

Application Data Sheet

No.46

GC-MS

Gas Chromatograph - Mass Spectrometer

Analysis of Potential Genotoxic Impurities in Active Pharmaceutical Ingredients (5) - Analysis of Alkyl Halides -

Alkyl halides are used as an alkylating agent for raw ingredients in the synthesis of pharmaceuticals or are generated as a byproduct of drug synthesis. They have been identified as potential carcinogens or genotoxins. This Application Data Sheet shows an example of analyzing 18 alkyl halides using headspace-GC-MS.

Experimental

Standard mixtures were prepared by diluting 18 types of alkyl halides in methanol to 0.2, 2, 10, 20, and 100 µg/mL concentrations. An internal standard solution was prepared by diluting fluorobenzene in methanol to a 20 µg/mL concentration. Test samples were prepared by placing 20 mg of the pharmaceutical ingredients in a 20 mL screw-cap vial (La-Pha-Pack P/N: 18 09 1307), diluting it with 10 mL of Milli-Q water, adding 10 µL of the internal standard solution, and then quickly sealing the vial by screwing on the magnetic screw-cap (La-Pha-Pack P/N: 18 09 1309). Standard aqueous samples were prepared by adding 10 µL of each standard alkali halide mixture and 10 µL of the internal standard solution to 10 mL Milli-Q water. The concentrations of the prepared standard aqueous samples were 0.2, 2, 10, 20, and 100 ng/mL (equivalent to 0.1, 1, 5, 10, and 50 ng/mg concentrations in the active pharmaceutical ingredients), respectively.

Analytical Conditions

FASST (Fast Automated Scan/SIM Type), which is capable of simultaneous Scan and SIM measurements, was used as the measurement mode. The analysis conditions are shown in Table 1.

Table 1: Analytical Conditions

GC-MS	:GCMS-QP2010 Ultra		
Autosampler	:AOC-5000 Plus (HS)		
Column	:Rtx-1 (60 m length, 0.25 mm I.D., df=1.0 µm)		
Glass Insert	:Deactivated Split insert with wool (PN: 225-20803-01)		
	[AOC-5000 Plus (HS)]		[GC]
	Incubation Temp. :80 °C		Injection Temp. :230 °C
	Incubation Time :30 min		Column Oven Temp. :40 °C (2 min) → (20 °C/min) → 250 °C (4 min)
	Syringe Temp. :100 °C		Injection Mode :Split
	Agitator Speed :250 rpm		Carrier Gas :Helium
	Fill Speed :500 µL/sec		Flow Control Mode :Linear velocity (25.5 cm/sec)
	Pull Up Delay :500 msec		Split Ratio :10
	Inject to :GC Inj 1		
	Injection Speed :500 µL/sec		[MS]
	Pre Inject Delay :500 msec		Interface Temp. :230 °C
	Flush Time :5 min		Ion source Temp. :230 °C
	GC Run Time :25 min		Tuning Mode :High sensitivity
	Injection Volume :1 mL		Measurement mode :FASST (simultaneous Scan/SIM measurements)
			Scan Mass Range :m/z 30 - 270
			Scan Event Time :0.05 sec
			Scan Speed :10,000 u/sec
			SIM Event Time :0.3 sec
	SIM Monitoring m/z:		
	Chloromethane 50, 52	1-Bromopropane 43, 122	
	Vinyl chloride 62, 64	2-Iodopropane 43, 170	
	2-Chloropropane 43, 78	Fluorobenzene 96, 70	
	Iodomethane 142, 127	1-Bromo-2-methylpropene 55, 134	
	1-Chloropropane 42, 78	1-Iodopropane 43, 170	
	<i>trans</i> -1,2-Dichloroethylene 61, 96	<i>trans</i> -1,2-Dibromoethylene 186, 105	
	2-Bromopropane 43, 122	<i>cis</i> -1,2-Dibromoethylene 186, 105	
	<i>cis</i> -Dichloroethylene 61, 96	<i>trans</i> -3-Bromo-2-methylacrylonitrile 66, 145	
	2-Chloroacrylonitrile 87, 52	<i>cis</i> -3-Bromo-2-methylacrylonitrile 66, 145	
	1-Chloro-2-methylpropene 55, 90		

Results

The total ion current chromatogram for the 100 ng/mL concentration standard aqueous solution (equivalent to 50 ng/mg concentration* in the active pharmaceutical ingredients) is shown in Fig. 3. The SIM chromatograms for six typical components in the 0.2 ng/mL concentration standard aqueous solution (equivalent to 0.1 ng/mg concentration* in the pharmaceutical) are shown in Fig. 4.

* 1,2-Dibromoethylene and 3-Bromo-2-methylacrylonitrile concentrations include both *cis* and *trans* forms.

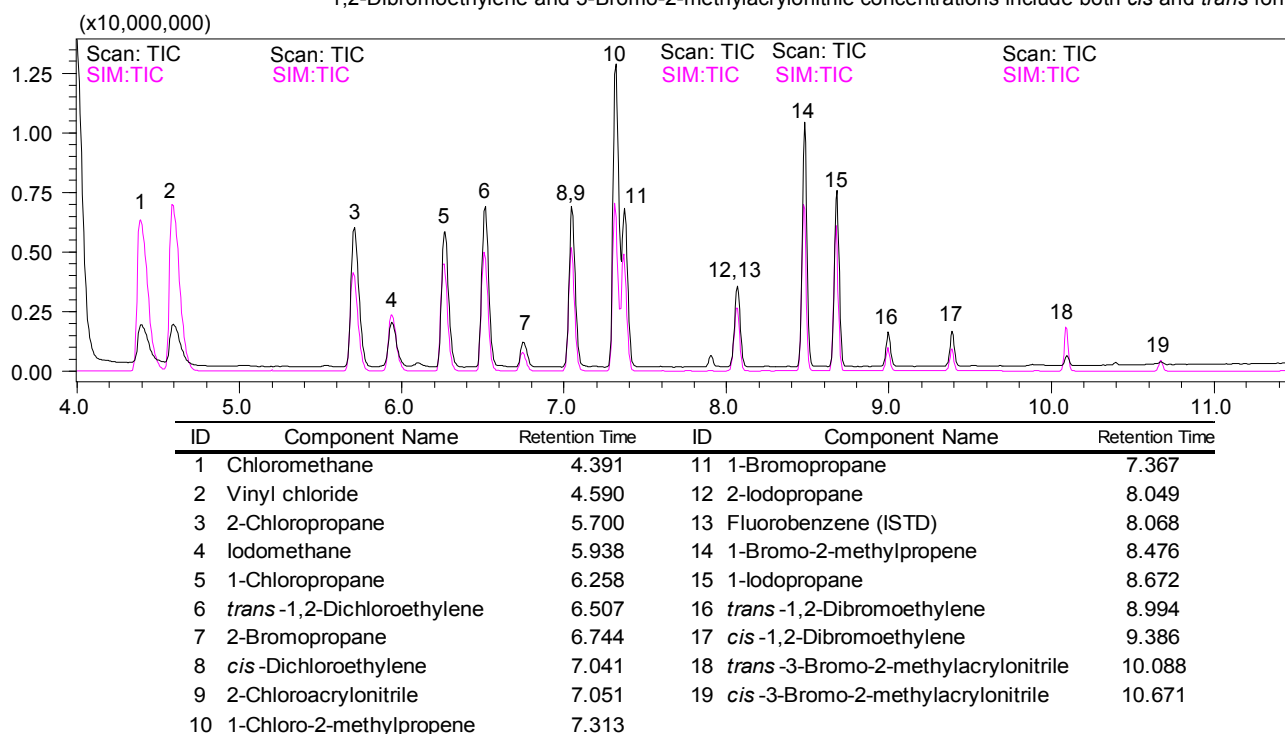


Fig. 3: Total Ion Current Chromatogram

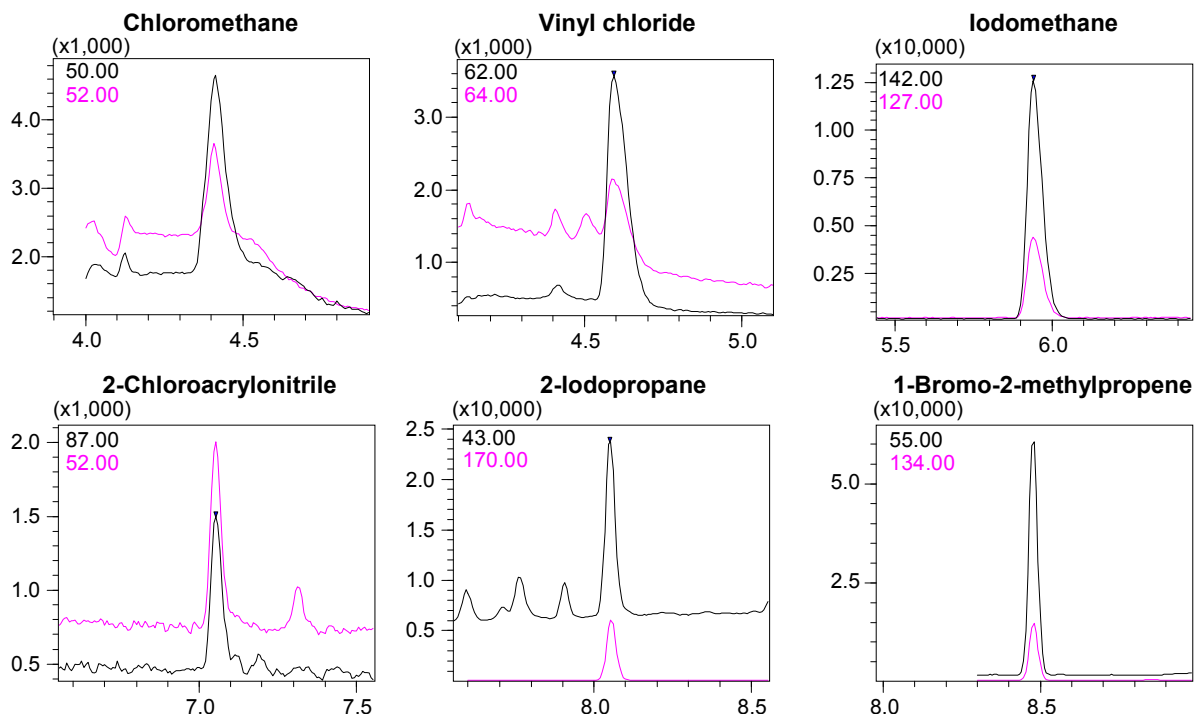


Fig. 4: Typical SIM Mass Chromatograms for 0.1 ng/mg Concentration in Active Pharmaceutical Ingredients