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Short communication

Control of solvent use in medical devices by proton transfer reaction mass spectrometry and ion molecule reaction mass spectrometry

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ABSTRACT

A homemade proton transfer reaction mass spectrometer (PTR-MS) and a commercial ion molecule reaction mass spectrometer (IMR-MS) have been applied to detect volatile organic compounds (VOCs) in the packaging bags of infusion sets made of polyvinylchloride (PVC) plastic. The most abundant characteristic ions in the PTR-MS and IMR-MS measurements are observed at m/z 99 and 98 respectively, which are the results of soft ionizations that a residual chemical undergoes the proton transfer reaction in PTR-MS and the charge transfer reaction in IMR-MS. On the basis of ionic intensity dependence on the reduced-field in the PTR-MS investigation, the residue can be unambiguously identified as cyclohexanone, a commonly used adhesive agent in PVC medical device manufacture. Quantitative measurement by PTR-MS shows that concentrations of cyclohexanone in the packages of two types of infusion sets are 11 and 20 ppm respectively. Due to fast response, absolute concentration detection, and high sensitivity, the PTR-MS and IMR-MS detection methods are proposed for the quality control of medical devices including the detection of illegal or excessive uses of chemical solvents like cyclohexanone.

1. Introduction

Cyclohexanone has been widely utilized as an adhesive solvent in the manufacture of a variety of medical devices made of polyvinylchloride (PVC) plastic [1]. Due to low volatilization, cyclohexanone may remain in the PVC products and can subsequently release into the stored solutions or the internal airspace of medical devices [2–5]. Consequently, when patients receive medical treatments such as intravenous therapy, blood transfusion, and hemodialysis, they will have the risk of taking in cyclohexanone. Although at present there have been no regulations or standards about the usage of cyclohexanone in PVC medical devices, it is known that cyclohexanone has negative effects on liver, kidneys, central nervous system, and respiratory system, and it is potentially tumorigenic and mutagenic upon exposure [4,6]. Because cyclohexanone is harmful, some standards related to occupational exposure have been issued by various organizations, including the threshold limit of 20 ppm (parts per million by volume) as the time weighted average over an 8-h workday (TWA) recommended by the American Conference of Governmental Industrial Hygienists [6] and the occupational exposure limit of 10 ppm as TWA by the European Union [7].

In the past, the analyses of cyclohexanone in PVC materials were performed mainly by means of chromatography and/or mass spectrometry techniques. For instance, Snell [3] examined twenty hemodialysis tubes using gas chromatography (GC) combined with the water extraction method, determining the concentrations of cyclohexanone to be in the range of 1.02–43.7 ppm. The author also noted that it was nearly impossible to clean out the cyclohexanone even if the tubes were washed with a solution of sodium chloride. Falk and Jacobsson [2] reported cyclohexanone concentrations of 0.55–9.24 mg L^{-1} in solutions stored in PVC bags based on the determination by gas chromatography mass spectrometry (GC–MS). In addition, high performance liquid chromatography (HPLC) [4] has also been used to measure cyclohexanone in the parenteral solutions migrated from the PVC bags through detecting the derivatization of cyclohexanone, and cyclohexanone concentrations were found to be in the range of 2.05–44.96 mg L^{-1}. These measurements are based on analyses of liquid extractions and require rather complicated sample pretreatments, quantitative calibrations, and rigorous analytical steps, thus analyzing a sample will take a long time. With these methods, it will be very difficult to make a rapid judgment of whether a solvent like cyclohexanone is present in the medical devices.

Proton transfer reaction mass spectrometer (PTR-MS) and ion molecule reaction mass spectrometer (IMR-MS) are two special chemical ionization techniques with the advantages of rapid response, high sensitivity, and so-called soft ionization. PTR-MS [8–10] uses H_3O^+ as reagent ions, which do not react with the

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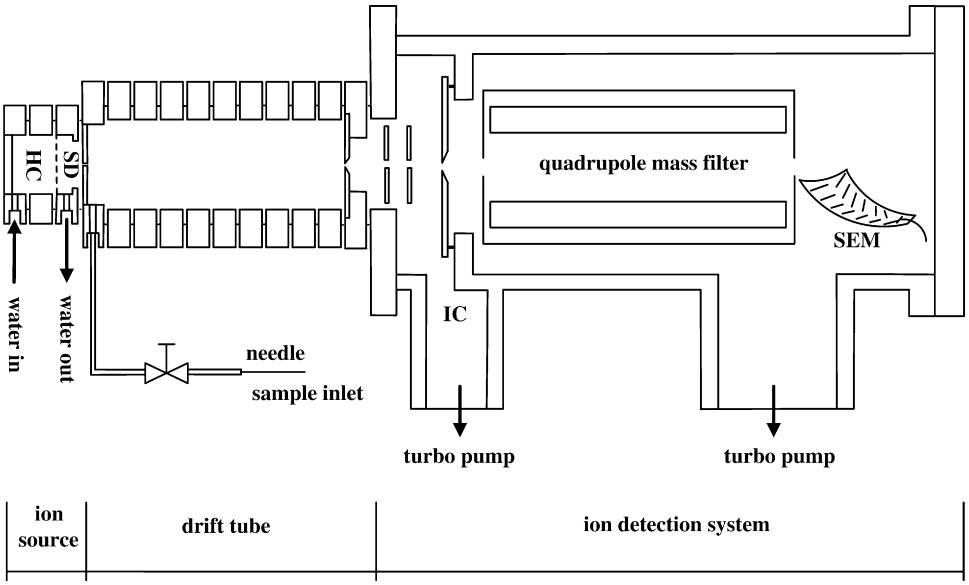

Fig. 1. Schematic diagram of PTR-MS apparatus. HC, hollow cathode; SD, source drift region; IC, intermediate chamber; SEM, secondary electron multiplier.

main components in air like N_2, O_2, and CO_2. In contrast, it can undergo proton transfer reaction with volatile organic compounds (VOCs) that have proton affinities (PA) higher than that of water. In PTR-MS, an electric field E is applied along the ion reaction drift tube to induce the ionic collisions with well-defined kinetic energy just over the ion-molecular bond energies within the cluster ions. Thus the product ions, forming in the proton transfer reaction of reagent ions H_3O^+ with most analytes M, are expected to appear in the form of MH^+. The ion collision energy in the drift tube is closely related to the reduced-field E/N, where N is the number density of gas in the drift tube. On a standard PTR-MS instrument, E/N is normally set to a regular value typically in the range of 120–160 Td (1 Td = 10^{-17} V cm^2 molecule^{-1}) to produce the protonated product for each compound. PTR-MS is especially suitable to real-time detection of trace VOCs in environmental monitoring, food inspection and medical diagnosis [8–10]. Different from the PTR-MS, IMR-MS [11] ionizes the analyte M through a charge transfer reaction using a selectable reagent ion Kr^+, Xe^+, or Hg^+. The ionization potential of Kr, Xe, and Hg are 14.00, 12.13, and 10.44 eV respectively, thus IMR-MS in principle can ionize and detect organic and inorganic compounds by selecting the right reagent ions.

The objective of the present study is to demonstrate that the usage of chemical solvent in PVC medical devices can be controlled by the PTR-MS and IMR-MS techniques. An unknown compound was detected within the packaging bags of infusion sets and it was unambiguously discriminated as cyclohexanone by collision-induced dissociation of product ions at different reduced-field E/N using PTR-MS. The quantitative determination of residual cyclohexanone at ppm level can be rapidly achieved by PTR-MS based on a newly derived equation without sample pretreatment and calibration. This shows that PTR-MS and IMR-MS are the promising tools for the control of chemical solvent use in medical devices.

2. Experimental

The PTR-MS used in the present study is a homemade apparatus as described in our previous work [12] and a more detailed introduction about PTR-MS technique can be found elsewhere [8–10].

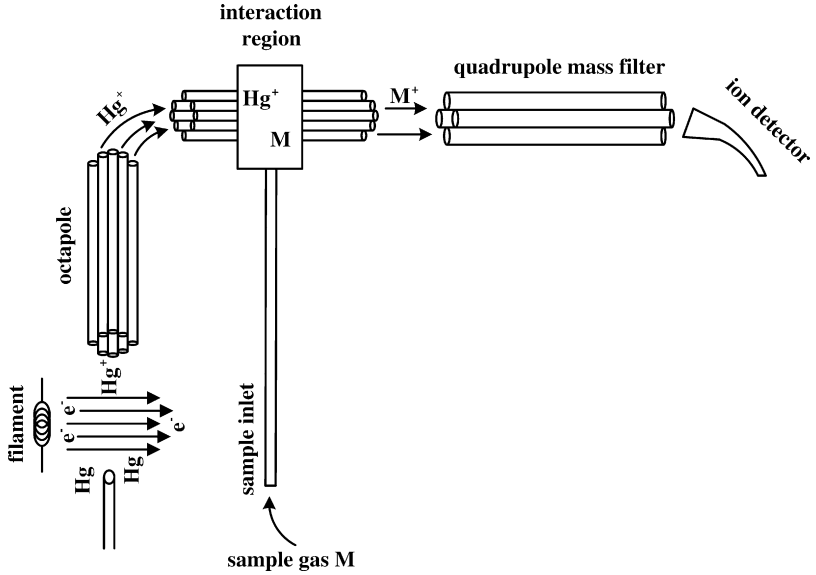

Fig. 2. Schematic diagram of the IMR-MS system.

Briefly, PTR-MS consists of discharge ion source, drift tube, and ion detection system (Fig. 1). The reagent ions H_3O^+ were produced through the water vapor discharge in a hollow cathode ion source, and were injected to the ion reaction drift tube. When the analyte M was added to the ion reaction region, it underwent rapid proton transfer reactions with the primary ions H_3O^+ if its PA exceeds that of H_2O [8].

$$M + H_3O^+ \rightarrow MH^+ + H_2O \quad (1)$$

The ions in the drift tube, after passing through a small differentially pumping intermediate chamber, were leaked into the vacuum chamber and were detected by the quadrupole mass spectrometer equipped with an ion pulse count system. In our PTR-MS measurement, the regular value of E/N was 140 Td. The E/N could be changed by adjusting the voltage across the whole drift tube while the pressure in the drift tube is kept at 1.0 Torr. The standard gas of toluene was used to check the accuracy of PTR-MS determination, and the results show that the concentrations measured by PTR-MS are in agreement with the prepared concentrations in the range 0.01–1.2 ppm [12].

Fig. 2 shows the IMR-MS used in the present experiments, which is a commercial instrument Airsense.net (V&F Instruments, Austria). IMR-MS used electron impact ionization to create the reagent ions, Hg^+ in our experiments. The reagent ions Hg^+ were transferred by the octapole rods to the ionic reaction region where the charge transfer reaction happened if the added analyte M has ionization potential lower than that of Hg.

$$M + Hg^+ \rightarrow M^+ + Hg \quad (2)$$

The IMR-MS instrument has a limit of detection at low ppb level and it may quantify analyte through the standard sample calibration.

Two kinds of disposable PVC infusion set with their original packages were obtained from pharmacies. They were made in two different factories and are labeled as Brands A and B in the experiments. The packages containing the infusion sets, and the plastic bags having cyclohexanone, were punctured via a syringe needle at the inlet of PTR-MS or an inlet tube of IMR-MS, by which the sample gas within the packaging bag was introduced to the ionic reaction region of the PTR-MS or IMR-MS instrument. The flow rate of the sampling gas is 8 mL min^{-1} in the PTR-MS measurement.

3. Results and discussion

3.1. Identification of cyclohexanone

Fig. 3 shows the mass spectra measured by PTR-MS for the gas in the packaging bags of the infusion sets. One can find that the mass spectra are basically same for the infusion set Brands A and B. The dominant peak at m/z 19 is due to the reagent ions H_3O^+. The main product ions appeared at m/z 99. This implies that in the packages of the infusion sets, there is an unknown chemical with molecular weight of 98 and a PA higher than that (691 kJ mol^{-1}) [13] of water.

To recognize this chemical, the internal gases in the packages of infusion set Brands A and B were measured in the IMR-MS instrument using Hg^+ as reagent ions. The mass spectra recorded are shown in Fig. 4. It can be noted that a very high ionic peak appeared at m/z 98 for both infusion set packages. This demonstrates that the unknown chemical in the bags indeed has a molecular weight of 98; moreover, its ionization potential should be lower than that (10.44 eV) of Hg.

Through the above PTR-MS and IMR-MS measurements, we can now conclude that the chemical detected in the packages of these infusion sets must have a molecular weight 98 with a PA more than 691 kJ mol^{-1} and an ionization potential less than 10.44 eV. Considering that cyclohexanone is often used as the welding agent

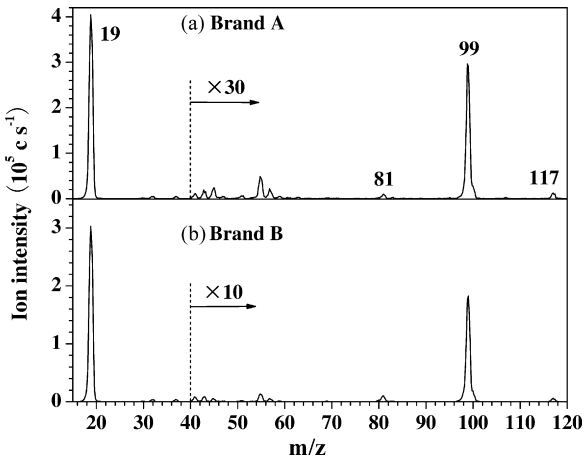

Fig. 3. Mass spectra measured by PTR-MS for the gas in the packaging bags of infusion sets for Brands A and B.

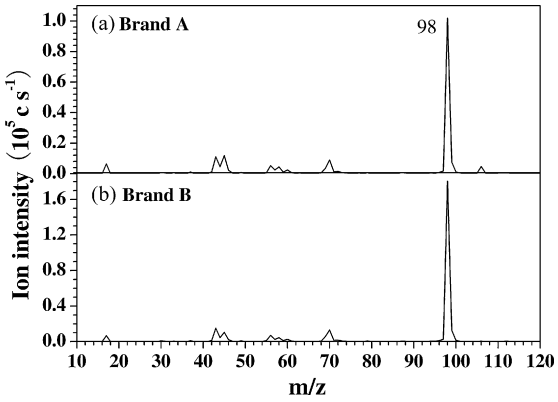

Fig. 4. Mass spectra measured by IMR-MS with reagent ions Hg^+ for the gas in the packaging bags of infusion sets for Brands A and B.

in PVC articles manufacture, and its molecular weight (98), PA (841.0 kJ mol^{-1}) and ionization potential (9.16 eV) [13] all meet the above characteristics, therefore we speculate that cyclohexanone is a most probable candidate for this chemical in the packaging bags.

In order to further verify the above conclusion, the vapor of a cyclohexanone sample was measured in the PTR-MS apparatus with different reduced-field E/N. Fig. 5 is the mass spectra measured at the regular reduced-field E/N = 140 Td. The most abundant product ions are the protonated cyclohexanone $C_6H_{10}OH^+$ at m/z 99. One can note that there are weak ionic signals at m/z 81 and 117 that were also observed in the PTR-MS measurements of the

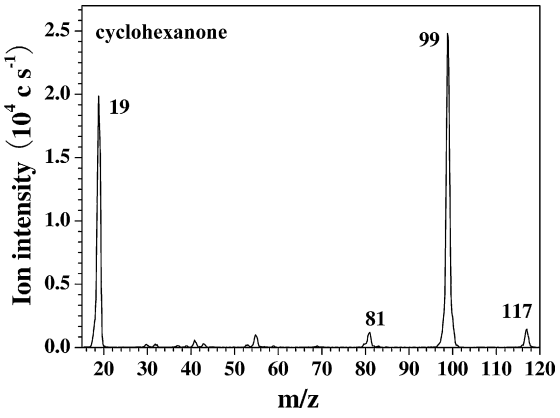

Fig. 5. Mass spectra of cyclohexanone sample vapor measured by PTR-MS.

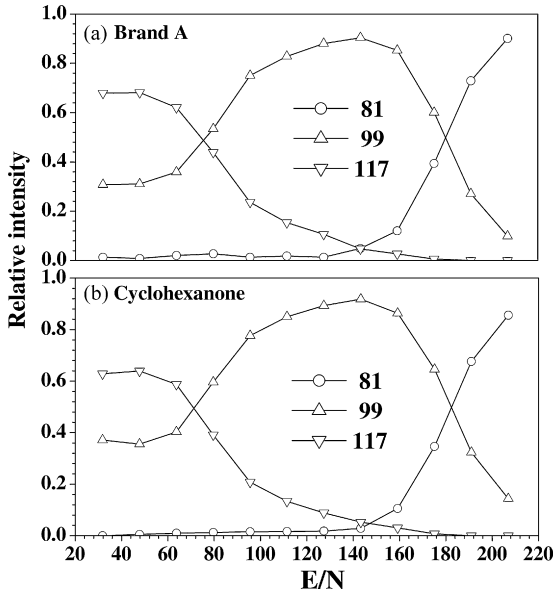

Fig. 6. The relative intensity dependences of ions m/z 81, 99 and 117 on the reduced-field E/N measured by PTR-MS for the gas in the packaging bags for Brand A and cyclohexanone sample vapor.

packaging bags (Fig. 3). Ions at m/z 81 may be the fragmental ions $C_6H_9^+$ arising from the collision-induced dissociation of the ions $C_6H_{10}OH^+$. Such kind of fragmentation has already been noticed in the earlier PTR-MS studies for other ketones [14]. The ions at m/z 117 are the cluster ions $C_6H_{10}OH^+(H_2O)$, and it can form via the ligand switching reaction of cyclohexanone with $H_3O^+(H_2O)$ [15].

In general, a high reduced-field E/N in PTR-MS can lead to the formation of fragmental ions due to the collision-induced dissociation of a protonated compound, which can be used to identify a compound [8]. The ion intensity dependences on the reduced-field E/N were measured for the ions at m/z 81, 99 and 117, and the results are displayed in Fig. 6. It can be seen that the changes in the ion intensities for the cyclohexanone sample and for the residual gas in the packages are identical. This unambiguously demonstrated that the chemical detected in the packages of these infusion sets is cyclohexanone, indicating that adhesive chemical solvent was used in the manufacture of these PVC medical devices.

3.2. Determination of cyclohexanone

A prominent advantage of PTR-MS technique is that it can determine the absolute concentration of trace VOCs according to well-established ion-molecular reaction kinetics. In the drift tube of PTR-MS, the density of analyte M normally is much larger than that of reagent ions H_3O^+, thus the density of product ions $[MH^+]$ at the end of the drift tube follows pseudo first order kinetics as expressed in Eq. (3)

$$[MH^+] = [H_3O^+]_0(1 - e^{-k[M]t}) \quad (3)$$

where $[H_3O^+]_0$ is the density of reagent ions in absence of analyte M, k is the reaction rate constant and t is the average reaction time the ions spend in the drift tube. In a trace analysis by PTR-MS, the density of the analyte M is low so that the decrease in the density of reagent ions is negligible. In this case, $k[M]t \ll 1$, Eq. (3) can further reduce to the following form:

$$[M] = \frac{[MH^+]}{[H_3O^+]_0}\frac{1}{kt} \quad (4)$$

Eq. (4) is often used in a routine PTR-MS measurement [8,9]. However, in our experiments the concentrations of cyclohexanone in the packages were found to be rather high because the intensity change of reagent ions H_3O^+ was not negligible when the gas in the packages was measured. In this case, the relation $k[M]t \ll 1$ was not tenable, therefore the regular Eq. (4) is no longer suitable to the concentration determination. For a more reliable measurement, the following Eq. (5), deduced from Eq. (3), was used in the present experiment to determine the concentration of cyclohexanone.

$$[M] = \ln\frac{[H_3O^+]_0}{[H_3O^+]_0 - [MH^+]}\frac{1}{kt} \quad (5)$$

where the ionic density $[H_3O^+]_0$ and $[MH^+]$ are proportional to the ionic count rate $I(H_3O^+)_0$ and $I(MH^+)$ respectively. The reaction rate constant k is 4×10^{-9} cm^3 s^{-1} molecule^{-1} [15]. The reaction time t is 0.1 ms. After considering the ionic transmission (0.12 at m/z 99 relative to m/z 19), the gases in five packaging bags were measured by PTR-MS for each type of infusion set according to Eq. (5). The concentrations of cyclohexanone detected for Brands A and B were on average 11 and 20 ppm respectively.

Although the IMR-MS measurement cannot give an absolute quantification, one can find in Fig. 4 that the ion intensity for Brand B is nearly two times of that for Brand A, this is in accordance with the proportion of the concentrations determined by PTR-MS.

4. Conclusion

PTR-MS and IMR-MS have been successfully applied to detect gas in the packaging bags of PVC infusion sets. Based on the soft ionization characteristics and the ionic fragmentation patterns, the volatile residue in the packages was unambiguously identified as cyclohexanone, which is an adhesive solvent often used in the PVC medical devices manufacture. Two types of infusion set were quantitatively investigated by PTR-MS, and the detected concentrations of the gaseous cyclohexanone in the packaging bags were 11 and 20 ppm respectively.

Compared with the traditional GC–MS analysis of VOCs in packaging materials [16], the PTR-MS and IMR-MS techniques have the advantage of rapid on-line detection with high sensitivity. Thus they are very promising to become the powerful tools for quality control of packaged medical devices, including the inspection of illegal or excessive use of chemical solvents like cyclohexanone.

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