2]

Localized Symptoms:[3]

Pain: This is common with bacterial infections. You can experience skin pain with a bacterial infection on the skin. A lung infection can cause pain when breathing, and you can feel abdominal (stomach) pain with an intestinal (or bowel) infection.

Skin Rash: Bacterial skin infections, such as impetigo, erythrasma, folliculitis, and methicillin-resistant Staphylococcus aureus (MRSA), can cause a red, itchy, and painful skin rash.

Swelling and redness: You may notice redness or swelling on parts of the body that you can see, such as the skin, throat, or ears.

Problems with organ function: Internal organs can become inflamed and swollen. While you can't see it, you may feel pain or other effects in these areas. For example, pyelonephritis (a kidney infection) could worsen kidney function

Some bacterial infections are:[1]

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How to Cite this Article: Shaik Fahima, Simultaneous Estimation of The Sulbactam and Durlobactam In Bulk And Tablet Dosage Form By RP-HPLC. World J Pharm Sci 2025; 13(01): 69-76; https://doi.org/10.54037/WJPS.2022.100905

1. Food poisoning (gastroenteritis).
2. Some skin, ear or sinus infections.
3. Some sexually transmitted infections (STIs).
4. Bacterial pneumonia.
5. Most urinary tract infections (UTIs).

Sulbactam Durlobactam medication is used to treat certain bacterial infections. This product contains 2 medications: sulbactam and durlobactam. Sulbactam is an antibiotic that works by stopping the growth of bacteria. Durlobactam is an enzyme inhibitor (beta-lactamase inhibitor) that helps sulbactam work better.[4]

In May 2023, sulbactam/durlobactam was approved in the USA for use in patients 18 years of age and older for the treatment of hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia (HABP/VABP) caused by susceptible isolates of Acinetobacter baumannii-calcoaceticus complex (ABC).[5]

Hospital-acquired bacterial pneumonia (HABP) and ventilator-associated bacterial pneumonia (VABP) can be caused by a wide variety of bacteria that originate from the patient flora or the health care environment.[6]

Sulbactam is a beta (β)-lactamase inhibitor and a derivative of the basic penicillin nucleus. When given in combination with β-lactam antibiotics, sulbactam produces a synergistic effect as it blocks the enzyme responsible for drug resistance by hydrolyzing β-lactams.[7]

Durlobactam is a diazabicyclooctane non-beta-lactam, beta-lactamase inhibitor. It is typically given in combination with sulbactam to protect it from degradation by certain serine-beta-lactamases.[8]

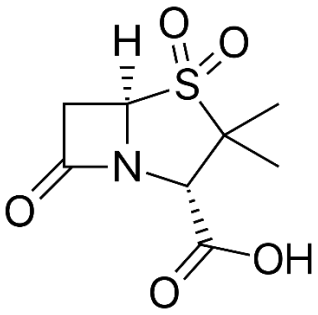

Figure.1: Structure of Salbactum

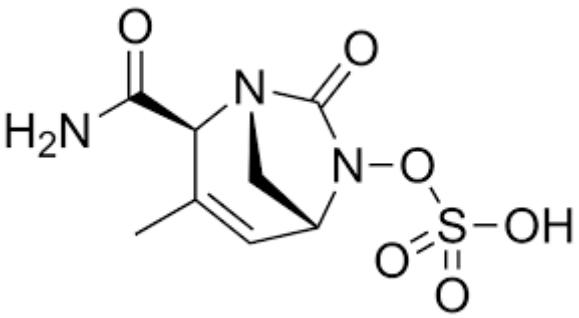

Figure.2: Structure of Durlobactum

Materials and Methods: Sulbactam and Durlobactam pure drugs (API), Combination Sulbactam and Durlobactam tablets (Xacduro), Distilled water, Acetonitrile, Phosphate buffer, , Methanol, Potassium dihydrogen ortho phosphate buffer, Ortho-phosphoric acid. All the above chemicals and solvents are from Rankem.

Instrumentation: The development and method validation were conducted using a WATERS HPLC 2695 SYSTEM equipped with quaternary pumps, Photo Diode Array detector and Auto sampler integrated with Empower 2 Software.

Objective: In order to fulfill ICH standards, we need to design and test an HPLC technique that can detect Sulbactam and Durlobactam in pharmaceutical formulations at the same time.

Table:1 Chromatographic Conditions

Mobile phase	**60% 0.1% OPA: 40% Acetonitrile**
Flow rate	1.0 ml/min
Column	Phenomenex C18 (4.6 x 250mm, 5µm)
Detector wave length	270nm
Column temperature	30°C
Injection volume	10µL
Run time	10.0 min

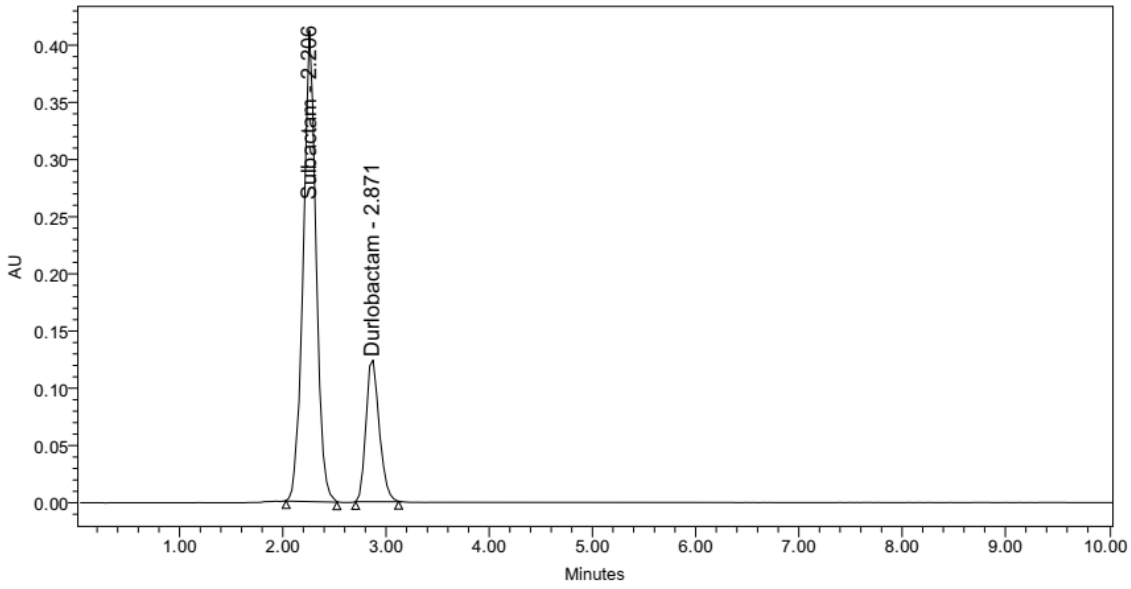

Figure.3: Optimized Chromatogram

Preparation of Standard stock solutions: Accurately weighed 10mg of Sulbactam, 5mg of Durlobactam and transferred to 10ml flasks and 3/4 th of diluents was added to these flask and sonicated for 10 minutes. Flask were made up with diluents and labeled as Standard stock solution. (1000µg/ml of Sulbactam and 500µg/ml **Durlobactam).**

Preparation of Sample stock solutions: 5 tablets were weighed and the average weight of each tablet was calculated, then the weight equivalent to 1 tablet was transferred into a 500ml volumetric flask, 5 ml of diluents was added and sonicated for 25 min, further the volume was made up with diluent and filtered by HPLC filters (2000µg/ml of Sulbactam and 1000µg/ml of Durlobactam).

System suitability parameters: The system suitability parameters were determined by preparing standard solutions of Sulbactam (100ppm) and Durlobactam (50ppm) and the solutions were injected six times and the parameters like peak tailing, resolution and USP plate count were determined. The % RSD for the area of six standard injections results should be not more than 2%.

Specificity: Checking of the interference in the optimized method. We should not find interfering peaks in blank and placebo at retention times of these drugs in this method. So this method was said to be specific.

Table:2 System suitability results

S no	Sulbactam			Durlobactam			
Inj	RT(min)	USP Plate Count	Tailing	RT(min)	USP Plate Count	Tailing	Resolution
1	2.208	7732	1.28	2.869	9400	1.2	6
2	2.212	7852	1.28	2.873	9980	1.19	5.8
3	2.214	7158	1.24	2.874	10319	1.19	5.8
4	2.214	7132	1.28	2.876	11105	1.18	5.9
5	2.224	7728	1.21	2.914	9808	1.21	6.3
6	2.279	7216	1.3	2.988	9587	1.21	6

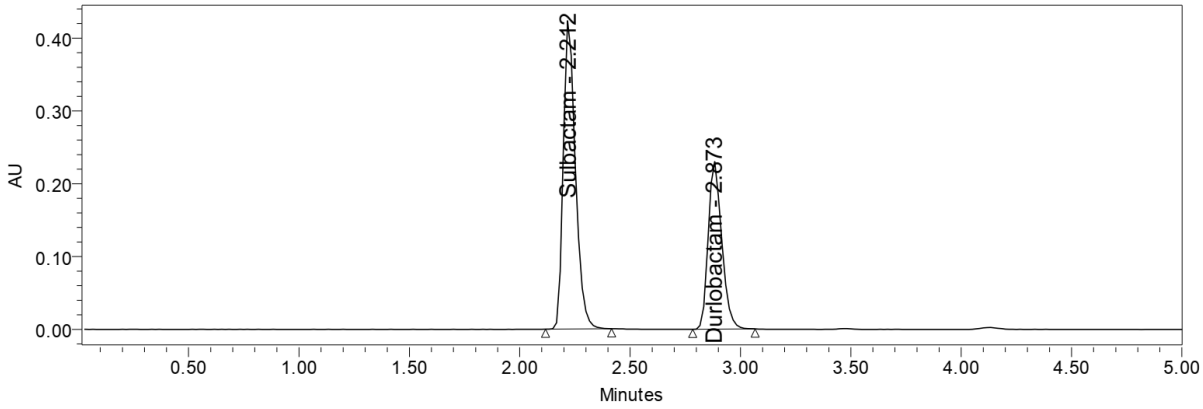

Figure.4: system suitability Chromatogram

Table:3 Specificity data

Sample name	Retention time(mins)
Sulbactam	2.206
Durlobactam	2.871

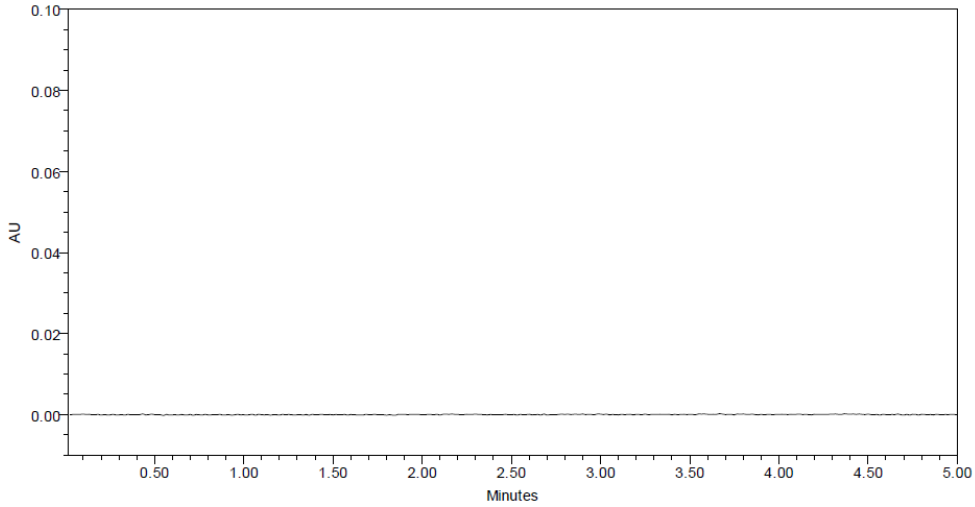

Figure.5 Blank

Linearity:

Calibration data is given in table and regression data in table 4 and calibration curve in figure 6 and 7

Table:4 Calibration data of Sulbactam and Durlobactam

Sulbactam		Durlobactam	
Conc (µg/mL)	**Peak area**	**Conc (µg/mL)**	**Peak area**
0	0	0	0
25	402410	12.5	241770
50	786734	25	474925
75	1165461	37.5	706333
100	1575220	50	956078
125	1957570	62.5	1192093
150	2344330	75	1411241

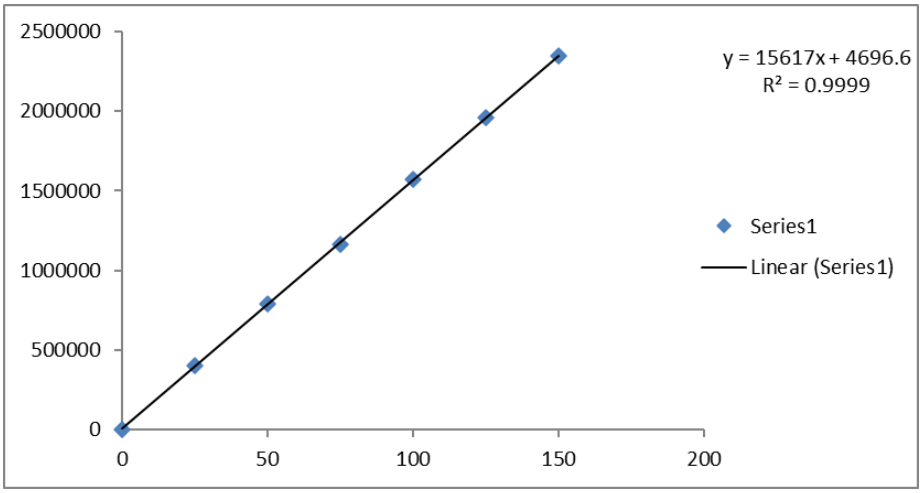

Figure.6: Calibration curve of Sulbactam

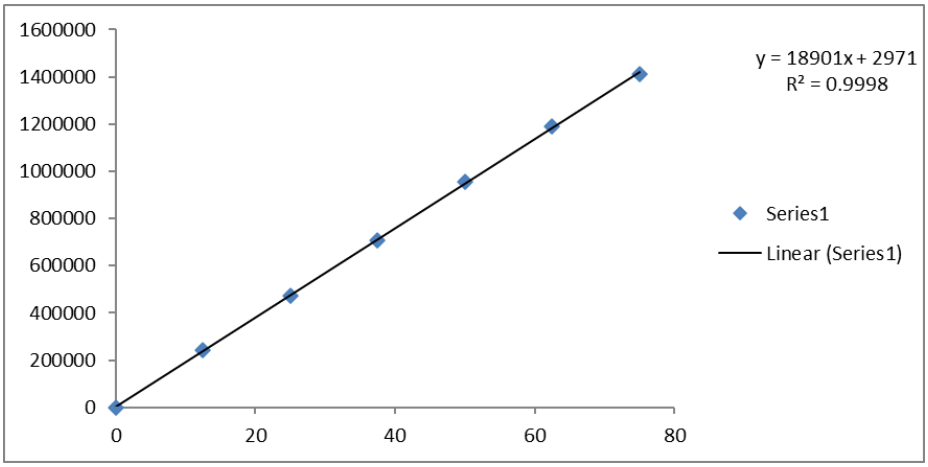

Figure.7: Calibration curve of Durlobactam

Accuracy:
Recovery data shown in table

Table:5 recovery data of Sulbactam and Durlobactam

	Sulbactam			Durlobactam		
% Level	**Amount Spiked (µg/mL)**	**Amount recovered (µg/mL)**	**% Recovery**	**Amount Spiked (µg/mL)**	**Amount recovered (µg/mL)**	**% Recovery**
50%	50	50.994	101.99	25	24.54209	98.17
	50	49.441	98.88	2	25.26216	101.05
	50	50.319	100.64	25	25.1974	100.79
100%	100	100.958	100.96	50	50.97101	101.94
	100	99.591	99.59	50	50.62367	101.25
	100	100.467	100.47	50	50.80837	101.62
150%	150	149.223	99.48	75	76.18322	101.58
	150	151.749	101.17	75	74.81758	99.76
	150	149.977	99.98	75	75.11063	100.15
% Recovery	**100.35%**			**100.70%**		

System precision was performed and the data was shown in table

Table:6 System precision of Sulbactam and Durlobactam

S. No	Area of Sulbactam	Area of Durlobactam
1.	1615103	977378
2.	1624387	985152
3.	1600006	970599
4.	1601721	971171
5.	1600097	963379
6.	1631506	983380
Mean	**1611543**	**975177**
S.D	**13672.1**	**8340.7**
%RSD	**0.8**	**0.9**

The % RSD for the peak areas of Sulbactam and Durlobactam obtained from six replicate injections of standard solution was within the limit.

Method Precision: The precision of the method was determined by analyzing a sample of Sulbactam and Durlobactam and shown in table

Table: method Precision

S. No	Area of Sulbactam	Area of Durlobactam
1.	1629420	992058
2.	1626262	984877
3.	1636635	986859
4.	1635464	990697
5.	1630581	983667
6.	1609817	976901
Mean	**1628030**	**985843**
S.D	**9722.0**	**5456.1**
%RSD	**0.6**	**0.6**

From the above results, the % RSD of method precision study was within the limit for Sulbactam and Durlobactam.

Robustness: Robustness conditions like Flow minus (0.9ml/min), Flow plus (1.1ml/min), mobile phase minus (65B:35A), mobile phase plus (55B:45A), temperature minus (25°C) and temperature plus(35°C) was maintained and samples were injected in duplicate manner. System suitability parameters were not much affected and all the parameters were passed. %RSD was within the limit.

Table:7 Robustness data for Gemcitabine and Paclitaxel.

S.no	Condition	%RSD of Sulbactam	%RSD of Durlobactam
1	**Flow rate (-) 0.9ml/min**	0.3	0.3
2	**Flow rate (+) 1.1ml/min**	0.8	0.6
3	**Mobile phase (-) 65B:35A**	0.2	0.2
4	**Mobile phase (+) 55B:45A**	0.4	0.4
5	**Temperature (-) 25°C**	0.4	0.4
6	**Temperature (+) 35°C**	1.2	1.3

Force Degradation Studies: table shows degradation conditions and the obtained degraded data and purity plot chromatogram.

Table:8 degradation conditions

Stress condition	Solvent	Temp(^{0}C)	Exposed time
Acid	2N HCL	60^0c	30 mins
Base	2N NAOH	60^0c	30 mins
Oxdation	20% H_2O_2	60^0c	30 mins
Thermal	Diluent	105^0c	6 hours
Photolytic	Diluent	-	-
Hydrolytic	Water	60^0c	

Table:9 degradation data

Type of degradation	Sulbactam			Durlobactam		
	Area	%Recovered	% Degraded	Area	%Recovered	% Degraded
Acid	1539445	95.30	4.70	931267	95.12	4.88
Base	1541514	95.43	4.57	933054	95.30	4.70
Peroxide	1530109	94.72	5.28	919870	93.95	6.05
Thermal	1578882	97.74	2.26	953392	97.38	2.62
Uv	1592287	98.57	1.43	962283	98.28	1.72
Water	1602600	99.21	0.79	969983	99.07	0.93

Assay:

Table:10 assay data

	Sulbactam			Durlobactam		
S.no	**Std Area**	**Sample area**	**% Assay**	**Std Area**	**Sample area**	**% Assay**
1	1615103	1629420	100.91	977378	992058	101.32
2	1624387	1626262	100.71	985152	984877	100.59
3	1600006	1636635	101.35	970599	986859	100.79
4	1601721	1635464	101.28	971171	990697	101.19
5	1600097	1630581	100.98	963379	983667	100.47
6	1631506	1609817	99.69	983380	976901	99.78
Avg	**1611543**	**1628030**	**100.82**	**975177**	**985843**	**100.69**
Stdev	**13672.1**	**9722.0**	**0.602**	**8340.7**	**5456.1**	**0.56**
%RSD	**0.8**	**0.6**	**0.6**	**0.9**	**0.6**	**0.6**

Assay was calculated by the formula:

$$\%\ \text{Assay} = \frac{AT}{AS} \times \frac{WS}{100} \times \frac{1}{10} \times \frac{100}{1} \times \frac{10}{1} \times \frac{P}{100} \times \frac{FV}{L.C} \times 100$$

AT	Average Peak area of sample in test solution
AS	Mean peak area of sample in standard solution
WS	Weight of drug working standard taken in mg
P	Assay of drug working standard in % on dried basis
L.C	Label Claim

Figure.8: formula

CONCLUSION:

A simple, Accurate, precise method was developed for the simultaneous estimation of the Sulbactam and Durlobactam in bulk and Tablet dosage form. Retention of Sulbactam and Durlobactam were eluted at 2.206 min and 2.871 min. %RSD of the Sulbactam and Durlobactam were and found to be 0.8 and 0.9 respectively. %Recovery was obtained as 100.35% and 100.70% for Sulbactam and Durlobactam respectively. LOD, LOQ values obtained from regression equations of Sulbactam and Durlobactam were 0.63, 1.90 and 0.11, 0.34 respectively. Regression equation of Sulbactam is y = 15617x + 4696.6, and y = 18901x + 2971 of Durlobactam. Retention times were decreased and that run time was decreased, so the method developed was simple and economical that can be adopted in regular Quality control test in Industries.

ACKNOWLEDGEMENT:

The authors are thankful to Department of Pharmaceutical Analysis, Safa College of Pharmacy, Kurnool and Spectrum Pharma Research Solutions, Hyderabad, Telangana, India

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