

Original Article**MONITORING OF SPATIAL PRESENCE OF RESIDUAL SOLVENTS IN THE VICINITY OF PHARMACEUTICAL INDUSTRIAL AREA**Anil Gopala*¹, Barji Druva Sarika², Sadanandam Palle² & Jyothi Vantikommu²¹Verder Scientific Private Limited, Nacharam, Hyderabad, India²Centre for Chemical Sciences and Technology, Institute of Science and Technology, Jawaharlal Nehru Technological University, Hyderabad, Telangana, India-500085

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ABSTRACT

Manufacturing of pharmaceuticals and enhancement of the characteristics of the active pharmaceutical ingredients (API) involves the use of large quantities of volatile organic solvents (VOC). The risk and health hazards associated with the presence of these solvents limit the quality of API. To minimize their presence, a process of desolvation is employed that leads to the spatial escape of residual solvent. Such solvent vapor intrusion into the ambient air is an aspect of concern for human health, which necessitates the monitoring of their concentrations in ambient air. This paper illustrates a novel monitoring concept by providing an optimized screening method to assess the spatial presence of these residual solvents in ambient air in the surrounding areas of the pharmaceutical industry by using automated thermal desorption (ATD) hyphenated to gas chromatography coupled to mass spectrometry (GCMS). This study unravels the presence of the residual solvents in acceptable levels in vivo in the air as per the regulatory bodies (USP 467, WHO) at the location investigated.

Keywords: Air, residual solvents, active pharmaceutical ingredient, GCMS-ATD, USP, WHO**INTRODUCTION**

USP 4671 identified 60 residual solvents and classified them based on toxicity profile as Class 1 solvents, which are human carcinogens, Class 2 solvents are non-genotoxic animal carcinogens and Class 3 solvents that with low toxic potential. The regulatory bodies, United States Pharmacopeia (USP 467) which provides the regulation of residual solvent limits for intake in dosage form, and World Health Organization (WHO) providing criteria for atmospheric air regulation though independent, are in concurrence with each other and

specify similar exposure limits. These residual solvents are generally analyzed and regulated in the API by using headspace extraction of solvent from sample matrix, and followed by the injection into Gas chromatography coupled with Flame ionization detector (GC-FID).²⁻⁴ Few of the literature reports were restricted to analysis of volatile organic compounds in ambient and indoor air.⁵⁻¹⁹ This is the first effort to monitor residual solvents in ambient air in the surrounding areas of a pharmaceutical industry,

MATERIALS AND METHODS

In this study, air samples were collected from two sampling points (Figure 1) located about 1 km (Front and Back) in the pharmaceutical industrial zone, Hyderabad, India by placing the sampler at height of 60 cm from the ground level at $25 \pm 2^\circ\text{C}$ in winter season at 8 pm using Sequential Tube Sampler (STS 25 PerkinElmer™) with two different adsorbent systems (Carbopack 300™ (PerkinElmer), Tenax-TA™ 60/80

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(PerkinElmer)) during this study. A flow sampling of 100 ml/min was employed for 10 min sampling period. Carbo-pack 300™ is a multi-adsorbent material consisting of sequentially loaded three adsorbent materials (Carbotrap C, Carbotrap B & Carbosieve SIII). Carbo-pack 300™ provides sampling of solvents based on varied range of volatility and polarity. Carbosieve SIII retains nC3 which are low molecular highly volatile compounds, Carbotrap B retains solvents from nC5-nC12 which are most likely medium molecular volatile compounds and Carbotrap C is a graphitised carbon black material it retains solvents from nC8-nC20.20 Tenax TA™ adsorbent system is a porous polymer of 2,6-diphenylene oxide providing efficient adsorption and desorption of volatile contaminants of higher boiling point up to 300°C, which has a relative water retention and resistant to oxygen. 21 PerkinElmer™ Turbomatrix 650 Automated Thermal Desorber system connected to PerkinElmer™ Clarus 680 GC-MS system was used as the instrumental platform for the analysis. The adsorbent tube was desorbed for 15 min at 300°C the sample was collected in Peltier cooled box at -30°C and it was desorbed at 300°C. 0.32µm diameter fused silica transfer line of 5 m, which connects the ATD and GCMS through PerkinElmer™ Elite-1 (15 m x 0.25 mm x 1 µm) MS capillary column. The oven temperature program was set at 35°C with a ramp rate of 15°C/min to reach the final set temperature at 200°C. The total GC run time was set for 50 min.

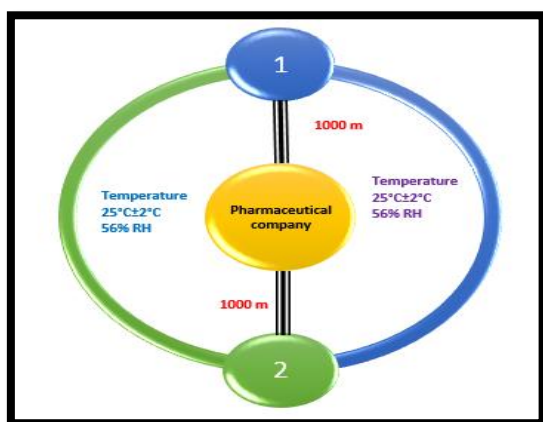


Fig 1. Schematic diagram of radial locations for air sample collections

RESULTS AND DISCUSSION

Carbotrap 300™ revealed the presence of two residual solvents in the air around the pharmaceutical industry at both the locations. These were identified as class 2

residual solvent, methylene chloride and class 3 residual solvent, acetic acid (Figure 2). Methylene chloride existence in air can be due to its low boiling point of 39°C and high vapour pressure of 376 mm of Hg. The presence of acetic acid can be due to its hydrophilic nature as it has very low vapour pressure of 13 mm of Hg.

The figure 2 displays the overlap of mass spectrometric profiles of the residual solvents collected from two locations using Carbotrap adsorbent system. The overlap profile shows a distinctive shift in retention time of acetic acid, it is owing to its hydrophilic nature, low molecular weight coupled with lower desorption efficiency of Carbotrap 300™ for volatile polar hydrophilic compounds²² for the significant deviation of retention time of acetic acid.

Carbotrap 300™ is a multisorbent material having both hydrophobic and hydrophilic nature which tends to give different desorption time which also could be a probable reason for distinctive shift of acetic acid chromatograms. The method using Carbotrap 300™ adsorbent system can be an effective screening tool for residual solvents.

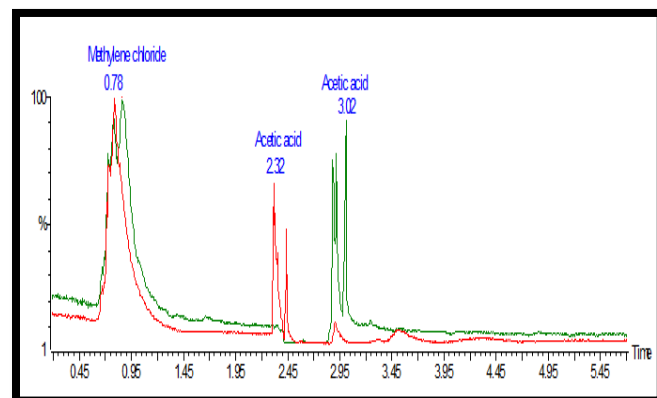


Fig 2. Chromatogram of Air Sample collected at two radial locations using Carbotrap 300™ as Adsorbent System

Tenax TA™ adsorbent system specifically adsorbs volatiles and semi-volatiles from air due to its capacity to retain high boiling compounds hence selected for quantification.²³⁻²⁵ Figure 3 represents the overlap of mass spectrometric profiles of the residual solvents collected from two locations using Tenax TA™ adsorbent system. From this it is observed that the retention time of the methylene chloride and acetic acid were stable and the elution patterns were identical.

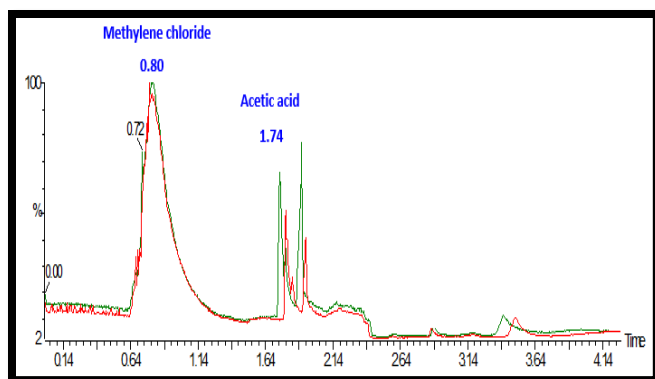


Fig 3. Chromatogram of Air Sample Using Tenax TA™ Adsorbent System

The quantitative determination of the two solvents in the samples was performed using standards prepared in methanol. Quantification results of methylene chloride and acetic acid for the two locations were shown in table 1.

Table 1: Quantification results of methylene chloride and acetic acid at two locations

Location	Methylene chloride (ppm)	Acetic acid (ppm)
Front	327.4 ± 0.7	1323.7 ± 0.8
Back	426.9 ± 0.7	1447.0 ± 0.8

To relate the concentration of residual solvents in environment in lieu with USP 467, WHO25 guidelines following conclusions were summarized. USP 467 limits for methylene chloride in the pharmaceutical product is ≤ 600 ppm per 10 g of drug (per day dose exposure) and acetic acid is ≤ 5000 ppm per 10g of drug (per day dose exposure). WHO provides guidelines for ambient air limit exposure of methylene chloride as 700 ppm² (per day exposure) and it does not have the exposure limit for acetic acid.

Though acetic acid concentration is more in air, it is considered to be acceptable as this undergoes photocatalytic oxidation to form carbon dioxide, methane and water, which are nontoxic. It can also undergo chlorination in presence of sunlight to form chloroacetic acid, which is stronger acid, but this

formation is less marked. The nighttime sample collection may also be reason for marked high concentration of acetic acid in air.

From this study we can elucidate that among Class 1 solvents, which are potentially toxic to both human health and environment were absent in ambient air. These Class 1 solvents were absent in air as these solvents are not actually used in pharmaceutical preparation due to their adverse effects. Class 1 chemicals may be involved sometimes in API due to internal reaction synthesis mechanism or presence as an impurity in other solvents.

CONCLUSIONS

The analysis results indicate that residual solvents around at the two sampling sites in the pharmaceutical industrial zone in Hyderabad are non-toxic in nature and well within the accepted limits specified by USP and WHO. The proposed protocol has wider applications in ambient air quality control, as it could be used not only for analysis of residual solvents in the atmosphere, but also for the analysis of other volatile organic contaminants. This tests need to be adopted by local pollution control organization and report results every day/week similar to the environmental pollution data published to increase confidence of residential people, flora & fauna.

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