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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)]

Incubation Temp.	:80 °C
Incubation Time	:30 min
Syringe Temp.	:100 °C
Agitator Speed	:250 rpm
Fill Speed	:500 μL/sec
Pull Up Delay	:500 msec
Inject to	:GC Inj 1
Injection Speed	:500 μL/sec
Pre Inject Delay	:500 msec
Flush Time	:5 min
GC Run Time	:25 min
Injection Volume	:1 mL

[GC]

Injection Temp.	:230 °C
Column Oven Temp.	:40 °C (2 min) → (20 °C/min) → 250 °C (4 min)
Injection Mode	:Split
Carrier Gas	:Helium
Flow Control Mode	:Linear velocity (25.5 cm/sec)
Split Ratio	:10

[MS]

Interface Temp.	:230 °C
Ion source Temp.	:230 °C
Tuning Mode	:High sensitivity
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

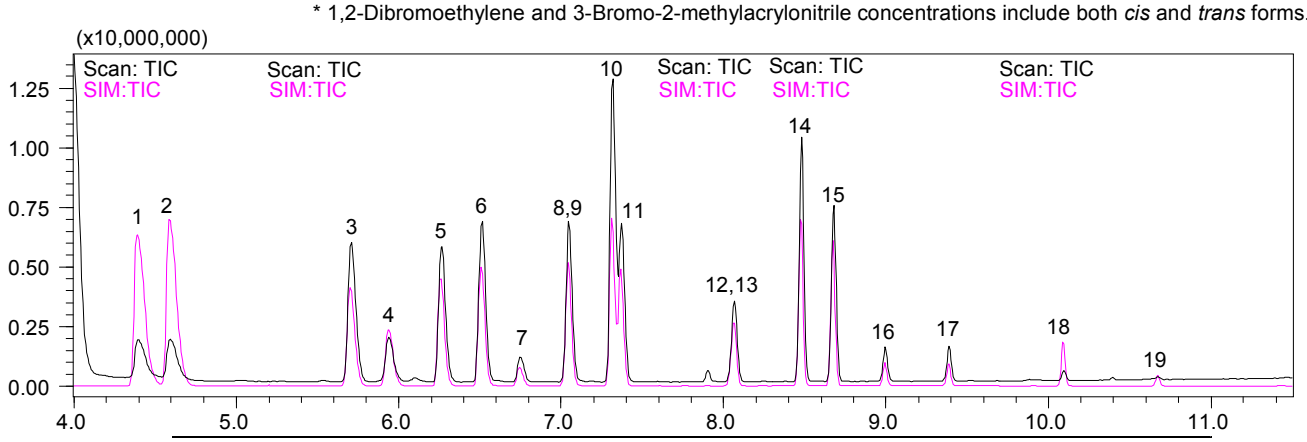
SIM Monitoring *m/z*:

Chloromethane	50, 52
Vinyl chloride	62, 64
2-Chloropropane	43, 78
Iodomethane	142, 127
1-Chloropropane	42, 78
trans-1,2-Dichloroethylene	61, 96
2-Bromopropane	43, 122
cis-Dichloroethylene	61, 96
2-Chloroacrylonitrile	87, 52
1-Chloro-2-methylpropene	55, 90
1-Bromopropane	43, 122
2-Iodopropane	43, 170
Fluorobenzene	96, 70
1-Bromo-2-methylpropene	55, 134
1-Iodopropane	43, 170
trans-1,2-Dibromoethylene	186, 105
cis-1,2-Dibromoethylene	186, 105
trans-3-Bromo-2-methylacrylonitrile	66, 145
cis-3-Bromo-2-methylacrylonitrile	66, 145

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.



ID	Component Name	Retention Time	ID	Component Name	Retention Time
1	Chloromethane	4.391	11	1-Bromopropane	7.367
2	Vinyl chloride	4.590	12	2-Iodopropane	8.049
3	2-Chloropropane	5.700	13	Fluorobenzene (ISTD)	8.068
4	Iodomethane	5.938	14	1-Bromo-2-methylpropene	8.476
5	1-Chloropropane	6.258	15	1-Iodopropane	8.672
6	*trans*-1,2-Dichloroethylene	6.507	16	*trans*-1,2-Dibromoethylene	8.994
7	2-Bromopropane	6.744	17	*cis*-1,2-Dibromoethylene	9.386
8	*cis*-Dichloroethylene	7.041	18	*trans*-3-Bromo-2-methylacrylonitrile	10.088
9	2-Chloroacrylonitrile	7.051	19	*cis*-3-Bromo-2-methylacrylonitrile	10.671
10	1-Chloro-2-methylpropene	7.313			

Fig. 3: Total Ion Current Chromatogram

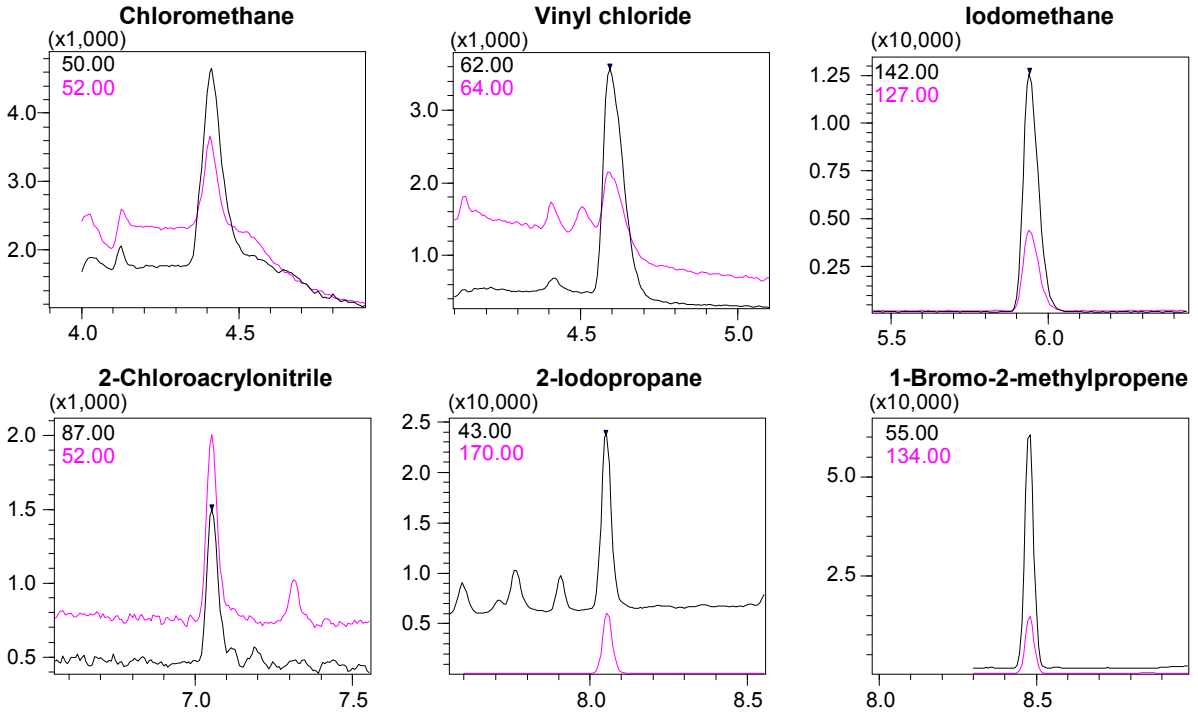


Fig. 4: Typical SIM Mass Chromatograms for 0.1 ng/mg Concentration in Active Pharmaceutical Ingredients

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