ELSEVIER

Journal of Hazardous Materials 43 (1995) 13–30

JOURNAL OF HAZARDOUS MATERIALS

Ion mobility spectrometry for continuous on-site monitoring of nicotine vapors in air during the manufacture of transdermal systems

G.A. Eiceman[a,*], S. Sowa[b], S. Lin[a], S.E. Bell[c]

[a] *Department of Chemistry and Biochemistry, New Mexico State University, Las Cruces, NM 88004, USA*
[b] *Cygnus Therapeutic Systems, Redwood City, CA 94063, USA*
[c] *Department of Chemistry and Biochemistry, Eastern Washington University, Cheney, WA 99004, USA*

Received 8 December 1994; accepted in revised form 14 January 1995

Abstract

Ion mobility spectrometry (IMS) can provide continuous on-site monitoring of nicotine in air exceeding in real-time the current OSHA eight hour exposure standard of 0.5 mg/m^3. A hand-held IMS with water reagent gas, exhibited near instantaneous response, detection limits of 0.006 mg/m^3 and median relative standard deviations of 3.1% for vapor levels between 0.01 to 0.25 mg/m^3. Ion mobility spectra for nicotine showed characteristic product ions which were mass-identified as monomer ($M \cdot H^+$) and dimer ($M_2 \cdot H^+$) ions. Continuous monitoring of ambient air during the manufacture of nicotine-based transdermal systems demonstrated that short-lived, elevated concentrations of iso-propanol occurred when surfaces on the production equipment were cleaned. However, the concentration profile for nicotine in ambient air showed a gradual rise to a plateau with only minor ripple. High variability in personal samplers was attributed to localized concentrations of nicotine in the production equipment as identified using the hand-held IMS analyzer.

Keywords: Nicotine; Air; Monitoring; Ion mobility spectrometry

1. Introduction

Nicotine or 3-(1-methyl-2-pyrrolidyl)pyridine ($C_{10}H_{14}N_2$) is a volatile organic compound which can be isolated from *Nicotiana tabacum* or *N. rustica* [1]. Exposure to nicotine for humans can come through inhalation of cigarette smoke or through exposure [2] to air contaminated with environmental tobacco smoke (ETS). Nicotine has a substantial vapor pressure of 4×10^{-2} torr at 25 °C and vapor concentrations of

* Corresponding author. Tel.: 505-646-2146; Fax: 505-646-6094

SSDI 0304-3894(95)00023-2

nicotine can rise to 0.045 mg/m^3 in some indoor atmospheres [3]. Under such conditions, nicotine in urine of non-smokers exposed to ETS can contain about 5% of that observed for smokers [2] and intake can amount to 0.3 mg/d [3]. Other exposures to nicotine arise from use of tobacco-based products such as snuff or smokeless tobacco [4] and from the use of nicotine as a non-persistent, non-systemic contact insecticide or a fumigant in closed spaces [2].

Nicotine is also a concern in the occupational exposure for personnel at manufacturing sites for nicotine-based transdermal systems. In these facilities, a reservoir of nicotine is fed to production equipment while workers maintain control over flows of neat nicotine and various plastic or foil layers supplied to the equipment. Although facilities are well-ventilated to reduce worker exposures, ambient air monitoring is required to insure worker safety. A present difficulty with traditional monitoring methods is the prolonged delay in obtaining experimental airborne vapor levels of nicotine. Such delays are caused by the time needed to collect and prepare sample for analysis and by the methods for determining nicotine in treated samples. The standard method for determining nicotine vapor in ambient atmospheres is based upon active or passive sampling where ambient air is brought in contact with an adsorbent bed of a porous polymer. After a sampling episode, the adsorbent polymer is extracted with a solvent and the extract used for gas chromatographic analysis [5–7]. The method is reliable and sensitive with detection limits of 0.17 and 0.02 μg/m^3 for 1 and 8 h collections, respectively.

Although these methods exceed the OSHA standard of 0.5 mg/m^3 for an 8 h shift, the time and effort required to determine nicotine in ambient air are burdensome. Moreover, the final results will reflect a time-weighted average where short-lived spikes in the profile of concentration versus time will disappear from the averaging step. A real-time, continuous, on-site analyzer was deemed necessary to assist in worker protection and in informed management of equipment and facilities. Technologies based upon atmospheric pressure chemical ionization (APCI) principles had previously exhibited sensitive and selective response to nicotine in air [2] and a recent configuration of APCI-based technology is portable ion mobility spectrometry [8].

1.1. Ion mobility spectrometry

Ion mobility spectrometry (IMS) is an instrumental method suited for the characterization of organic compounds based upon mobility or size-to-charge ratio of ions in the gas phase [9]. In IMS, air samples are drawn into a reaction region where vapors are ionized at ambient pressure in air through APCI reactions. Such reactions generally involve the transfer of a proton from a reservoir of charge, the reactant ions, to the sample vapors to yield product ions as shown in Eq. (1):

$$\underset{\text{Reactant ion}}{(H_2O)_nH^+} + \underset{\text{Analyte}}{M} \rightleftharpoons \underset{\text{Product ion}}{M\cdot H^+} + nH_2O. \quad (1)$$

Product ions from these APCI reactions are characterized in a drift region of the IMS analyzer as shown in Fig. 1. The basis of ion characterization is drift time through

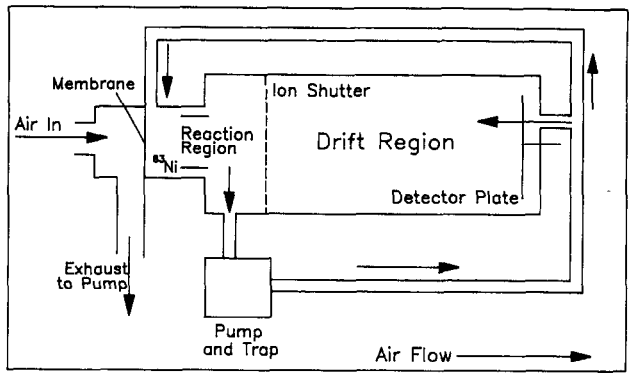

Fig. 1. Schematic of drift tube for hand-held ion mobility spectrometer. The drift tube consists of two regions including a reaction region where ion-molecule reactions occur and a drift region where ions are characterized using gas phase ion mobilities in a weak electric field.

a voltage gradient in air and ion speed depends upon size to charge ratio. Since IMS operates on principles different from that of mass spectrometry, instrumentation can be made small (i.e. hand-held), low powered, and rugged. Ion characterizations result in an ion mobility spectrum or plot of detector current versus time of drift, and such spectra can be used for identification of vapors. Drift times are usually 3–15 ms in a 3–10 cm drift tube with voltage gradients of ca. 200 V/cm.

Instrumentation in IMS has followed a pattern of development from large laboratory units to hand-held analyzers during the last two decades. Originally, IMS was envisioned as a capable gas chromatographic detector with potential advantages over mass spectrometry (MS) in size, weight, power and convenience [9]. Also, IMS exhibited low picogram detection limits and response to a wide range of chemicals [8]. However, the intrinsic simplicity of IMS and potential to be fashioned into a hand-held analyzer attracted military establishments in the UK and US. By 1980, a small sophisticated chemical analyzer (known as the Chemical Agent Monitor or CAM) based on IMS was deployed for in-field screening of material for contamination by nerve and blister agents. The portable and rugged nature of CAM created fast interest in the environmental field screening communities. The highly directed engineering of CAM for nerve agents constrained successful applications to molecules where proton affinities are high and selectivity in response can be enhanced through APCI reaction chemistry and mobility spectra. A portable ion mobility spectrometer has been successfully applied to detecting nicotine [10] in respired breath, skin vapors and air in a limited manner. While quantitative performance was demonstrated, ion chemistry was not explored.

1.2. Objectives for study

The principal objectives of this project were (A) a full evaluation of IMS response to nicotine including quantitative calibration and delineation of APCI chemistry, and

(B) the completion of an on-site monitoring study at a production facility for nicotine-based transdermal systems. Specific interests included instrument response parameters (for a hand-held fieldable IMS) such as limits of detection, calibration curve, analyzer stability, and foundations of response from APCI reactions. Interest for on-site monitoring was centered on identifying sources of nicotine in production equipment and on monitoring the ambient air for solvents and nicotine vapors released during manufacturing periods.

2. Experimental

2.1. Instrumentation

Two hand-held IMS instruments were employed in laboratory and on-site studies and included an unmodified Chemical Agent Monitor (CAM) from Graseby Ionics, Ltd. (Watford, Herts., UK) and a modified CAM known as Scrubber-CAM, also from Graseby Ionics, Ltd. In the Scrubber-CAM, the original permeation source was removed so the ionization chemistry was based on water reagent gas. In the unmodified CAM, ketone vapors are added intentionally to the gas flow before return to both the ion source and the drift regions of the ion mobility spectrometer. In each CAM, flows are recirculated and conditioned using molecular sieves. Operating parameters for both CAMs were established by the manufacturer and included 10 mCi ^{63}Ni sources; 36 mm long drift region; drift gas flow, 200 ml/min; field strengths, 244 V/cm; inlet sample flow, 0.5 l/min; shutter pulse width, 180 μs; shutter repetition rate, 40 Hz; and drift tube temperature, ambient. The CAM was operated in positive polarity. In a CAM, the inlet sample flow is isolated from the ionization region through a methylsilicone membrane (10–15 μm thick) which assists in maintaining stable moisture level in the internal supporting gases. The inlet nozzle is roughly 40 °C and the intended temperature for the membrane is 100 °C to facilitate analyte permeation. Signals were processed using digital signal averaging with an interface board and software (Advanced Signal Processor or ASP, Graseby Ionics, Ltd.) installed on IBM-AT compatible computers. Parameters selected with the ASP software included number of scans per spectrum, 64 and number of samples per spectrum, 512. The CAM with acetone reagent gas was used for exploratory studies including a preliminary calibration and interference tests. The Scrubber-CAM was also examined for response and selected for use in all on-site monitoring studies. A final calibration of the Scrubber-CAM was made immediately following the monitoring studies.

A TAGA 6000 tandem mass spectrometer (MS/MS) from Sciex, Inc. (Toronto, Ontario, Canada) was used in IMS/MS and collision-induced dissociation (CID) studies to determine the identity of ion clusters created in the IMS. The MS/MS was operated under nominal conditions [11] with an exception that the corona discharge source was replaced with a CAM drift tube. The end of the drift tube was an insulator and was placed against the plate used for corona discharges; the last conducting ring in the drift region was placed at 1400 V and was 1 cm from this plate (at 650 V+). The ion mobility spectrometer was at ambient temperature and the ion shutter was opened

fully to provide improved ion yield to the mass spectrometer. The IMS/tandem MS was used only for identification of ions created in the IMS under conditions similar to those in the hand-held units. In CID studies, an ion was selected in the first quadrupole, the ion was injected into an argon gas curtain in a second quadrupole, and the fragments were analyzed in the third quadrupole.

Supporting instrumentation included a vapor generator, a gas chromatograph, a GC/MS, and air sampling devices. The vapor generator was a Kin Tek model 360 unit and was used to produce vapors from a diffusion source. The diffusion source was a small vial containing 100 mg of montmorillonite clay spiked with 50 μl of nicotine. The vapor generator was supplied with 100 ml/min of air from an Aadco Inc. model 737 pure air supply. Temperatures for the vapor generator were set from 25 to 80 °C to deliver various concentrations of nicotine from 0.006 to 0.25 mg/m^3. These vapor levels were confirmed through independent methods [2] using constant volume samplers (model 224-43XR or equivalent from SKC, Inc., Eight–Four, PA). A Hewlett-Packard (HP) Model 5890 gas chromatograph (GC) was equipped with 25 m capillary column with slightly polar phase (5% phenyl, 95% methylpolysiloxane). Conditions for analysis were: injector temperature, 260 °C; detector temperature 270 °C; column temperature, 60–200 °C at 10 °C/min. Finally, a HP model 5890 GC with 5971 mass selective detector was used to confirm the identity and purity of the nicotine used in calibrations and APCI reaction studies.

2.2. Procedures

Laboratory studies

Generation of Nicotine in Air: Vapors of nicotine (Kodak Chemical Co., Rochester, NY) were generated using a diffusion source for nicotine thermostated to specified temperature and air flow rate. Temperatures from 25 to 65 °C in 5 °C intervals were allowed to equilibrate for 2–4 h between temperature changes. These times allowed conditioning of surfaces providing a continuous stream of nicotine vapors in air at steady concentrations. The flow of air from the vapor generator was diluted 1:5 with ambient air in the inlet nozzle of the IMS. For calibration, the IMS was positioned near the vapor generator exhaust line and at least 25 replicate spectra were acquired at each vapor level within 5 min.

Reference method for determining nicotine in air. The method for determining nicotine vapors from the vapor generator and in the ambient air on-site at the production facility was based upon NIOSH method S293 [4]. Air samples were collected using personal air samplers at flow rates of 100 or 200 ml/min. The analyte was collected on XAD-2 resin in a glass tube which was capped and stored for laboratory analysis. The resin was transferred directly to an autosampler mini-vial and 1 ml of ethyl acetate containing diphenylamine (internal standard). The extract was used without further treatment for gas chromatographic analysis.

Production line monitoring

A survey using personal samplers was undertaken from 10 June 1992 to 11 September 1993 and consisted of 105 samples collected from individuals equipped

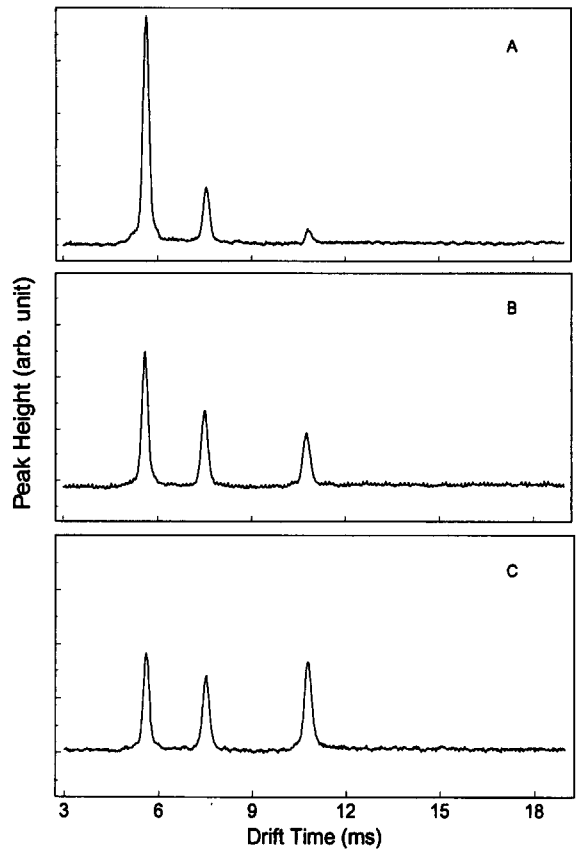

Fig. 2. Ion mobility spectra for nicotine with water reagent gas at three vapor concentrations of nicotine in air. Concentrations (mg/m^3) were (A) 0.02, (B) 0.1, and (C) 0.25. The influence of vapor concentrations on mobility spectra can been seen in the relative intensities of reactant ion peak, monomer ion peak, and dimer ion peak. See text for a discussion of the chemistry that is responsible for forming the monomer and dimer ions.

with SKC, Inc. personal sampling pumps. The samples were taken and analyzed according to NIOSH method S293.

A Scrubber-CAM with water reagent gas was positioned 1 m from a production unit for nicotine transdermal systems. The IMS was configured to automatically and continuously obtain and store ion mobility spectra for ambient air every 60 s. Data collection was started at 0709 h on 26 January 1994 and ended after the production run was stopped and cleaning of equipment with solvent started at 1220 h.

Localized vapor levels for nicotine in the production equipment were measured by positioning the hand-held IMS for ca. 2 min in a region of interest. Spectra were collected, stored, and identified by consecutively incremented spectrum numbers.

3. Results and discussion

3.1. IMS and IMS/MS of nicotine

Ion mobility spectra, with water reagent gas, for nicotine vapors at several concentration levels are shown in frames A–C of Fig. 2. In frame A, the reactant ion peak (RIP, at 5.8 ms) was evident along with two product ion peaks for relatively low concentrations of nicotine (0.02 mg/m^3). At higher nicotine vapor concentrations, the peak at 10.8 ms was increased; both the RIP and the product ion at 7.5 ms were exhausted at even higher concentrations (not shown). This pattern was consistent with product ions of monomer and dimer ions as shown in Eqs. (2) and (3).

$$\underset{\text{Reactant ion}}{(H_2O)_nH^+} + \underset{\text{Nicotine}}{C_{10}H_{14}N_2} \rightleftharpoons \underset{\text{Monomer ion}}{C_{10}H_{14}N_2 \cdot H^+} + nH_2O, \tag{2}$$

$$\underset{\text{Monomer ion}}{C_{10}H_{14}N_2 \cdot H^+} + \underset{\text{Nicotine}}{C_{10}H_{14}N_2} \rightleftharpoons \underset{\text{Dimer ion}}{(C_{10}H_{14}N_2)_2 \cdot H^+}. \tag{3}$$

Mass spectra for the ions created by APCI reactions with nicotine in the IMS are shown in part in Fig. 3 from IMS/MS characterization and from CID experiments. In frame A, the mass spectrum is shown for ions from nicotine at ca. 0.1 mg/m^3; evident in the mass spectrum were ions at *m/z* 163 and *m/z* 325 which suggested $M \cdot H^+$ and M_2H^+, respectively. These assignments were confirmed through the CID experiments where the dimer ion, *m/z* 325 for $(C_{10}H_{14}N_2)_2H^+$, underwent a loss of 162 to an ion at *m/z* 163 (Fig. 3(B)). This corresponded to the loss of one nicotine molecule, $C_{10}H_{14}N_2$, from the dimer ion. Results for CID analysis of the ion at *m/z* 163 showed no fragmentation and corresponded to the monomer ion ($M \cdot H^+$) or $(C_{10}H_{14}N_2) \cdot H^+$, confirming Eqs. (2) and (3). The nicotine reagent used in these studies was assayed by GC/MS and found to be free of detectable impurities. This was consistent with absence of detectable impurities in either the IMS spectra and mass spectra, both of which are sensitive to impurities.

Reactant ions were evident, principally at *m/z* 37, 55, and 73, in the mass spectrum (frame A, Fig. 3) and were hydrated protons of the kind $(H_2O)_nH^+$ where $n = 2$–4 under the conditions of relatively low moisture of gases in the IMS. Previous APCI-MS studies with nicotine [2] showed MH^+ and small amounts of $MH^+ \cdot H_2O$ under relatively moist conditions; hydrated monomer ions of nicotine were not observed since supporting gases were relatively dry. When acetone (Ac) was used as a reagent gas to enhance selectivity of response through APCI reactions, the mobility spectra showed comparable features to those for water reagent gas. Namely, the spectrum consisted of two product ions well separated in drift times. However, the monomer ion with acetone reagent gas was shifted to drift times longer than that for the monomer ion with water reagent gas. This suggested clustering between acetone and the monomer ion and CID experiments demonstrated ion clusters of the kind $M \cdot Ac \cdot H^+$. No clusters between acetone and the dimer ion were observed. Nonetheless, in the presence of a strong proton affinity reagent gas such as acetone, the proton affinity of nicotine was sufficiently strong to result in the exchange protons to the

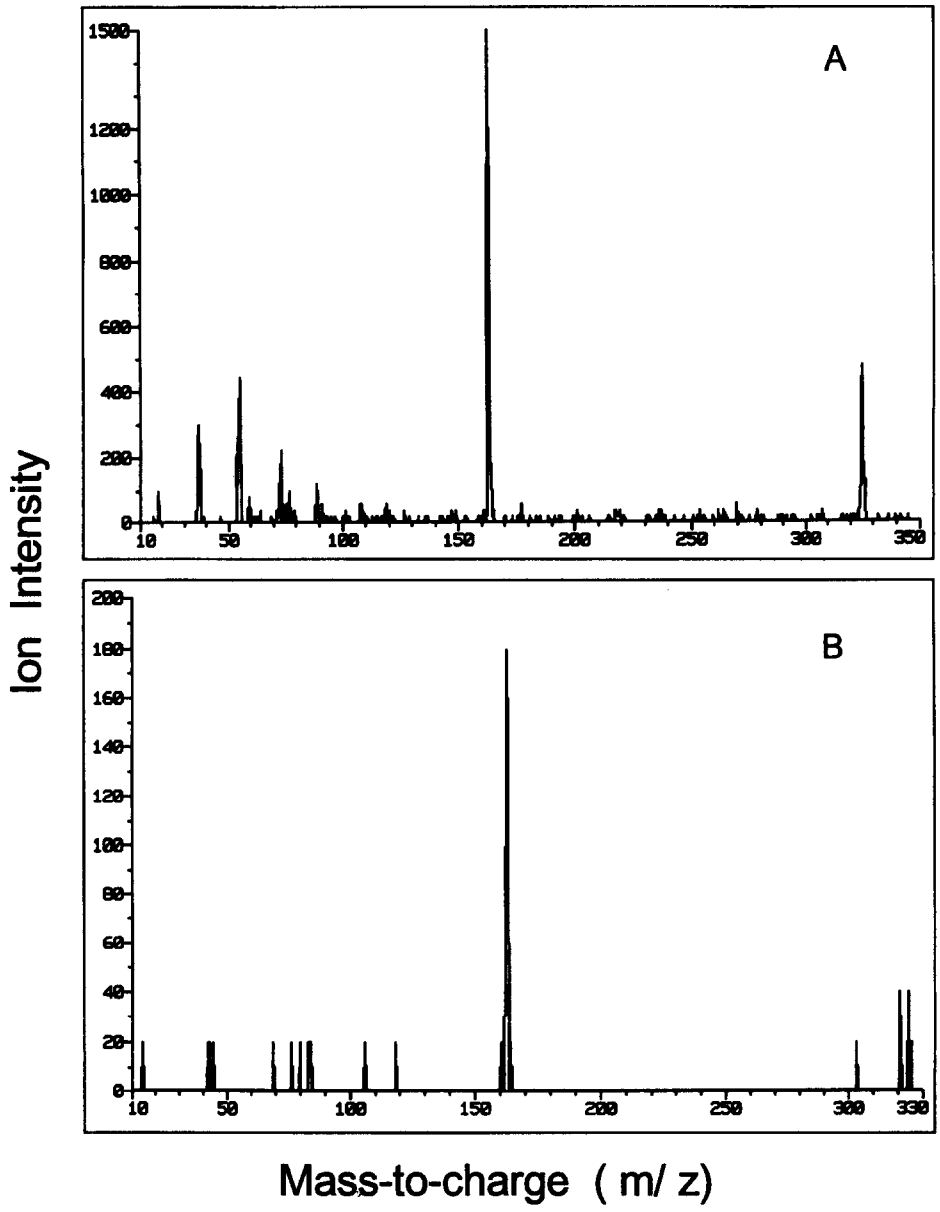

Fig. 3. Mass spectra from IMS/MS studies of nicotine reaction chemistry in air at atmospheric pressure. In frame A as mass spectrum shows product ions from nicotine vapors with water-based reactant ions. In frame B results are shown from CID analysis of the dimer ion, *m/z* 325.

exclusion of common organic vapors such as alcohols, alkanes, and aromatic hydrocabons.

Quantitative performance of the hand-held IMS using vapors from the vapor generator is shown in Figs. 4 and 5. The vapor levels were verified using the standard

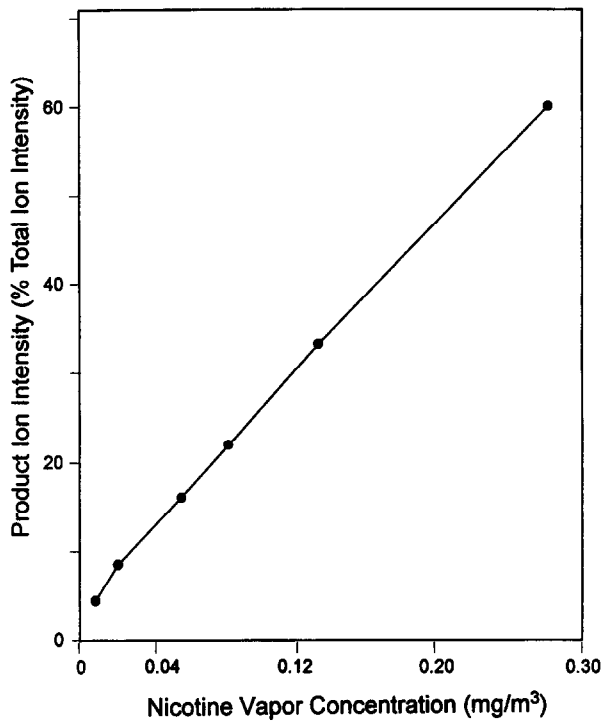

Fig. 4. Calibration curve for hand-held IMS analyzer using confirmed vapor concentrations. The y-axis is total product ion intensity normalized to total ion intensity.

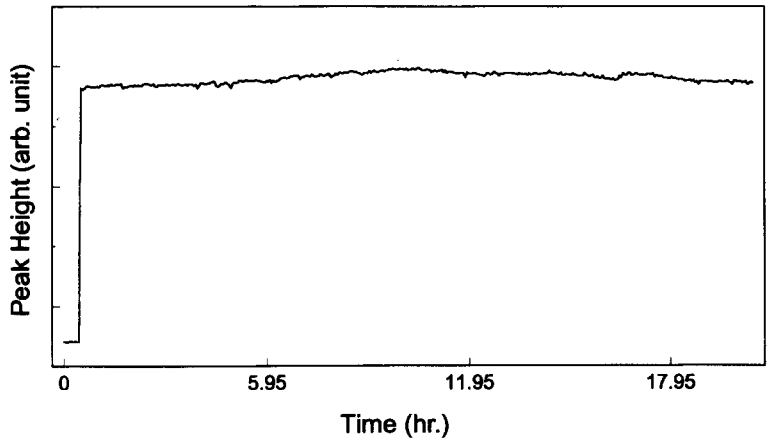

Fig. 5. Stability of vapor generator and IMS response over a 20 h monitoring episode as observed for the monomer ion intensity.

method for nicotine in air [2]. A quantitative response curve is shown in Fig. 4 for total product ion intensity (i.e. the sum of monomer and dimer ion peak heights) normalized against total ion intensity. The data used to construct this curve are shown in Table 1 and a plot of response versus concentration (Fig. 4) exhibited linear performance from 0.01 to 0.25 mg/m^3. Plots also could be made for individual product ions. The reactant ion peak or RIP showed consistent decreases with increased nicotine levels (see Table 1) and can serve as another measure of vapor concentrations; generally, the RIP intensity is an indicator of total atmospheric purity [12]. At concentrations greater than 0.25 mg/m^3 the monomer ion curve became non-linear and quantitative measurements could be drawn from the dimer ion plot. At levels of nicotine greater than 0.25 mg/m^3, as the intensity for the monomer ion declined, charge from available protons was accumulated in the dimer ion peak as shown in Eq. (3). The dimer ion peak was 34 mV intensity at 0.05 mg/m^3 and increased steadily until ca. 2 mg/m^3 where a plateau was reached and the ion source was saturated. Within the concentration range shown in Fig. 4, the reproducibility of intensity, summed for the monomer and dimer product ions, was 1.8–16% RSD, with a median value of 3.1% RSD. The monomer ion showed a peak height of 73 mV at 0.01 mg/m^3 and noise was 15 mV [13]. The detection limit (S/N = 3:1), calculated from these values, was 0.006 mg/m^3.

The stability of both vapor generator and hand-held IMS is shown in Fig. 5 where long-term stability of the generator was demonstrated and reproducibility over this time, when normalized for total ion intensity, was better than 2% RSD for over 200 spectra at vapor levels of 0.1 mg/m^3. These results demonstrated that a hand-held IMS analyzer showed suitable stability for application in monitoring of ambient air over 8 h and that prior calibrations with the vapor generator were reliable.

Table 1
Statistics from replicate ion mobility spectra for nicotine at various concentrations in air

Vapor concentration of nicotine (mg/m^3)							
	Peak height (mV)[a]	0.01	0.02	0.05	0.08	0.13	0.25
Reactant ion peak	X[b]	1490	1398	1143	1080	871	435
	σ	8.0	11.7	7.4	6.0	7.4	9.5
	% RSD	0.52	0.84	0.65	0.56	0.85	2.2
Monomer ion peak	X	73	135	196	258	326	327
	σ	5.0	5.3	6.1	6.2	6.2	7.1
	% RSD	6.5	3.9	3	2.4	1.9	2.2
Dimer ion peak	X	0	0	34	62	135	394
	σ			5.4	6.1	4.1	7.1
	% RSD			16	9.9	3.1	1.8

[a] Peak heights are corrected for baseline and were derived from baseline-to-baseline calculations.
[b] Average of 25 replicate spectra with 64 averages per spectrum.

The CAM, equipped with water-based chemistry, exhibited distinct ion mobility spectra for alcohols, ketones and other organic solvents excepting halogenated solvents with low proton affinities. Prior detailed studies for interferences in a CAM with acetone reagent gas illustrated a selectivity of over 10000:1 for common solvents against high proton affinity analytes such as nicotine. Limited interference studies were made here and were consistent with prior findings. Thus, a water-based CAM offered response to nicotine and other solvents of interest such as iso-propanol while an acetone-based CAM excluded such solvents from response. A water-based CAM was selected for on-site monitoring described below.

3.2. On-site monitoring studies

Preliminary evaluation of production site

Results from monitoring air in the vicinity where personnel operate the production equipment are shown in Fig. 6 as a plot of nicotine concentration versus sample

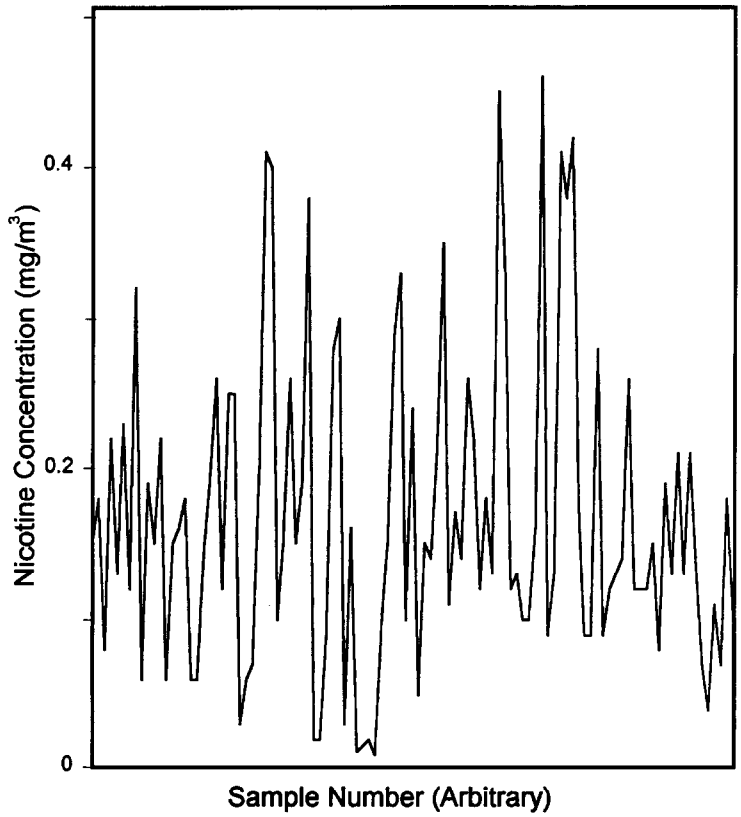

Fig. 6. Nicotine concentration in personal samplers versus sample number. Samples were taken and numbered in a chronological manner over a four month period for workers at a nicotine transdermal system production facility.

number, ordered chronologically over four months. However, samples were drawn from several workers on a given day making the sample number axis somewhat arbitrary. Still, the variability in nicotine levels was dramatic and suggestive of widely fluctuating nicotine levels in the air or localized, elevated vapor levels, or some other highly variable influence. For example, the range of concentrations was 0.01–0.46 mg/m^3 with an average (n = 105) and standard deviation of 0.167 and 0.104 mg/m^3, respectively. Two studies were undertaken to assess the vapor gradients around the manufacturing device and to evaluate vapor levels at a fixed location near the equipment.

Continuous on-site monitoring of air using IMS

Results from monitoring at a single location near the production equipment are shown in Fig. 7 where the peak intensities are shown for the reactant ion peak (frame A), the monomer ion peak for iso-propanol solvent (frame B), the dimer ion peak for iso-propanol (frame C), and the monomer ion peak for nicotine (frame D). Spectra were acquired continuously at 60 s intervals and key events during the manufacturing, referenced to spectrum number, are listed in Table 2. The RIP was a measure of the iso-propanol monomer ion (frame B) through an inverse relationship between RIP intensity and iso-propanol vapors as shown by Eq. (4):

$$\underset{\text{Reactant ion}}{(H_2O)_nH^+} + \underset{\text{Iso-propanol}}{C_3H_9O_2} \rightleftharpoons \underset{\text{Iso-propanol monomer ion}}{C_3H_9O_2 \cdot H^+} + nH_2O. \quad (4)$$

Iso-propanol was used abundantly for routine cleaning of the rollers used to feed plastic, metal and adsorbent sheet stock into and throughout the production equipment. Residues could accumulate on these rollers and could disrupt the proper functioning of equipment. Thus, equipment was regularly stopped and iso-propanol was spread freely on cloths to clean the rollers. Several large excursions of iso-propanol were evident in frame B (Fig. 7) at spectrum numbers 60–70, 120–130, 140–150, and 310–320. This last spike caused the monomer ion to be completely exhausted in favor of the dimer ion as shown in Eq. (3) and corresponded to the end-of-production cleaning of the manufacturing equipment with iso-propanol and heptane.

In contrast to the punctuated use of iso-propanol, the nicotine vapor levels as seen in frame D did not exhibit a similar pattern. Instead, a baseline level for nicotine near or below the detection limit was evident in the first nine minutes of sample before production began. Upon the start of production, nicotine vapor levels began to rise immediately and continued to rise until a plateau was reached at spectrum numbers

Fig. 7. Peak intensity profiles during a stationary monitoring study at a distance of 1 m from production equipment for transdermal system. The frames are for (A) reactant ion peak, (B) monomer ion for iso-propanol, (C) dimer ion for iso-propanol, and (D) monomer ion for nicotine. A spectrum was stored every 60 s on a continuous basis and the spectrum number incremented from the start at 0709 h. Increased concentrations of vapors caused declines in the intensity of the RIP and increased in the intensities for product ions.

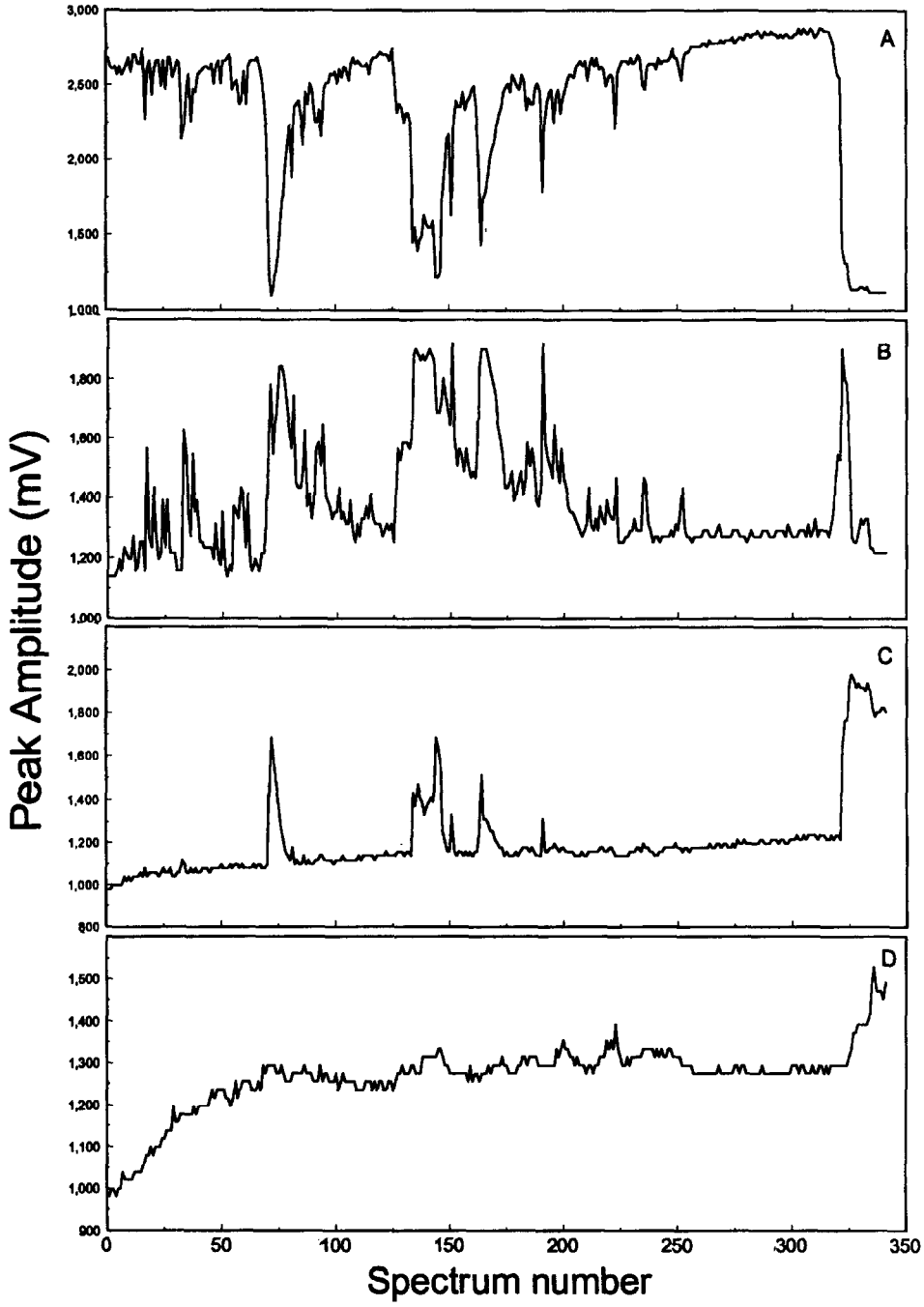
A
B
C
D
Peak Amplitude (mV)
Spectrum number
3,000
2,500
2,000
1,500
1,000
1,800
1,600
1,400
1,200
1,000
2,000
1,800
1,600
1,400
1,200
1,000
800
1,500
1,400
1,300
1,200
1,100
1,000
900
0
50
100
150
200
250
300
350

Table 2
Chronology of continuous monitoring of nicotine transdermal system

Clock time (2400 h)	Spectrum No.	Comment
0709	001	Begin IMS analyzer and data system
0718	009	Manufacturing equipment started
0738	029	Stopped production for 4 min
0839	090	Worker break started
0903	112	Worker break stopped
0930	142	Air vents started
1112	245	Stopped production
1119	250	Closed waste materials bag
1220	311	Clean-up using excesses of iso-propanol and heptane

Routine cleaning with iso-propanol of roller surfaces for films stock, for laminated product were not recorded.

60–70, roughly one hour after production was started. A workers' break for 20 min, beginning at spectrum number 90, was reflected in a slight decline in the nicotine vapor levels starting at 95 min and lasting another 20 min until spectrum number 120. The cessation of production at spectrum number 246, and removal of waste bins containing nicotine residues from waste product, also afforded a slight decline in nicotine monomer ion. The solvent levels also declined during this period. However, the concentration of nicotine vapors increased when cleaning began in earnest (spectrum numbers 325 and following) as nicotine laden materials were stripped from internal regions of the production equipment. During this cleaning episode, the vapor concentration of nicotine was 0.08 mg/m^3 as calculated from Fig. 4. This agreed favorably with a value of 0.06 mg/m^3 as determined from the standard OSHA method, run in parallel with the IMS monitoring study. These results illustrate that the exposure to nicotine, in this instance where an individual is placed at 1 m from the equipment, might be well-represented by a time weighted average method.

In view of the stable levels of nicotine in the ambient air, a plausible explanation of the large variations for individual exposures (Fig. 6) was localized elevated concentrations of nicotine at spots in the production equipment. Workers with different tasks at different locations (as designated in Fig. 8) in around the manufacturing equipment could receive exposures dependent upon both localized vapor concentrations and time spent near that location. Such locally high vapor levels were plausible from a cursory inspection of the equipment and a mapping of vapor levels would be necessary to assess this suspicion. Such a map would be difficult and expensive to create using traditional sorbent trap methods. In contrast, an entire production unit could be mapped during a 15 min exercise using a hand-held IMS as discussed below.

Detailed mapping of vapor sources

Results from a survey of local vapor levels at various places on the equipment are shown in Fig. 9 where IMS response is shown for the RIP (frame A), iso-propanol

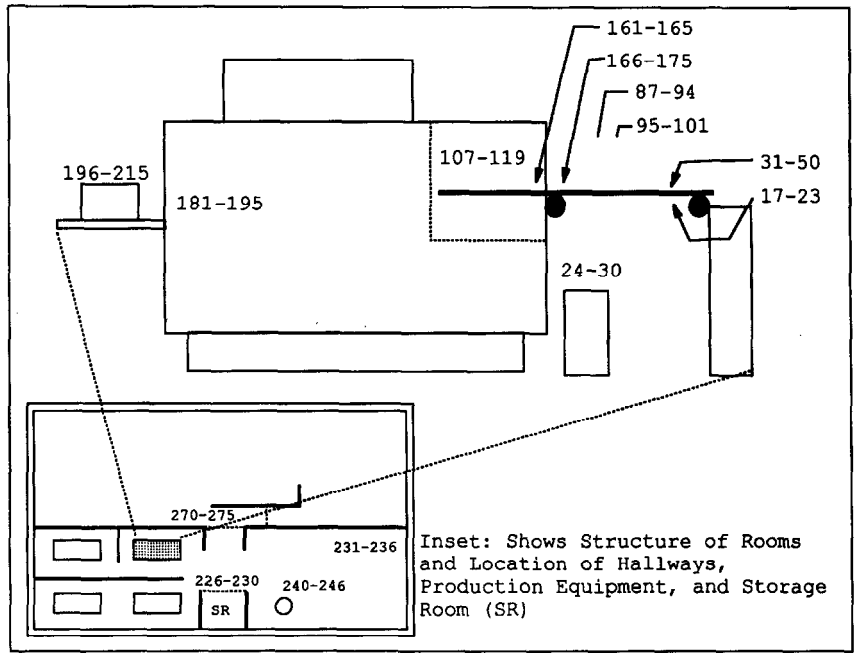

Fig. 8. Diagram of production equipment for manufacture of transdermal systems showing locations for sampling. Locations are referenced as spectrum numbers to Table 3 and Fig. 9.

monomer peak (frame B), and nicotine monomer peak (frame C). Spectrum number is related to a specific location at the production equipment where the hand-held IMS was positioned for roughly 10 spectra as summarized in Table 3. There is no particular order of sampling; however, vapor levels around the production equipment can be referenced to a specific location through matching spectrum numbers in Fig. 9 to the equipment map in Fig. 8. In Fig. 9 (frame A), dramatic differences in localized concentrations of all vapors is evident in the plot for RIP intensity. In frame B, vapor levels for solvents (principally iso-propanol) showed various elevated concentrations throughout the equipment with a few exceptions. This is not surprising considering the generous use of iso-propanol to keep working surfaces clean through wiping surfaces with solvent-laden cloths. In contrast, substantial levels of nicotine were localized to ca. five sites. This is evident in the spikes in intensity for the nicotine monomer ion in frame C (Fig. 9) and in Table 3.

The presence of elevated concentrations of nicotine, localized to a few areas of the production equipment was impossible to determine with the earlier monitoring study described above. The emission of nicotine at elevated levels from various parts of the equipment, when combined with diffusion and mixing of air in the vicinity of the equipment, provided a generally uniform vapor concentration of nicotine vapors at a sampling distance of 1 m. However, the regions of elevated concentrations of nicotine vapors, as seen in the IMS survey, were consistent with the personal sampling study (Fig. 6) where individuals were assigned specific tasks at a given location around

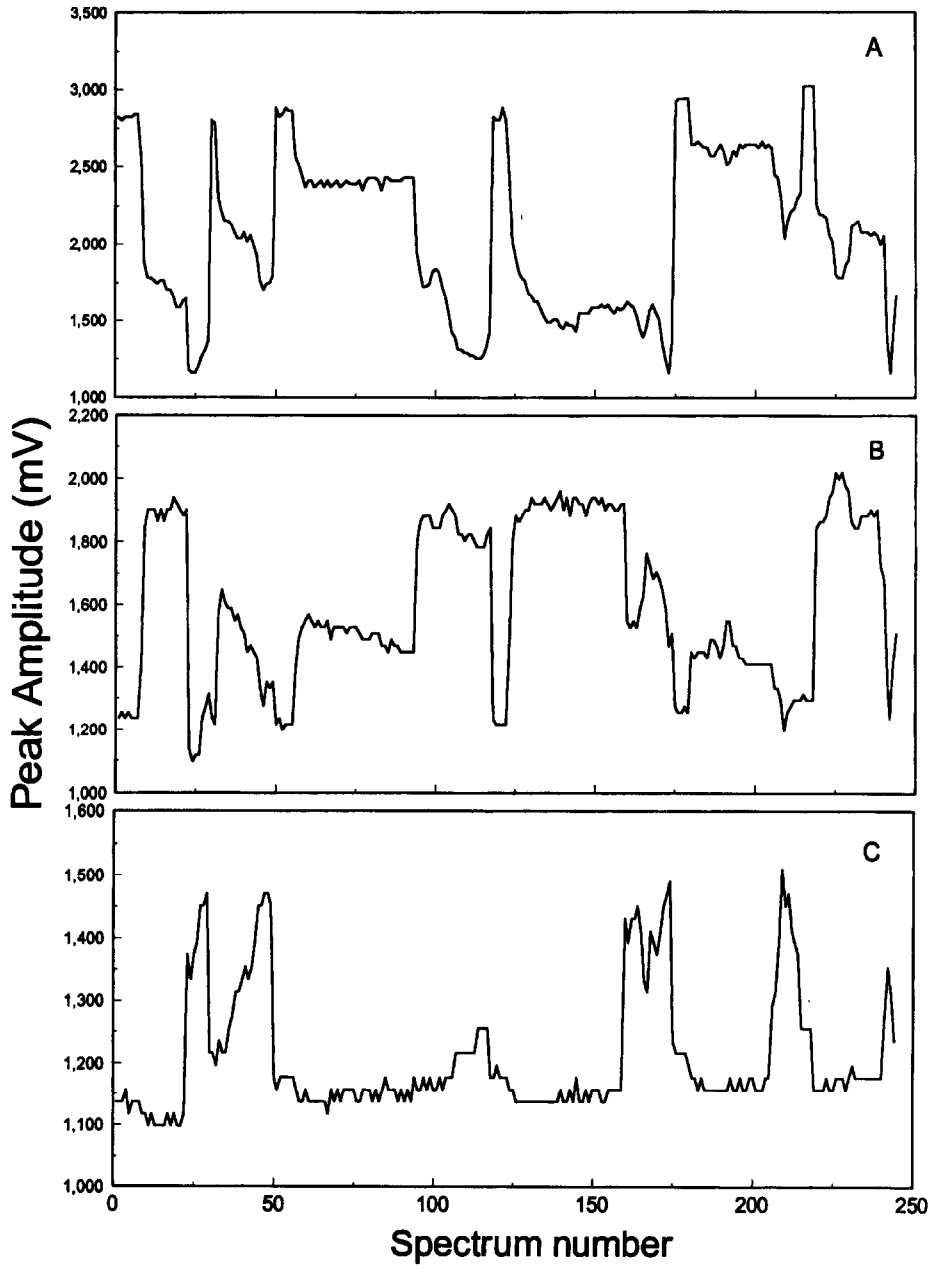

Fig. 9. Record of peak intensities from survey of localized concentrations of nicotine with manufacturing equipment for transdermal systems. Locations can be referenced by spectrum numbers to Table 3 and Fig. 8.

Table 3
Record for vapor mapping of production equipment for nicotine using hand-held ion mobility spectrometer

Spectrum Nos.	Location	Solvent ion intensity	Nicotine ion intensity
01–07	IMS with protective cap installed	–[a]	–[a]
08–16	Ambient air	–[a]	–[a]
17–23	Below conveyor belt	+++[d]	–[a]
24–30	At red bag	++[c]	+++[d]
31–50	Above belt	–[a]	+++[d]
51–55	Cap on IMS	–[a]	–[a]
56–86	Cap off IMS, ambient air	++[c]	–[a]
87–94	Near belt	+++[d]	–[a]
95–106	Near belt	+++[d]	–[a]
107–119	Above roller	++[c]	+++[d]
120–160	Background	–[a]	–[a]
161–165	Before dye cutter	++[c]	+++[d]
166–175	After dye cutter	++[c]	+++[d]
176–180	Cap on	–[a]	–[a]
181–195	Operator station	+[b]	–[a]
196–215	Near liquid pump	–[a]	+++[d]
216–219	Cap on	–[a]	–[a]
220–225	Hallway near site	+[b]	–[a]
226–230	In front of storage	–[a]	–[a]
231–239	In adjacent room	+[b]	–[a]
240–246	At waste container	++[c]	–[a]

[a] No vapors detected.
[b] Monomer ions observed: low concentrations of vapors.
[c] Monomer and dimer ions observed: medium concentrations of vapors.
[d] Only dimer ions observed: comparatively high concentrations of vapors.

the production equipment. Thus, the wide variations in nicotine vapor levels seen in the results from the personal sampling study were due to exposures at specific locations around the production equipment than to a general accumulation of nicotine in the ambient atmosphere. This suggests that area wide monitors for worker protection here have no intrinsic advantage and instead, that personal monitors should be employed to monitor real-time exposures to nicotine during production of transdermal systems. Such small IMS monitors have been demonstrated and should be effective nicotine monitors.

4. Conclusions

Ion mobility spectrometry provided distinct APCI reactions for nicotine leading to characteristic mobility spectra based upon a monomer-dimer ion equilibrium. The limits of detection for continuous monitoring with a hand-held IMS and without sample treatment exceeded OSHA standards and afforded real-time signals for vapor concentrations of nicotine in air. The advantages for on-site monitoring with a

portable sophisticated IMS analyzer were evident in two monitoring episodes where the patterns of nicotine were determined for: (a) the accumulation in air at a transdermal system production site and (b) the localized nicotine levels at production equipment. Vapor levels of nicotine around the production equipment arose from a few localized sources while vapor concentrations for iso-propanol, used to clean equipment surfaces, were elevated throughout the equipment.

References

[1] Hubert Martin and Charles R. Worthing (Ed.), Pesticide Manual, 5th edn., p. 384.
[2] E.C. Horning, M.G. Horning, D.I. Carroll, R.N. Stillwell and I. Dzidic, Life Sci., 13 (1973) 1331.
[3] M. Muramatsu, S. Umemura, J. Fukui, T. Arai and S. Kira, Int. Arch. Occup. Environ. Health, 59 (1987) 545.
[4] E.R. Gritz, B. Vaer-Weiss and N.L. Benowitz, Clin. Pharmocol. Ther., 30 (1981) 201.
[5] Manual of Analytical Methods, Part II, Vol. 3, National Institute for Occupational Safety and Health, Cincinnati, OH, Method S293 (1977).
[6] M.W. Odgen, J. Assoc. Off. Anal. Chem., 72 (1989) 1002.
[7] EPA Compendium of Methods for the Determination of Air Pollutants in Indoor Air, US Environmental Protection Agency, Washington, DC, Methods IP-2A (1989).
[8] G.A. Eiceman, Critical Rev. Anal. Chem., 22 (1991) 471.
[9] G.A. Eiceman and Z. Karpas, Ion Mobility Spectrometry, CRC Press, Boca Raton, FL, 1993.
[10] F. Keenan and M. Cooke, Anal. Proc. Including Anal. Commu., Vol. 13, 1994, p. 27.
[11] C.S. Harden, A.P. Snyder and G.A. Eiceman, Organic Mass Spectrometry, 28 (1993) 585.
[12] Q. Meng, Z. Karpas and G.A. Eiceman, Intl. J. Environ. Anal. Chem., in press.
[13] G.L. Long and J.D. Winefordner, Anal. Chem., 55 (1983) 712A.