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**Research Article**

# Simultaneous Detection and Quantification of 12 Residual Solvents in avermectin Sodium Active Pharmaceutical Ingredient by Headspace Gas Chromatography with Flame Ionization Detector

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## Abstract

In the industrial production process of avermectin sodium, the quantitation of residual solvents from the manufacturing process is critical for ensuring product quality and safety. This study aimed to develop and validate a headspace gas chromatography with flame ionization detection (HS–GC–FID) method for the simultaneous determination of 12 residual solvents in avermectin sodium active pharmaceutical ingredient (API). The targeted solvents include methanol (MET), ethanol (ET), acetone (ACE), isopropanol (IPA), acetonitrile (ACN), dichloromethane (DCM), tert-butanol (tBA), methyl tert-butyl ether (MTBE), ethyl acetate (EA), tetrahydrofuran (THF), toluene (Tol), and butyl acetate (BuOAc). Following method optimization, all 12 solvents were well-separated with a resolution >1.5 between closely eluting peaks. The method demonstrated excellent linearity, with mass concentrations of the solvents showing a strong correlation with chromatographic peak areas (coefficient of determination, $R^2 \geq 0.99$). Accuracy was confirmed by recovery studies, yielding average recovery rates below 10.0%, while precision was found to be within acceptable limits. The validated method proved to be accurate, specific, and highly sensitive, making it suitable for the rapid and simultaneous determination of residual solvents in avermectin sodium API. This approach ensures compliance with regulatory requirements and supports quality control in pharmaceutical manufacturing.

**Keywords:** Headspace Gas Chromatography; Avibactam Sodium; Residual Solvents; Active Pharmaceutical Ingredient

## Introduction

Avibactam is a diazabicyclooctane (DBO) derivative with the chemical name [(1R,2S,5R)–2–(aminocarbonyl)–7–oxo–1,6-diazabicyclo [3.2.1] oct–6–yl] hydrogen sul-fate [1]. Unlike traditional β–lactamase inhibitors, avibactam exhibits a unique, reversible mechanism of action. The inhibition process begins when the serine residue of β–lactamases nucleophilically attacks the amide bond of avibactam, resulting in ring opening and the formation of a covalent enzyme-inhibitor complex [2]. This complex represents the inhibited state of the enzyme, yet unlike classical inhibitors, no hydrolysis occurs. Instead, avibactam can undergo recyclization, reforming its β-lactam ring and re-generating the active molecule. The rate of nucleophilic ring opening significantly exceeds that of recyclization, ensuring that β–lactamases remain predominantly inhibited. Crucially, avibactam's structure can be restored through reversible reactions, which contributes to its prolonged inhibitory effect [3]. Avibactam demonstrates broad-spectrum inhibition against multiple classes of β-lactamases, including class A enzymes (e.g., CTX–M–15, KPC–2), class C enzymes (AmpC), and some class D enzymes (e.g., OXA–48) [4,5]. Clinically, the ceftazidime–avibactam combination has proven effective against Entero-bacteriaceae producing AmpC, KPC, and extended-spectrum β-lactamases (ESBLs) [6].

The synthesis of avibactam and its derivatives involves complex multi-step reactions requiring various organic solvents [7-11]. However, complete removal of organic solvents from final products is often unattainable, and their residual traces may compromise both therapeutic efficacy and patient safety due to inherent toxicity and irritant properties. This necessitates rigorous residual solvent analysis in the quality control of avibactam and its derivatives [12,13]. The International Council for Harmonisation (ICH) Q3C guideline mandates strict control of residual solvents throughout pharmaceutical manufacturing, and the regulation classifies solvents into three categories based on toxicity profiles and establishes permissible exposure limits for each [14]. To ensure compliance and stream-line quality assessment, a robust platform method for residual solvent analysis is crucial. Such a method would serve as a versatile foundation for avibactam production, enabling rapid adaptation to specific program requirements while maintaining analytical con-sistency across different derivatives. However, literature on residual solvent detection in avibactam and its derivative products remains scarce, highlighting a critical gap in cur-rent analytical methodologies for this important class of β–lactamase inhibitors.

Headspace capillary gas chromatography with flame ionization detection (HS–GC–FID) has emerged as the gold standard for residual solvent determination in pharmaceuticals, owing to its exceptional sensitivity, wide dynamic range, and robust performance [15-17]. Ramanjaneyulu et al. established a selective and sensitive HS-GC method for simultaneous analysis of 11 residual solvents (MET, ET, ACE, DCM, MTBE, n-hexane, 1-propanol, EA, THF, DIPEA, and DMF) in rufloxacin hydrochloride. This method demonstrated excellent sensitivity at ppm levels while offering reduced runtime [18]. Similarly, Noorbasha et al. validated a GC method for paclitaxel that simultaneously quantifies MET, ET, ACE, IPA, DCM, n–hexane, EA, THF, and DIPEA. The method proved to be simple, sensitive, and specific, with demonstrated linearity, precision, accuracy, and robustness suitable for both drug substance and product analysis [19]. Gudibanda et al. further advanced the field by developing a novel HS–GC method with enhanced sensitivity for twelve solvents (MET, ET, ACN, IPA, DCM, MTBE, EA, THF, 1,4–dioxane, DMF, hexane fractions, and Tol) in oseltamivir phosphate API and dosage forms [20]. Therefore, based on the synthetic route of avibactam sodium and in accordance with the Chinese Pharmacopoeia (2020 edition) and ICH guidelines, we developed a gas chromatography method for the simple and rapid detection and quantification of over 12 potential residual organic solvents in avibactam sodium and conducted the comprehensive methodological research. This study establishes a technical foundation to ensure the safe production of high–quality avibactam sodium APIs and their derived formulations in future manufacturing processes.

## Results and Discussion

The development and optimization of a generic headspace gas chromatography with flame ionization detection (HS–GC–FID) method for the simultaneous separation of multiple residual solvents is critical for achieving efficient and reliable analytical results during pharmaceutical development [21,22]. In this study, we established a novel gas chromatographic method for the quantitative determination of 12 residual solvents in avibactam sodium active pharmaceutical ingredients (APIs). To demonstrate the method's applicability for routine analysis of all target solvents, we conducted comprehensive validation in accordance with ICH Q2(R2) guidelines, the Chinese Pharmacopoeia (2020 edition), and current good manufacturing practice (cGMP) requirements [23-25]. The validation study systematically evaluated key analytical performance characteristics, including specificity, linearity, sensitivity, precision, and accuracy.

### Specificity

The specificity test was a critical component of the method development process, designed to verify the optimal performance of the chromatographic system. Blank solvent (1mL), individual reference solutions (1 mL each), and a mixed reference solution (1mL) were prepared and injected into the GC system. The resulting chromatograms were carefully analyzed to determine the retention times of each component and evaluate the degree of separation achieved. This systematic approach ensured the method's ability to distinguish and quantify the target analytes without interference.

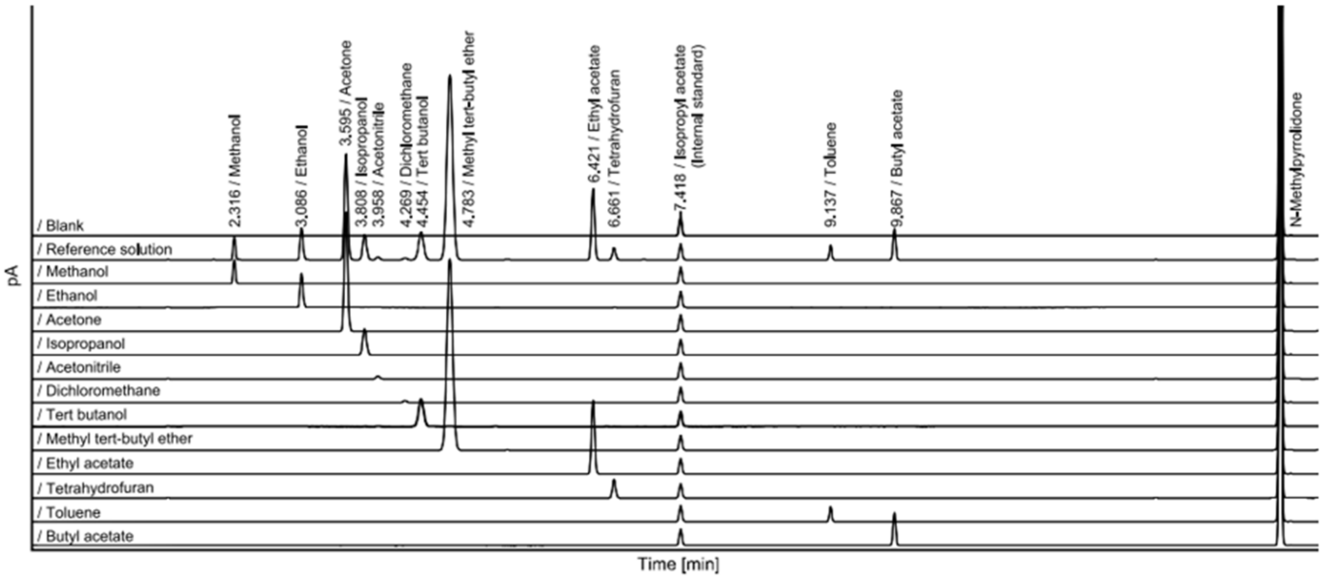

**Figure 1:** The chromatography of the 12 residual solvents and blank using the developed GC-FID method.

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The chromatographic results were presented in Figure 1. The solvents eluted in the following order: methanol (MET), ethanol (ET), acetone (ACE), isopropanol (IPA), acetonitrile (ACN), dichloromethane (DCM), tertbutanol (tBA), methyl tert–butyl ether (MTBE), ethyl acetate (EA), tetrahydrofuran (THF), toluene (Tol), and butyl acetate (BuOAc).

The method validation confirmed excellent specificity, with no interfering peaks detected in either the blank solvent or reference solutions (Figure 1). As summarized in Table 1, all target residual solvents exhibited distinct retention times and achieved baseline separation. Resolution values for all adjacent peak pairs in the mixed reference standard solution exceeded 1.5, demonstrating complete chromatographic separation of the analytes. These validation results confirm that the developed GC method is selective and suitable for the accurate determination of residual solvents in avibactam sodium.

**Table 1:** The retention time and separation degree of 12 residual solvents.

| Residual Solvent | Retention Time | Separation Degree |
|---|---|---|
| MET | 2.32 | / |
| ET | 3.09 | 13.74 |
| ACE | 3.59 | 7.43 |
| IPA | 3.81 | 2.72 |
| ACN | 3.96 | 1.92 |
| DCM | 4.27 | 4.01 |
| tBA | 4.45 | 1.92 |
| MTBE | 4.78 | 2.79 |
| EA | 6.42 | 16.96 |
| THF | 6.66 | 3.47 |
| Tol | 7.42 | 11.53 |
| BuOAc | 9.14 | 30.18 |

**Table 2:** Linear results for each residual solvent (n = 3).

| Residual Solvent | Regression Equations | R2 | Linearity Range (μg/mL) |
|---|---|---|---|
| MET | $y = 0.0041x - 0.0040$ | 0.9999 | 6.01~600.56 |
| ET | $y = 0.0042x - 0.0021$ | 0.9999 | 5.00~993.92 |
| ACE | $y = 0.0160x - 0.0665$ | 0.9999 | 2.01~1002.40 |
| IPA | $y = 0.0042x + 0.0042$ | 0.9999 | 10.02~996.16 |
| ACN | $y = 0.0055x - 0.0007$ | 0.9999 | 3.79~81.76 |
| DCM | $y = 0.0027x - 0.0011$ | 0.9999 | 12.08~116.00 |
| tBA | $y = 0.0062x + 0.0169$ | 0.9999 | 5.01~996.00 |
| MTBE | $y = 0.0469x - 0.2099$ | 0.9998 | 1.00~992.80 |
| EA | $y = 0.0099x - 0.0033$ | 1 | 2.50~997.84 |
| THF | $y = 0.0114x + 0.0032$ | 0.9998 | 2.20~147.84 |
| Tol | $y = 0.0088x + 0.0051$ | 0.9999 | 1.76~170.80 |
| BuOAc | $y = 0.0036x + 0.0205$ | 0.9998 | 5.02~1000.32 |

## Linearity

Each concentration of the linearity solutions was injected in triplicate into the GC system, and the peak areas of the solvents were recorded for each level. The calibration curves were constructed by plotting the concentration (x–axis) against the average peak area (y–axis), followed by linear regression analysis. The solvent peak areas exhibited excellent linearity across the tested concentration range, with correlation coefficients (R2) > 0.999 (Table 2). This strong linear relationship for all 12 residual solvents ensures accurate quantification of residual solvents in avibactam sodium API using the proposed method.

## Limit of Detection (LOD) and Limit of Quantification (LOQ)

The sensitivity of the HS–GC–FID method was determined based on the ICH method, with the LOD defined as a S/N ratio of 3:1, and the LOQ with a S/N ratio of 10:1. As shown in Table 3, the LOD for all residual solvents ranged from 0.30 to 3.66 μg/mL, and the minimum achievable LOD was 0.30 μg/mL for MTBE. The LOQ for all residual solvents ranged from 1.00 to 12.08 μg/mL, and the minimum achievable LOQ was 1.00 μg/mL for MTBE. The results shown that the method established in this study can sensitively detect the residual amount of 12 solvents in in avibactam sodium API.

**Table 3:** LOD and LOQ results for each residual solvent.

| Residual Solvent | LOD (μg/mL) | LOQ (μg/mL) |
|---|---|---|
| MET | 1.82 | 6.01 |
| ET | 1.52 | 5 |
| ACE | 0.61 | 2.01 |
| IPA | 3.03 | 10.02 |
| ACN | 1.15 | 3.79 |
| DCM | 3.66 | 12.08 |
| tBA | 1.52 | 5.01 |
| MTBE | 0.3 | 1 |
| EA | 0.76 | 2.5 |
| THF | 0.67 | 2.2 |
| Tol | 0.53 | 1.76 |
| BuOAc | 1.52 | 5.02 |

## Precision

The precision of an analytical procedure reflects the degree of agreement among multiple measurements obtained from repeated sampling of a homogeneous sample under specified conditions. This parameter is typically quantified through statistical measures such as variance, standard deviation, or coefficient of variation. In the current method validation, system precision was evaluated by performing five replicate injections of standard solutions and expressed as the relative standard deviation (RSD) of the obtained data.

As presented in Table 4, the precision results demonstrated excellent reproducibility, with all solvents showing RSD values below 5.0%–well within the predefined acceptance criterion of not more than 15%. These findings confirm that the method's precision characteristics fully comply with the stringent requirements outlined in the ICH guidelines for analytical procedure validation. The consistently low RSD values across all tested solvents indicate robust system performance and reliable measurement reproducibility.

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**Table 4:** The precision results for each residual solvent.

| Residual Solvent | Concentration | Peak area (pA/s) | | | | | | Mean peak area (pA/s) | RSD (%) |
|---|---|---|---|---|---|---|---|---|---|
| | (ug/mL) | 1 | 2 | 3 | 4 | 5 | 6 | | |
| MET | 300.48 | 148.83 | 147.5 | 146.64 | 151.05 | 157.33 | 153.45 | 150.8 | 2.45 |
| ET | 500.16 | 249.33 | 247.59 | 245.22 | 255.71 | 270.81 | 253.24 | 253.65 | 3.32 |
| ACE | 502.96 | 959.7 | 955.29 | 939.3 | 987.97 | 1007.05 | 961.71 | 968.5 | 2.31 |
| IPA | 500.88 | 252.66 | 251.29 | 247.18 | 259.79 | 274.15 | 257.42 | 257.08 | 3.37 |
| ACN | 37.92 | 27.15 | 26.96 | 26.59 | 27.72 | 28.99 | 27.83 | 27.54 | 2.82 |
| DCM | 60.4 | 18.45 | 18.33 | 18.01 | 18.99 | 19.57 | 18.94 | 18.72 | 2.74 |
| tBA | 500.64 | 371.1 | 369.83 | 361.42 | 382.32 | 402.48 | 364.27 | 375.24 | 3.69 |
| MTBE | 500 | 2827.81 | 2833.71 | 2737.06 | 2922.3 | 2970.2 | 2892.43 | 2863.92 | 2.62 |
| EA | 500.08 | 600.34 | 597.78 | 582.49 | 618.09 | 635.51 | 609.24 | 607.24 | 2.75 |
| THF | 73.28 | 102.04 | 101.59 | 99.36 | 105.1 | 107.49 | 104.28 | 103.31 | 2.55 |
| Tol | 88 | 90.16 | 89.9 | 87.57 | 92.93 | 97.92 | 93.27 | 91.96 | 3.58 |
| BuOAc | 502 | 215.31 | 215.59 | 208.43 | 222.34 | 234.67 | 219.32 | 219.28 | 3.69 |

## Accuracy

**Table 5:** The recovery results for each residual solvent.

| Residual Solvent | Recovery (%) | | | Average Recovery (%) | RSD (%) |
|---|---|---|---|---|---|
| | QCL | QCM | QCH | | |
| MET | 94.37 | 92.86 | 90.84 | 91.76 | 1.59 |
| | 93.56 | 91.52 | 90.1 | | |
| | 92.24 | 89.06 | 91.33 | | |
| ET | 100.88 | 99.6 | 97.55 | 97.14 | 2.46 |
| | 98.91 | 97.39 | 94.58 | | |
| | 95.95 | 92.32 | 97.06 | | |
| ACE | 97.61 | 95.49 | 94.43 | 96.25 | 1.12 |
| | 97.77 | 95.66 | 95.56 | | |
| | 97.65 | 96.5 | 95.55 | | |
| IPA | 99.74 | 99.02 | 98.65 | 97.8 | 1.45 |
| | 98.6 | 97.77 | 96.31 | | |
| | 97.47 | 94.65 | 97.99 | | |
| ACN | 96.1 | 94.85 | 92.78 | 93.41 | 1.77 |
| | 95.18 | 93.63 | 91.07 | | |
| | 93.98 | 90.41 | 92.74 | | |
| DCM | 99.36 | 98.34 | 97.49 | 98.04 | 0.71 |
| | 98.79 | 97.76 | 97.22 | | |
| | 98.48 | 97.18 | 97.7 | | |
| tBA | 105.03 | 104.23 | 104.03 | 103.22 | 1.29 |
| | 103.93 | 103.18 | 101.75 | | |
| | 103.09 | 100.51 | 103.25 | | |
| MTBE | 96.72 | 94.4 | 96.29 | 97.71 | 1.72 |
| | 98.19 | 97.22 | 99.12 | | |
| | 99.6 | 100.26 | 97.59 | | |
| EA | 97.76 | 96.61 | 96.88 | 97.2 | 0.45 |
| | 97.77 | 96.62 | 97.23 | | |
| | 97.77 | 96.95 | 97.21 | | |
| THF | 98.84 | 97.24 | 96.52 | 97.95 | 0.89 |
| | 99.04 | 97.53 | 97.45 | | |
| | 99.21 | 98.44 | 97.31 | | |

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| | | | | | |
|---|---|---|---|---|---|
| Tol | 107.99 | 107.05 | 106.64 | 105.99 | 1.37 |
| | 106.77 | 105.91 | 104.51 | | |
| | 105.88 | 103.05 | 106.08 | | |
| BuOAc | 115.2 | 113.98 | 113.54 | 112.87 | 1.54 |
| | 113.74 | 112.96 | 110.96 | | |
| | 112.98 | 109.72 | 112.73 | | |

The accuracy is a critical validation parameter, represents the closeness of agreement between measured values obtained by the analytical method and accepted reference values, reflecting the trueness of the method. In this study, accuracy was assessed through recovery experiments by spiking standard solvents into pooled avibactam sodium API samples at three levels: 80%, 100%, and 120% of the specification limit. As detailed in Table 5, the average recoveries for all solvents ranged from 91.76% to 112.87%, with all individual recovery values falling within the acceptable range of 80.0–120.0%, as stipulated by the Chinese Pharmacopoeia (2020 edition). These results demonstrate that the method exhibits excellent accuracy, with recovery rates consistently meeting regulatory requirements. Furthermore, the low relative deviations observed confirm the method's reliability and suitability for its intended analytical purpose. This validation confirms that the method provides accurate and precise measurements, ensuring confidence in its application for quality control testing.

Calculate the peak area according to the internal standard method, and the results are shown in Table 6. It can be known from the detected results that MET, ET, ACE and ACN were detected, and other organic solvents were not detected (ND) in the five batches of the sodium averbactam API samples. The content of MET in the sample of batch L-2002210901V was 0.002%. The content of ACN in the sample of batch L-202230701 was 0.004%. The contents of ET in the samples of batches L-2002210901V, L-2002210902V, L-2002210903V, L-202230701 and AP046-N00201R were 0.18%, 0.16%, 0.13%, 0.33% and 0.32% respectively. The ACE content in batches L-2002210901V, L-2002210902V, L-2002210903V, L-202230701, and AP046-N00201R samples were 0.02%, 0.02%, 0.003%, 0.005%, and 0.01%, respectively. The results indicated that the residual amounts of 12 solvents in the five batches of sodium averbactam API all comply with the relevant provisions of the 2020 edition of the Chinese Pharmacopoeia.

**Table 6:** Determination results of samples.

| Residual Solvent | Content (%) | | | | |
|---|---|---|---|---|---|
| | L-2002210901V | L-2002210902V | L-2002210903V | L-202230701 | AP046-N00201R |
| MET | 0.002 | ND | ND | ND | ND |
| ET | 0.18 | 0.16 | 0.13 | 0.33 | 0.32 |
| ACE | 0.02 | 0.02 | 0.003 | 0.005 | 0.01 |
| IPA | ND | ND | ND | ND | ND |
| ACN | ND | ND | ND | 0.004 | ND |
| DCM | ND | ND | ND | ND | ND |
| tBA | ND | ND | ND | ND | ND |
| MTBE | ND | ND | ND | ND | ND |
| EA | ND | ND | ND | ND | ND |
| THF | ND | ND | ND | ND | ND |
| Tol | ND | ND | ND | ND | ND |
| BuOAc | ND | ND | ND | ND | ND |

## Materials and Methods

### Materials

HPLC–grade N–Methylpyrrolidone (NMP) was purchased from Shanghai Aladdin Scientific Co. (Shanghai, China). HPLC-grade methanol, ethanol, isopropanol, and acetonitrile were purchased from Tianjin Kemiou Chemical Reagent Co. (Shanghai, China). Analytical grade acetone, isopropyl acetate (IPAC), and dichloromethane were purchased from Chengdu Kelong Chemical Co. (Chengdu, China). Analytical-grade methyl tert-butyl ether, ethyl acetate, tetrahydrofuran, toluene, and butyl acetate were purchased from Chongqing Chuandong Chemical Co. (Chongqing, China). Five batches of the sodium averbactam API samples (batch number: L-2002210901V, L-2002210902V, L-2002210903V, L-202230701, and AP046-N00201R) were producted by Fuan Pharmaceutical Co. (Chong-qing, China). Deionized water was used throughout.

### Apparatus and Operations

The headspace GC–FID analysis was performed on an auto-headspace sampler (Agilent GC 7694A, (Agilent Technology Co., Shanghai, China) connected to a GC system (Agilent GC 7890B, Shanghai, China) equipped with a hydrogen flame ionization detector (FID) and a DB-624UI capillary columns (30m×0.32mm×1.8μm, Santa Clara, CA, USA). Programmed temperature rise was set as following: maintain the initial temperature at 40°C for 5 minutes, then increase the temperature at a rate of 20°C/min to 120°C and hold for 2 minutes, and then increase the temperature at a rate of 20°C/min to 200°C and hold for 5 minutes. The nitrogen was used

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as the carrier at a flow rate of 2.0 mL/min, and the split ratio was 20:1. The detector temperature was set as 250℃, and the injection port temperature was 200℃. The conditions of headspace sampler were set as following: equilibrium temperature = 80℃; equilibrium time = 30 min; quantitative loop temperature = 90℃; transmission line temperature=100℃. 1 mL of the blank, reference solutions and sample solutions were injected into the GC–FID system for analysis.

## Preparation of Reference and Sample solutions

### Preparation of internal standard solution

A total 100 mg of IPAC was accurately weight, dissolved and diluted in NMP to pre-pare a solution of 0.1mg/mL, and shake well.

### Preparation of reference solution

A total of 0.75 g of methanol, 0.1 g of acetonitrile, 0.15 g of dichloromethane, 0.18 g of tetrahydrofuran, 0.22 g of toluene, and 1.25 g each of ethanol, acetone, isopropanol, tert–butanol, methyl tert–butyl ether, ethyl acetate and butyl acetate were weighed and place in a 50 mL volumetric flask. These organic solvents were dissolved and diluted with the in-ternal standard solution to the mark, shaken well and used as the reference stock solution. Accurately measured 1 mL of the reference substance stock solution, place in a 50 mL volumetric flask, diluted to the mark with the internal standard solution, shaken well, and used as the reference solution.

### Preparation of the sample solution

A total of 0.2 g of sodium averbactam API samples were accurately weight, precisely added 2 mL of the internal standard solution, heat in 80 °C water bath until dissolved, and shaken well.

## Method Validation

The developed GC-FID method was evaluated in terms of its specificity, linearity, LOD, LOQ, precision, accuracy.

### Specificity

The internal standard solution, and reference solutions of 12 solvents were respectively injected into the gas chromatograph. analyzed under the set analysis condition, and the chromatograms were recorded.

### linearity

Linearity parameter was demonstrated by preparing six concentration levels from LOQ to 200% (i.e., LOQ, 40, 80, 100, 120 and 200%) of working concentration level through the dilution of standard mixture stock solution. The linearity range for MET, ET, ACE, IPA, ACN, DCM, tBA, MTBE, EA, THF, Tol, and BuOAc were assessed by plotting the concentrations of the 12 solvents against measured GC-FID response. The linearity for 12 solvents were assessed using six different concentrations for both of the compounds in triplicate (n = 3).

### Limit of detection (LOD) and Limit of quantification (LOQ)

Using a multiple dilution method, the sensitivity of the proposed HS–GC approach for the simultaneous assessment of 12 solvents was evaluated in terms of "LOD and LOQ". The LOD of this method was defined as three times the signal to noise ratio (S/N = 3) of the lowest concentration, and the LOQ was defined as ten times the signal to noise ratio (S/N = 10) of the lowest concentration.

### Precision

The mixed reference stock solution of 12 residual solvents was diluted with internal standard solution to prepare test solutions at a mass concentration of 300.48, 500.16, 502.96, 500.88, 37.92, 60.40, 500.64, 500.00, 500.08, 73.28, 88.00 and 502.00 μg/mL, respectively. Six aliquots of the test solution were separately injected into the GC system. The peak areas of the 12 solvents were detected and recorded, and the mean values along with the RSD were calculated to determine the precision of the develop method.

### Accuracy

The QC samples were prepared by pooling and mixing a portion of each 5 batches sodium averbactam API samples. A total of 0.2 g of the pooled sodium averbactam API samples precisely added 2 mL of the internal standard solution, heat in 80 ℃ water bath until dissolved, shaken well, and used as the QC0 sample. Recovery control samples at three levels, i.e., quality control low–level (QCL), quality control mid–level (QCM), and quality control high–level (QCH), were prepared by spiking the reference solutions of 12 kinds of residual solvents into the QC0 samples. The levels of spiked residual solvents were 80 %, 100 %, and 120 %, and the corresponding concentrations were shown in the table 7. The QC samples were prepared in replicate (n = 3). The mean recovery and RSD of measurements (n = 9) were used to evaluate the method accuracy.

**Table 7:** The levels and corresponding concentrations of spiked residual solvents

| Residual Solvent | Spiked concention (μg/mL) | | |
|---|---|---|---|
| | **80%** | **100%** | **120%** |
| MET | 240.22 | 300.28 | 360.34 |
| ET | 397.57 | 496.96 | 596.35 |
| ACE | 400.96 | 501.2 | 601.44 |
| IPA | 398.46 | 498.08 | 597.7 |
| ACN | 32.7 | 40.88 | 49.06 |
| DCM | 46.4 | 58 | 69.6 |
| tBA | 398.4 | 498 | 597.6 |
| MTBE | 397.12 | 496.4 | 595.68 |
| EA | 399.14 | 498.92 | 598.7 |
| THF | 59.14 | 73.92 | 88.7 |
| Tol | 68.32 | 85.4 | 102.48 |
| BuOAc | 400.13 | 500.16 | 600.19 |

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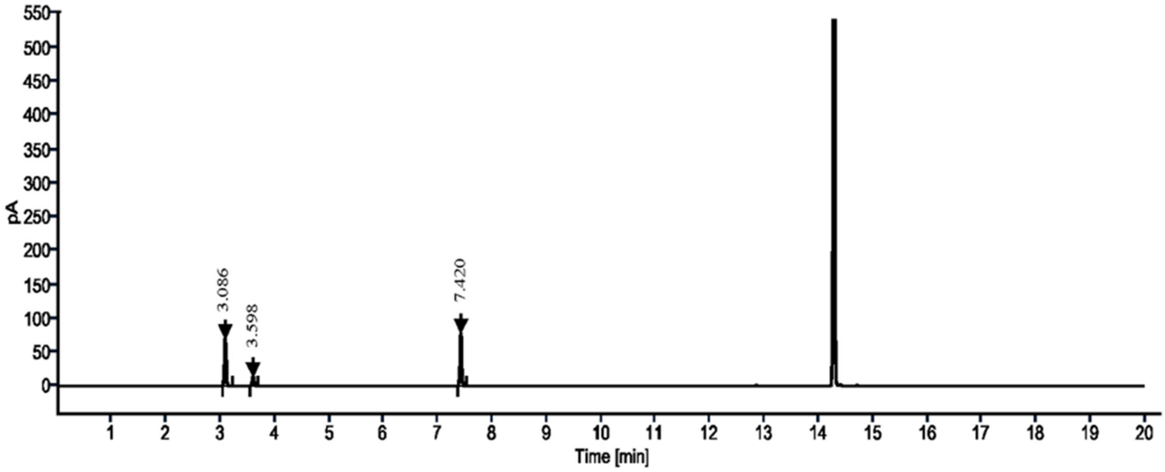

**Figure 2:** The chromatogram of sample (Batch Number: L-2002210902V).

## Conclusions

In this work, we developed and validated a robust gas chromatography method for the simultaneous detection and quantification of twelve potential residual organic sol-vents. This comprehensive methodological study included full validation of all critical parameters, establishing a reliable analytical framework for quality control. The developed method provides a solid technical foundation to ensure the production of high-quality avibactam sodium APIs and their pharmaceutical formulations, supporting current good manufacturing practice (cGMP) requirements for pharmaceutical production.

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