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Short communication

Rapid determination of residual trichloromethane in drugs

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Abstract

Thermal desorption–gas chromatography is reported as a rapid, efficient and sensitive method for separating and determining the trace volatile organic impurities in drugs with a detection limit of 23 nmol. The optimum operating conditions were found and $CHCl_3$ in atropine sulfate and caffeine was determined with satisfactory results. This method is suitable for determining trace volatile impurities in solid samples and high-boiling liquid samples.

Keywords: Trichloromethane

1. Introduction

The determination of trace volatile components is an important factor in international trade in medicines. Many countries required that drugs such as caffeine and atropine which are to be imported must have accurate data on residues of volatile organic solvents such as chloroform and acetone. It is necessary, therefore, to have efficient, sensitive and reliable analytical methods for the rapid determination of these volatile compounds.

The traditional methods for determining volatile impurities in medicines are headspace gas chromatography (HSGC) and solvent extraction–gas chromatography (SE–GC), which all have some weakness. In HSGC, the determination is often effected in the volume of a headspace bottle, under conditions of constant temperature with volatile loss of samples in the collection and injection procedure, which may lead to negative results for trace components, i.e., the detection sensitivity is not very high. The health of operator may be affected by the noxious vapours of organic solvents when the SE–GC method is used, and precise determination of the analyte(s) cannot be expected, especially for substances with low boiling points. Hence these two methods are not the optimum for drug analysis.

After testing several methods, we found that thermal desorption–gas chromatography (TD–GC) is a good method for determining residues of volatile organic solvents in various samples. The types of sample to which thermal desorption is often applied include environmental air samples [1,2], waters [3], flavours [4], chemical warfare samples [5], pesticides [6] and others [7,8], but there have been few reports on the analysis of drugs [9]. The TD–GC method provides a rapid and reproducible means of determining volatile components in solid or liquid samples,

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especially for samples with low boiling points. No pretreatment of liquid and solid samples is required, and only preabsorption for gas samples. Therefore, TD–GC is very suitable for determining trace amounts of residual components, such as impurities, solvents and reagents in medicines. Because our main purpose was to determine trace amounts of residual solvent and only two peaks in the chromatogram of the drugs of interest, we chose $CHCl_3$ as the test sample. The detection limit of $CHCl_3$ is 2.7 μg, which satisfies the requirements for determining trace volatile impurities in medicines.

2. Experimental

2.1. Apparatus

A Model 8702 thermal desorber (Shanghai Fourth Analytical Instrument Factory, Shanghai, China) was connected to a GC-9002 gas chromatograph (Shanghai Xinhu Precision Analytical Instrument Factory, Shanghai, China) via a 100 cm length of stainless-steel column tubing of 2 mm I.D. held at 148°C. The eluted components were detected by flame ionization detection (FID). The chromatograms and data were recorded and calculated with a Chromatopac C-R3A (Shimadzu, Tokyo, Japan). A schematic diagram is shown in Fig. 1.

2.2. Reagents and drugs

The concentrations of $CHCl_3$ standard solution were 13.20, 72.11 and 284.27 μg/μl, and were prepared by dissolving 0.0660, 0.7211 and 2.8427 g of $CHCl_3$ (analytical-reagent grade) in pure CS_2 and diluting to 5, 10 and 10 ml, respectively. Pure CS_2 was obtained from CS_2 (analytical-reagent grade) according to the concentrated sulfuric acid–formaldehyde method [10], so that no signal was detected by FID. Standard methane gas was provided by Wuxi Scientifical Gas Company. Drug samples (caffeine and atropine sulfate) were obtained from a pharmaceutical factory.

2.3. Chromatographic conditions

A stainless-steel column (100 cm × 2 mm I.D.) packed with porous beads (SS-408, 60–80 mesh; Shanghai Reagents Factory, Shanghai, China) was aged for 5 h at 160°C. The temperatures of thermal desorption, column, injector and detector were 93, 148, 150, and 150°C, respectively. The flows of carrier gas, hydrogen and air were 40, 50 and 400 ml/min successively. The thermal desorption time is 2 min.

2.4. Procedure

Accurately weigh a cleaned sample tube packed with glass-wool and fit the plastic caps (or silicone-rubber plugs). Set one cap and some glass-wool aside, add about 200–300 mg of powdered drug sample to the tube, then insert the glass-wool and cap and weigh it accurately again; the difference between the two weighing is the mass of the sample. Remove the two caps and fix the tube quickly on the thermal desorber (note: there is no leakage of gas). After 2 min, change

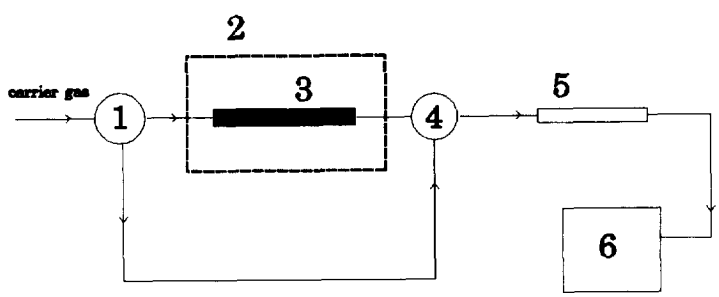

Fig. 1. Schematic diagram of apparatus. 1 = Electromagnetic valve; 2 = thermal desorption oven; 3 = sample tube with glass-wool; 4 = machine valve (synchronized perfectly with 1); 5 = analytical column; 6 = detector and recorder.

the gas current for analysis. When constructing a calibration graph, inject a known amount of standard chloroform solution on to the glass-wool directly, then fix the tube quickly on the equipment and perform the test.

3. Results and discussion

3.1. Selection of stationary phase

The medium-polarity stationary phase used, porous beads SS-408, similar to Porapak R, was chosen for the analytical column after testing other solid absorbers and liquid stationary phases (15% DEGS and 10% OV-225), which were found not to be suitable for separating the impurities in drugs because the peak of $CHCl_3$ and another small peak were overlapped.

3.2. Optimization of operating conditions

The three factor–four level orthogonal test was used to observe the effects of temperature and time of thermal desorption, the column temperature and carrier gas flow-rate on sensitivity and resolution. The results with peak height (H) and resolution (R) as the main evaluation indices are shown in Table 1. Based on the experimental results and the statistical evaluation, the conditions adopted were as follows: thermal desorption temperature, 93°C; carrier gas flow-rate, 40 ml/min; column temperature, 148°C; and thermal desorption time, 2 min.

3.3. Inspection of the method

The linear range, relative standard deviation (R.S.D.) and recovery were tested. The linear range of the calibration graph for $CHCl_3$ is from 8.0 to at least 738.5 μg; the linear regression equation is A (mV s) = 0.0236 + 0.234 C (μg). The correlation coefficient of the two variables is $r = 0.9969$. The S.D. of the method, tested with 0.8 μl of $CHCl_3$–CS_2 standard solution (227.4 μg of $CHCl_3$), is 0.0128 mg ($n = 8$) and the R.S.D. is 6.82%. The recovery, determined with drug samples, was 89% (caffeine) and 88.2% (atropine sulfate).

3.4. Quantitative determination

The caffeine and atropine samples, which had been analysed using the HSGC at the factory with negative results, were analysed three to five times and the average $CHCl_3$ concentrations were caffeine (in sample batch No. 40507) 76 ppm, atropine sulfate (batch No. 940403) 49 ppm and atropine sulfate (batch No. 10407) 19 ppm. It is clear that TD–GC method has higher sensitivity, and the detection limit, based on $S/N = 3$, is 22.6 nmol (2.7 μg of $CHCl_3$).

Table 1
Results of the orthogonal test

Test No.	Thermal desorption temperature	Carrier gas flow-rate (ml/min)	Column temperature (°C)	Thermal desorption (min)	Peak height (μV)	Resolution
1	80	15	123	1	632	2.101
2	80	30	138	2	742	2.321
3	80	40	153	3	799	2.952
4	93	30	123	3	668	1.784
5	93	40	138	1	876	2.519
6	93	15	153	2	858	2.564
7	105	40	123	2	664	1.729
8	105	15	138	3	548	1.541
9	105	30	153	1	570	1.839

4. Conclusion

The TD–GC method is useful for determining trace amounts of residual components, such as impurities, solvents and reagents, in medicines. The S.D. of the method is 0.0128 mg ($n = 8$) and the R.S.D. is 6.82%. The recovery is relatively satisfactory and the detection limit is 22.6 nmole. The method has proved to be very reliable in routine use and can satisfy the requirements for determining trace amounts of volatile components in drugs.

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