Microchemical Journal 133 (2017) 506–509

Contents lists available at ScienceDirect

Microchemical Journal

journal homepage: www.elsevier.com/locate/microc

Determination of residual dimethyl sulfate in hexaconazole technical (fungicide) by head space gas chromatography mass spectrometry

Narendra H. Petha [a,*], Rama S. Lokhande [a], Devender T. Seshadri [b], Raju M. Patil [c]

[a] Jaipur National University, Jaipur, India
[b] Indofil Industries Limited, India
[c] Institute of Science, Mumbai, India

ARTICLE INFO

Article history:
Received 27 February 2017
Received in revised form 29 March 2017
Accepted 11 April 2017
Available online 12 April 2017

Keywords:
Dimethyl sulfate
Hexaconazole
Methylation
HS-GC–MS
SIM mode
Method development
Method validation

ABSTRACT

Dimethyl sulfate is used as alkylating agent in manufacturing process but because of its genotoxicity nature it should be monitored at trace levels (1 mg/kg). A simple pre-column derivatization i.e. alkylation of butyl alcohol gives corresponding ether (methoxybutane) which is analyzed by head space gas chromatography mass spectrometry (HS-GC–MS). The retention time of derivative is 5.32 min. Analysis was carried out in Selected Ion Monitoring (SIM) mode. The linear regression analysis data for the calibration curve showed a good linear relationship with a regression coefficient of 0.999 in the concentration range of 0.035 mg/kg to 9.234 mg/kg. The method was validated for specificity, linearity, LOD, LOQ, precision and accuracy.

1. Introduction

In the pharmaceutical and chemical industries dimethyl sulfate (DMS) has very wide applications as a reagent for methylation of phenols, amines and thiols and carboxylic acids. It is mainly used as a reagent for methylation in many pharmaceutical and pesticide syntheses [1]. DMS also has sulfating properties and is therefore used in manufacturing dyes, fabric softeners etc. DMS has a lower cost and higher reactivity in comparison to other methylating agents and therefore is preferred over other reagents by the industry. The International Agency for Research on Cancer has classified DMS as a Class 2 carcinogen [2] based on the carcinogenicity test results so trace level [3] determination becomes very important.

In pharmaceutical products earlier approaches dealt with gas chromatographic (GC) analysis by direct sample injection [4,5] with FID or MS detection. The major drawback of such an analytical method relates to the frequent need for cleaning the inlet port to avoid formation of ghost peaks produced by thermal degradation of the matrix and dimethyl sulfate [6] deposited on the internal surface of the liner. Isolation of DMS from the matrix through different techniques prior to injection in the GC can be considered as a practical solution to the above mentioned problem. Liquid–liquid extraction of DMS with ethyl *t*-butyl ether has been used but limited to aqueous soluble active ingredient (AI) and intermediates with satisfactory results [7], however not so useful for aqueous insoluble compounds.

To overcome such limitations, derivatization of DMS has been reported. For example, the reaction of DMS in aqueous media with sodium thiosulfate leads to formation of methyl thiocyanate, which can be directly analyzed by head-space GC–MS [8] but formation of the methyl isothiocyanate by-product was observed only in minor amounts.

Pentafluorothiophenol was also used to act as a methylation substrate for DMS, allowing analysis of the derivative by head-space GC–MS [9]. 2-Mercaptopyridine was successfully used for derivatization of DMS. The fluorescence product was determined by RPLC and detected by fluorescence [10]. Alternatively, trialkylamines (more precisely triethylamine, in the case of DMS) were used as derivatization reagents for alkylating compounds [11]. A quantitative derivatization was obtained after heating at 50–60 °C for 1 h. The resulting quaternary ammonium ion was subsequently separated from the reaction mixture, the reaction rate was found to be slow and less sensitive observed when making derivatization.

In proposed work an attempt has been made to develop simple, safe and fast pre-column derivatization using non-hazardous and cheap reagent, 1-butyl alcohol, to analyze DMS in hexaconazole technical (agriculture fungicide). Presently, no such method is available for the determination of residual DMS present in commercial hexaconazole technical. Method includes alkylation of butyl alcohol with residual dimethyl sulfate in head space vial and injection into gas chromatography

* Corresponding author at: Indofil Industries Limited, Off S. V. Road, Azad Nagar, Sandoz Baug P.O., Thane-400 607, Maharashtra, India.
E-mail address: npetha-icc@modi.com (N.H. Petha).

http://dx.doi.org/10.1016/j.microc.2017.04.016
0026-265X/

Table 1
Gas chromatograph conditions for DMS analysis.

Instrument	Agilent 7890 GC		
Column	DB-624, 30 m × 1.4 mm × 0.25 μ		
Carrier gas	Helium		
Injector temperature (°C)	240		
Injection type	HS (head space) control		
Column oven program	Heating rate (°C/min)	Initial temperature (°C)	Hold time (min)
	–	40	10
	30	220	5
Flow rate (mL/min)	1.5		
Injection volume (mL)	1.0 (head space)		
Injection mode	Spit 5:1		
Run time (min)	21.0		

mass spectrometry. Analysis was carried out using SIM mode to enhance detection limit. The developed method was validated according to SANCO [12] and CIPAC [13] guidelines to evaluate the capability of the method.

2. Experimental

2.1. Material

Dimethyl sulfate was purchased from Sigma Aldrich. 1-Butyl alcohol (AR), dimethyl formamide (AR) and sodium hydroxide (LR) was purchased from Merck. Hexaconazole technical was taken from Indofil Industries Limited.

2.2. Methods

Chromatographic method conditions used were as follows (Tables 1–3).

2.2.1. Preparation of reagents

2.2.1.1. Alkaline n-butanol. 0.5 g of sodium hydroxide was weighed and dissolved in 100 mL of n-butanol, warmed for 15 min and filtered through filter paper and filtrate was used as alkaline n-butanol.

2.2.2. Preparation of solutions

2.2.2.1. Dimethyl sulfate standard. A quantity of 50.1 mg dimethyl sulfate standard was weighed into a 100 mL volumetric flask and diluted up to the mark with butanol (Solution-A). Pipetted 2.0 mL from the Solution-A into 50 mL volumetric flask and diluted up to the volume with butanol (Solution-B). 1.0 mL from Solution-B was pipetted into 10 mL volumetric flask and diluted up to the volume with butanol to produce the working standard concentration of 0.010 mg/mL (Solution-3). 1.0 mL of dimethyl formamide, 1.0 mL from Solution-3 and 1.0 mL of alkaline butanol was added into 20 mL head space vial and subjected to analysis by head space analyzer.

2.2.2.2. Hexaconazole technical sample. A quantity of 1000 mg Hexaconazole technical was weighed and transferred into a 20 mL head space vial. 1.0 mL of DMF, 1.0 mL of alkaline butanol and 0.5 mL of 1-butanol was then added in vial and subjected to analysis by head space analyzer.

Table 2
Gas chromatography mass spectrometer conditions for DMS analysis.

Instrument	Agilent 7000 Triple Quad MS
MS transfer line temperature (°C)	250
MS source temperature (°C)	230
Function type	SIM (selective ion monitoring)
SIM ions	45, 88
Solvent delay (min)	4.5

Table 3
Head space analyzer conditions for DMS analysis.

Instrument headspace unit	Agilent 7697A Headspace Sampler
Headspace mode	Static Headspace Extraction (SHE)
Oven temperature (°C)	110
Loop temperature (°C)	150
Transfer line temperature (°C)	180
Equilibrium time (min)	10.0
Vial pressure equilibrium time (min)	0.2
Withdraw time (min)	0.3
Injection time (min)	0.5
Transfer line	Fused silica (0.53 mm)

3. Results and discussion

3.1. Methodology

To ensure maximum mass transfer and formation of methoxybutane in sealed headspace vial various parameters were optimized such as effect of alkaline butanol vs. only butanol, vial equilibration temperature, vial equilibration time, volume of alkaline butanol and sample quantity.

3.1.1. Effect of alkaline butanol

The reaction of alkoxides with alkyl sulfates (DMS) is an important general method for the preparation of ethers, and is known as the Williamson synthesis. Alkoxide ion formation is important as a means of generating a strong nucleophile that will readily form C—O bonds in SN2 reactions. Thus butanol reacts very slowly with dimethyl sulfate to give corresponding methyl ether, but sodium butoxide in butanol solution reacts very rapidly. This effect was checked by using butanol and saturated alkaline butanol, more intense peak was observed using sodium butoxide under same analysis condition.

3.1.2. Vial equilibration temperature

Mass transfer of DMS i.e. formation of ether was checked by applying temperature to the vial so as to increase reaction rate and to have maximum conversion in minimum time. The maximum conversion was observed at 110 °C temperature of vial which is shown in Fig. 1.

3.1.3. Vial equilibration time

For an efficient sample analysis, rapid and near-complete mass transfer is highly desired. So the effect of time was checked for the maximum output at 5.0, 10.0 and 15.0 min. Results in Fig. 2 show that a near-complete mass transfer in headspace vial can be achieved within 10.0 min at the given temperature.

3.1.4. Volume of alkaline butanol

The role of volume of alkaline butanol in the conversion rate was checked by taking 0.5, 1.0 and 1.5 mL of alkaline solution in sealed

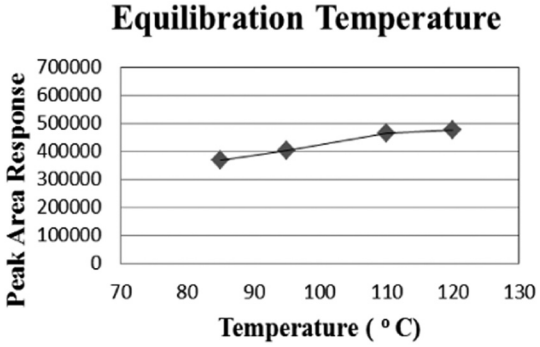

Fig. 1. Effect of temperature.