Development and validation of an automated static headspace gas chromatography method for determination of dichloromethane in ampicillin sodium by using capillary column technology

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ABSTRACT

A simple, robust and accurate static head space gas chromatographic (SHS-GC) quantitation method equipped with flame ionization detector (FID) has been developed and validated for determination of dichloromethane in Ampicillin sodium (AMP). The separation was achieved with a capillary column (DB-624) 30 meter long, 0.25 mm inner diameter packed with 6.0 percent polycyanopropylphenyl siloxane and 94.0 percent of polydimethyl siloxane (1.4 µm). The developed SHS-GC method showed symmetric peak shape reasonable retention time for dichloromethane. A linear relationship was obtained over the range of 2-240 µg mL^{-1} with a correlation coefficient (r^2) of 0.997. The recovery, system precision and robustness of the method were within the acceptable values. The limit of detection (LOD) and limit of quantitation (LOQ) were 0.00005 % and 0.0002 % respectively. This assay provides a simple and quick way of screening for dichloromethane in ampicillin sodium. The method was validated according to international conference on harmonization (ICH) guidelines in terms of specificity, linearity, precision, accuracy, and limit of detection, limit of quantitation, robustness and solution stability.
Keywords: Capillary column, ampicillin sodium, DB-624, Dichloromethane

Introduction:

Residual solvents (RS) are organic volatile chemicals used or produced in the making of excipients or drug substances (API) or in the preparation of drug products (drug formulations). The presence of RS is important in all steps of the pharmaceutical process (multiple reaction monitoring, separation, formulation research and development, in process and intermediate impurities). It is well known that a distinctive molecule synthesis route usually consists of four to ten reaction steps and five or more different solvents are employed in the process. These solvents are not completely detached by practical manufacturing techniques and their traces may remain in the final active pharmaceutical ingredient (API) and drug products. The presence of these unwanted solvents (known as organic volatile impurities or residual solvents) even in minor quantity may influence a potential toxic risk to pharmaceutical drug products and have been a concern of manufacturers for many years. Furthermore, RS can also affect the quality and stability, not only drug substances but also drug products (pharmaceutical dosage form). Thus an amount of such solvents is limited by international conference on harmonization (ICH) guidelines Q3C [1-5].

RS are mainly classified into three classes on the basis of the toxicity level and the degree to which they can be considered an environmental hazard. Class I solvents are known carcinogens, harmful to environment and humans, so the use of these type of solvents should be avoided. Class II solvents are non genotoxic animal carcinogens or possible causative agents of other irreversible toxicity such as neurotoxicity or teratogenicity. Thus RS should be limited in pharmaceutical products because of their inherent toxicity. Class III solvents are solvents with a low toxic potential to human, no health based exposure limit is needed. These solvents have PDEs (permitted daily exposure) of 50 mg or more per day [1, 2, 6, 7].

Ampicillin sodium (Fig.1) is a beta-lactam, semi synthetic antibiotic with a broad spectrum of bactericidal activity against many gram-positive and gram-negative bacteria. Ampicillin sodium chemically is sodium (2S, 5R, 6R)-6-[[(2R)-2-amino-2-phenylacetyl] amino]-3, 3-dimethyl7-oxo-4-thia-1-azabicyclo [3.2.0] heptane-2-carboxylate. It occurs as a white or almost white powder, hygroscopic, freely soluble in water, sparingly soluble in acetone, practically insoluble in fatty oils and in liquid paraffin, having a molecular formula of $C_{16}H_{19}N_3NaO_4S$ and a molecular weight of 371.39 g mol^{-1} [8-12].

Dichloromethane (DCM) volatility, miscibility and ability to dissolve a wide range of organic compounds make it a useful solvent for many chemical processes. It is used in synthesis process of ampicillin sodium. DCM (Fig. 2) is the least toxic of the simple chlorohydrocarbons, but it is

not without health risks, as its high volatility makes it an acute inhalation hazard. It can also be absorbed through the skin [8]. It is a Class II Residual solvent (limit 600 ppm) as per ICH Q3(C) guidelines.

Static headspace gas chromatography (SH-GC) also known as gas chromatography-headspace (GC-HS) is the technique of choice due to its high sensitivity, excellent separation abilities, low limit of detection and simplicity of the instrumentation used for the technique. The headspace (HS) sampling method has more appropriate sensitivity than the direct injection method because it can clearly separate volatile analytes from the sample matrix and effectively concentrate them [1, 2, 9, 10, 13]. Therefore this method results in less complex sample preparation, decreased instrument contamination, and increased GC column life.

To the best of our knowledge, there is no validated SHS-GC method available for analysis of residual solvents (DCM) using a capillary column in ampicillin sodium. However, GC method using glass packed column is available in Indian Pharmacopoeia (IP) 2014 and the limit of dichloromethane given in IP monograph is NMT 0.2 % w/w [10]. GC method using glass packed column are also available in USP 41-NF 36, 2018 as well as British Pharmacopoeia 2018, with acceptance criteria of NMT 0.2 % w/w [11, 12, 19]. Also GC methods using Glass columns are outdated these days hence a secure, precise safe and sensitive method GC-HS using capillary column was developed [13-20].

In the present investigation, we report development and full validation of a novel SH-GC analytical method with FID (Flame Ionization Detector) for determination of dichloromethane. DCM is a class 2 residual solvent with limit NMT 600 ppm, hence for better sensitivity and detection head space method was developed. The validation was made according to ICH guidelines in terms of several parameters e.g., linearity, specificity, precision, accuracy, limit of detection, limit of quantitation and robustness. Besides, the method is also applied to determine the residual solvents in both bulk ampicillin sodium as well as ampicillin sodium for injection. These solvents should be estimated and checked so that they may not exceed the amount specified by the ICH guidelines. In order to secure the safety and assure good manufacture practices (GMP), a precise quantification of residual solvents is essential. Regulatory agencies (EDQM, USFDA, PMDA, MCC and MHRA) and pharmacopoeias suggest headspace gas chromatography as the most suitable technique for residual solvent testing for active substances and formulations soluble in water.

Experimental:

Materials and methods

Ampicillin sodium (active pharmaceutical ingredient having purity>99%) was provided by Akums, Haridwar, India. Dichloromethane (GC grade) was obtained from Merck Pvt. Ltd. (Mumbai, India). Milli–Q water having a resistivity of 18.2 MΩ cm (Milli–Q water purification system, Elix, Milli–Q A10) was used during the analysis.

Instrumentation and chromatographic conditions

The GC-HS system consisted of an Agilent Technologies (Santa Clara, CA, USA) 7890A gas chromatograph system and headspace autoinjector GC sampler 80, Agilent Technologies, coupled with a flame ionization detector (FID). The gas chromatographic conditions were operated in split mode (split ratio, 25:1) with a carrier gas (nitrogen ultrapure grade)flow rate was 0.5 mL min^{-1} and a column head pressure of 10 psi and injector temperature was 180°C. The temperature (column oven) program used consisted of an initial temperature hold at 50°C for 10 min, ramped up to 130°C at a rate of 12°C min^{-1} and holding the temperature at 130°C for 5 min then the temperature was ramped up to 220°C at a rate of 12°C min^{-1} and holding the temperature at 220°C for 5 min (post run) (table 1). The GC detector (FID) was maintained at 250°C, hydrogen gas and zero air flow were used in the ratio 1:10 (40mL min^{-1}:400mL min^{-1}), makeup gas flow (nitrogen) was 30mL min^{-1} (table 2). The headspace injector syringe was the capacity of 2.5 mL, incubation (agitator) temperature (80 °C), time (1200 second) and speed (500 rpm), syringe temperature 90 °C, fill speed was 100 µL sec^{-1}. GC run time was 1300 sec and injection volume 500 µl (table 2). The chromatographic separation was carried out on a 30 m (length) × 0.25 mm (inner diameter) x 1.4µ (film thickness) column coated with 6.0 per cent polycyanopropylphenyl siloxane and 94.0 per cent of polydimethylsiloxane (DB-624, Agilent Technologies, USA). The EZchrome Elite software was used for the data integration. Water was used as diluent in all the standard and sample preparations.

Sample and Reference Vial preparation

Sample Solution

250 mg of Ampicillin Sodium test sample accurately weighed into a headspace vial. 2.0 ml of diluent added into the same headspace vial and immediately sealed.

Reference Solution

130mg (≈ 100 µl) of Dichloromethane accurately weighed into 100.0 ml flask containing about 20.0 ml of diluents, diluted up to the mark with diluent and mixed well. 5.0 ml of this solution

further diluted to 25.0 ml with diluent and mixed well. Density of dichloromethane was 1.325 g ml^{-1}. Transfer accurately 2.0 ml of reference solution into each headspace vial and sealed immediately.

Preparation of linearity stock solution (1000 ppm)

About 130 mg (≈ 100 µl) of dichloromethane weighed and transferred into 100.0 ml flask containing about 20.0 ml of diluent. Diluted up to the mark with diluent and mixed well.

Preparation of linearity solution

10.0 ml of linearity stock solution (1000 ppm) diluted to 100 ml with diluent and mixed well (100 ppm). Further 1.0 ml of 100 ppm solution diluted to 50 ml with diluent (0.0002 % LOQ-level, 2 ppm). 4.0 ml of linearity stock solution (1000 ppm) diluted to 25 ml with diluent (160 ppm-80 % level). 4.5 ml of linearity stock solution (1000 ppm) diluted to 25 ml with diluent (180 ppm-90 % level). 5.0 ml of linearity stock solution (1000 ppm) diluted to 25 ml with diluent (200 ppm-100 % level). 5.5 ml of linearity stock solution (1000 ppm) diluted to 25 ml with diluent (220 ppm-110 % level). 6.0 ml of linearity stock solution (1000 ppm) diluted to 25 ml with diluent (240 ppm-120 % level).

Preparation of accuracy stock solution (1000 ppm)

Weigh accurately about 130 mg (≈ 100 µl) of Dichloromethane into 100 ml flask containing about 20 ml of diluent, dilute up to the mark with diluent and mix it well. Accuracy standard stock solutions of 160ppm (80 %), 200 ppm (100%) and 240 ppm (120%) were prepared as per linearity standard solutions.

Preparation of Accuracy Test Solution (160 ppm-80% level)

250 mg of Ampicillin Sodium test sample weighed into a headspace vial. 2.0 ml of accuracy standard stock solution (160 ppm-80% level) added into the headspace vial and immediately sealed.

Preparation of Accuracy Test Solution (200 ppm-100% level)

250 mg of Ampicillin Sodium test sample weighed into a headspace vial. 2.0 ml of accuracy standard stock solution (200 ppm-100% level) added into the headspace vial and immediately sealed.

Preparation of Accuracy Test Solution (240 ppm-120% level)

250 mg of Ampicillin Sodium test sample weighed into a headspace vial. 2.0 ml of accuracy standard stock solution (240 ppm-120% level) added into the headspace vial and immediately sealed.

Preparation of Test Solution (Unspiked)

250 mg of Ampicillin Sodium test sample weighed into a headspace vial. 2.0 ml of diluent added into the same headspace vial and immediately sealed. Three replicates of each solution were performed.

System suitability

The percentage of relative standard deviation of peak area from replicate injections of reference solution should not be more than 15.0 %.

Precautions to be taken during analysis

Condition the column at high temperature (As per manufacturer's specifications) for at least 30 minutes before analysis.

Method validation

The method validation was done by evaluating specificity, limit of detection (LOD) and limit of quantitation (LOQ), linearity, accuracy, repeatability, ruggedness, system suitability and method precision of residual solvents as indicated in the ICH Q2 (R1) guideline.

Results and discussion:

Method development

An effective method development should result in a fast, simple and time efficient method that is proficient of being utilized in a manufacturing setting. Following were the stepwise tactics for the method development in our case.

Method Selection

Dichloromethane is a class II residual solvent with permissible limit of 600 ppm (ICH Q3C). It is a very volatile solvent with boiling point 39.6°C hence a very sensitive sampling technique was needed.

GC and GC-HS both techniques were explored. In GC sample needs to be completely dissolved in diluent solvent and clearly soluble which is directly injected at the injection port. But in GC-HS samples need not necessarily dissolve in diluent solvent since residual solvent in sample is to checked. In GC-HS the sample is heated at 80 °C for about 20 minutes, the volatile solvents present in the sample will come to the empty space (head space) of the vial. A gas tight syringe needle will draw the vapour and inject into GC column. Volatile solvents are extracted from the material before injection hence loss of vapors at the site of injection was very less as compared to GC where sample along with the residual solvent is injected, moreover sample has no direct impact on injector port in GC-HS when compared to GC.

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Column selection

The key objective of column selection was to suitably detect and quantify dichloromethane present in ampicillin sodium as well as its injectable formulations available in powder forms which are to be reconstituted before use. Dichloromethane is one of the common solvent used during the synthesis and manufacturing of ampicillin sodium for its purification and

recrystallization. Several columns were initially investigated to finalize a single method for the identification and quantitation of dichloromethane. Wall-coated open tubular capillary columns of various brands with a variety of phases and dimensions have been investigated, e.g., DB-5, (30 m length, 0.32 mm id with a stationary phase of 5 %-Phenyl-methylpolysiloxane, film thickness 0.25 µm), Elite Wax (30 m length, 0.32mm id with a stationary phase of, polyethylene glycol (PEG), film thickness 0.5 µm). Optima (30 m length, 0.53 mm i.d. with a stationary phase of 6 % cyanopropyl phenyl and 94% dimethyl polysiloxane film of 3.0 µ), DB-624 (30 m length, 0.32 mm i.d. with a stationary phase of 6 % cyanopropyl phenyl and 94 % dimethyl polysiloxane film of 1.8 µ).

In the above column, the response was found to be comparatively lower and peak shapes were found to be unsatisfactory. The peak shape width increased with increase in column bleed at higher temperature. Therefore, the chromatographic separation was carried out on a 30 m (length) × 0.25 mm (inner diameter) x 1.4µ (film thickness) column coated with 6.0 per cent polycyanopropylphenyl siloxane and 94.0 per cent of polydimethylsiloxane (DB-624, Agilent Technologies, USA). Inner diameter of 0.25 mm and film thickness 1.4 µ gave sharper peaks, increased signal to noise and decreased column bleed. It proved to be the best column that could fulfill all the needs of the method, i.e., higher sensitivity, shorter runtime and higher resolution.

Thermal program and thermal gradient

A linear thermal gradient was chosen to provide elution of the dichloromethane peak along with any other solvent or volatile impurity peaks if present in the sample during the chromatographic run for better quantification. An initial hold of 10 min at 50 ºC and a linear thermal gradient to 130 ºC at 12 ºC min^{-1} was found to give the best peak shape and retention without affecting the resolution. Further holding the temperature at 130 °C for 5 min then ramp up to 220 °C at a rate of 12 °C min^{-1} and again holding the temperature at 220 °C for 5 min (post run) was found to be a suitable temperature program to detect any other high boiling solvents present in the sample along with dichloromethane. The temperature hold at 220 °C for 5 min post run conditioned the column for the next run so as to avoid any interfering solvent peaks from the previous run.

Headspace method optimization

The headspace method was optimized to extract maximum amount of the solvents present in the sample for detection. For this the standard and sample vials were incubated at 60-90ºC for 15-30 min with constant shaking. The injection volumes of 200-800 µl were scrutinized to achieve satisfactory peak shape and response. A combination of sample vial heating at 80 ºC with 20 min

shaking and injection volume of 500 µl was found to be suitable for getting a good response. The syringe temperature was kept 90 ºC to prevent condensation of vapours while drawing the volatile vapours from vial kept in incubator.

Method Validation:

The GC-HS method for determination of dichloromethane has been validated to show specificity, linearity, precision, limit of detection, limit of quantification, accuracy and robustness.

Specificity

Blank and standard were injected to confirm the specificity. It was observed that there was no interference of any peak in the peak of interest of dichloromethane.

Precision and System Suitability

System Precision

Sample Preparation for precision:

130mg (≈ 100 µl) of Dichloromethane was transferred into 100.0 ml flask containing about 20.0 ml of diluent, further diluted up to the mark with diluent and mixed. Further 5.0 ml of this solution diluted to 25.0 ml with diluent and mixed well. (200 ppm reference solution 100 % level) density of dichloromethane 1.33 gml^{-1}. Accurately transferred 2 ml of reference solution into each headspace vial and immediately sealed.

Six replicate injections of standard solution at 100 % level were injected into the GC-HS system. The results along with the % RSD of area counts for dichloromethane shown in Table 3 indicate an acceptable level of precision for the analytical system. Acceptance criteria RSD should not be more than 15.0 %.

Limit of detection and limit of quantification (LOD & LOQ)

For determination of LOD and LOQ of dichloromethane different concentrations of solutions were prepared and injected. The signal to noise ratio was checked for each concentration. Table 4 showed signal to noise data of dichloromethane.

Acceptance criteria: LOD- signal to noise ≥3.0, LOQ- signal to noise ≥10.0.

Based on signal to noise ratio the LOD and LOQ levels were found to be 500 ppb and 2 ppm respectively. Replicate injections were applied at LOD and LOQ levels to check the system suitability criteria. Table 5 showed LOD and LOQ results of dichloromethane.

Linearity of response

The linearity of response for Dichloromethane was determined in the range of LOQ to 120% of the specified limit. Data presented in Table 6 and its graphical representation (Fig. 3) indicates

that the response is linear over the specified range. Acceptance criteria: Correlation coefficient should not be less than 0.99.

DCM standard solution 100 % concentrations showed in fig. 4 A, test solution spiked with 100 % standard (fig. 4 B), unspiked test solution (active pharmaceutical ingredient) (fig. 4 C), unspiked test solution (formulation injection) (fig 4 B).

Accuracy

Accuracy was carried out at levels 80 %, 100 % and 120 % of specification level. Table 7 showed accuracy results of dichloromethane.

Acceptance Criteria: % Recovery should be between 80 % - 120 %.

$$\% \text{ Recovery} = \frac{(A+B)}{C}$$

A= Standard Area

B= Test Area (Unspiked)

C= Area of Test spiked with standard

The recovery was found to be within specified limits.

Robustness

The robustness of an analytical procedure was measured to ascertain its capacity to remain unaffected by small, but deliberate variations in method parameters and provides an indication of its reliability during normal usage. Table 8 showed robustness results of dichloromethane.

The GC-HS analysis was carried out using the method outlined in the method of analysis Section and by carrying out the following alterations in the chromatographic conditions.

a) Changing column oven temperature ± 5°C from ideal condition.
b) Changing carrier gas flow rate ± 0.5 ml/min from ideal condition.
c) Changing split ratio ± 10% from ideal condition.
d) Changing the column to an equivalent one.

Ideal column: DB-624 30m*0.25mm*1.4µ film thickness

Changed column: Elite-624 30m*0.32mm*1.8µ film thickness

Acceptance criteria: complies with system suitability criteria.

Application of method:

This study provides a validated static headspace gas chromatography (SHS-GC) method by using a capillary column technology, method was well versed, validated and optimized GC-HS method was carried out with respect to the parameters such as specificity, linearity, accuracy, precision, limit of

quantification (LOQ) and limit of detection (LOD) in the light of ICH (Q3C) guidelines. This method also offered several applications such as rapidity, whereas improved sensitivity made it specific and reliable for its intended use. Developed method can be applied to analysis of various pharmaceutical dosage forms (injection, tablets) and active pharmaceutical ingredients (API) of ampicillin sodium.

Conclusion:

The results obtained in this study demonstrate that GC-HS (Gas Chromatographic-Head Space) method is selective, precise, linear, accurate and robust for determination of dichloromethane in Ampicillin Sodium. The method has satisfactory precision and linear relationship between concentration and response in the entire range from LOQ to 120% level. The recovery and robustness was good. The % RSD obtained in all the validation parameter is within the ICH Limits. This present static headspace gas chromatography method using capillary column and no use of internal standard as well as any other harmful organic solvent as a diluent is reasonably better method for determination of dichloromethane. Therefore the method is suitable for its intended use.

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Conflict of interest:

All the authors have no conflict of interest regarding this publication. This article does not contain any studies with human and animal subjects implemented by any of the authors.

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Figure legends:

Fig. 1 Chemical structure of Ampicillin sodium.

Fig. 2 Chemical structure of Dichloromethane.

Fig. 3 Linearity curve.

Fig. 4 A- DCM standard solution 100 % concentrations, B-Test solution spiked with 100 % standard, C-Unspiked test solution (active pharmaceutical ingredient), D- Unspiked test solution (formulation injection).

Abbreviations:

AMP:	Ampicillin Sodium
API:	Active Pharmaceutical Ingredient
BP:	British Pharmacopoeia
DB 624:	Dura Bond 624
DCM:	Dichloromethane
EDQM:	European Directorate for the Quality of Medicines
FID:	Flame Ionization Detector
GMP:	Good Manufacturing Practice
GC:	Gas Chromatography
ICH:	International Conference on Harmonization
IP:	Indian Pharmacopoeia
LOD:	Limit of Detection
LOQ:	Limit of Quantitation
MCC:	Medicines Control Council
MHRA:	Medicines and Healthcare products Regulatory Agency
NMT:	Not more than
NLT:	Not less than
PDE:	Permitted Daily Exposure
PEG:	Poly Ethylene Glycol
PPM:	Parts Per Million
PDMS:	Poly Dimethyl Siloxane
PMDA:	Pharmaceutical and Medical devices Agency
RSD:	Relative standard deviation
RS:	Residual Solvent
SHS-GC:	Static Head space- Gas Chromatography
USP:	United States Pharmacopoeia