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Application Data Sheet

No.42

GC-MS
Gas Chromatograph Mass Spectrometer

Analysis of Potential Genotoxic Impurities in Active Pharmaceutical Ingredients (4)
- Analysis of Haloalcohols and Glycidol Part 2 -

This Application Data Sheet reports on results with respect to a method for quantitating haloalcohols (2-chloroethanol, 2-bromoethanol, and 2-iodoethanol) and glycidol in an active pharmaceutical ingredient (API) utilizing the GCMS system. For the analysis conditions as well as the total ion current chromatogram and mass spectra for the haloalcohols and glycidol, refer to GCMS Application Data Sheet No. 41, "Analysis of Potential Genotoxic Impurities in Active Pharmaceutical Ingredients (3), Analysis of Haloalcohols and Glycidol Part 1."

Experimental

The haloalcohols (2-chloroethanol, 2-bromoethanol, and 2-iodoethanol) and glycidol were dissolved in acetonitrile, and mixed standard solutions (0.025 µg/mL, 0.125 µg/mL, 0.25 µg/mL, 1.25 µg/mL, 2.5 µg/mL, and 25 µg/mL) were prepared. The 200µL of standards were extracted and derivatized as illustrated in Fig. 1[1]. The concentrations of these standard samples were equivalent to 1 ng/mg, 5 ng/mg, 10 ng/mg, 50 ng/mg, 100 ng/mg, and 1,000 ng/mg concentrations in the APIs.
In the recovery test, trazodone, which was confirmed not to contain the target compounds, was dissolved in chloroform and adjusted to 25 mg/mL. 200 µL was extracted, then 25 ng of the haloalcohols and glycidol respectively were added, as the pretreatment shown in Fig. 1. In this case, the concentrations of the haloalcohols and glycidol in the API were both 5 ng/mg.

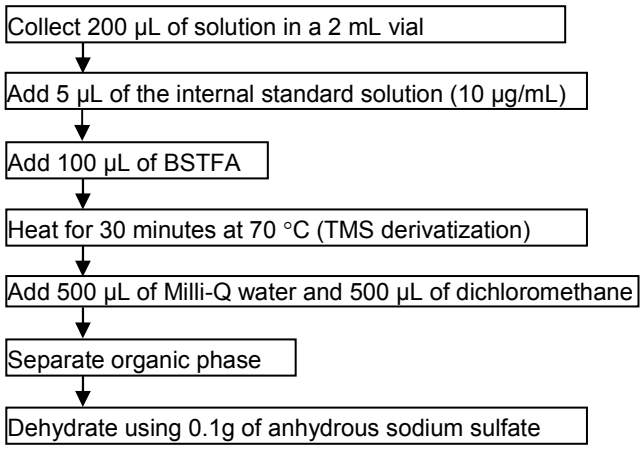

Fig. 1 Sample Preparation Procedure

Sensitivity

Fig. 2 shows the SIM mass chromatograms created by measuring a 0.025 µg/mL standard sample (equivalent to 1 ng/mg in the pharmaceuticals). For each of the compounds investigated, a sensitivity of S/N > 10 was obtained.

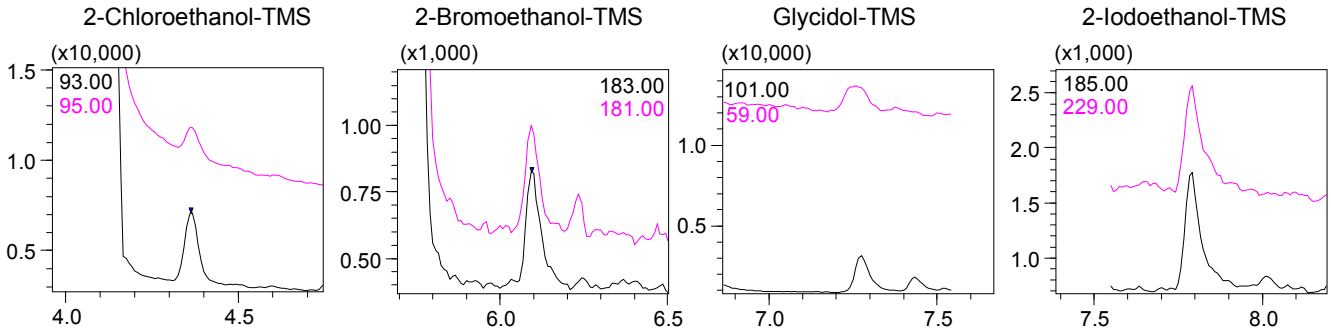

Fig. 2 SIM Mass Chromatograms for 0.025 µg/mL Standard Solution (equivalent to 1 ng/mg in the APIs)

Linearity of the Calibration Curve

Fig. 3 shows the calibration curves created in the concentration range of 0.025 μg/mL to 25 μmg/mL (equivalent to 1 ng/mg to 1,000 ng/mg in the API). The correlation coefficients (R) using 2-bromoethanol-D4-TMS as the internal standard were at least 0.9998, and favorable linearity was obtained.

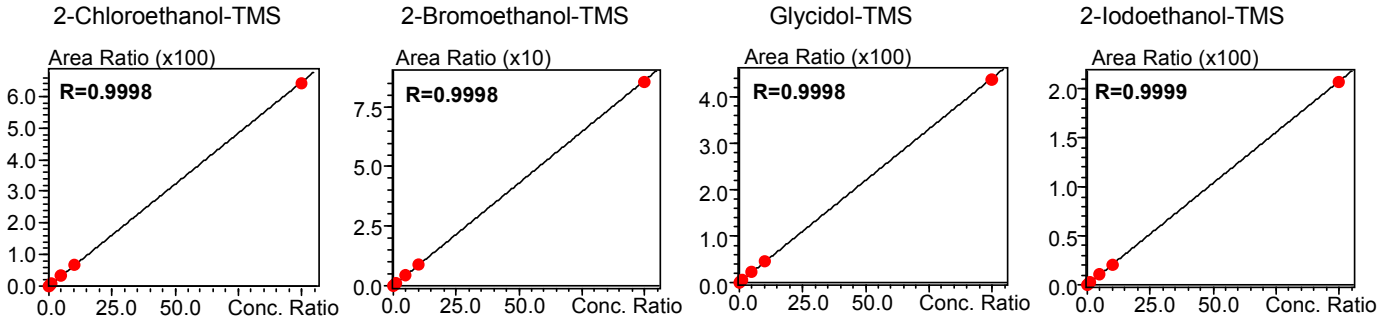

Fig. 3 Calibration Curves of Haloalcohols and Glycidol

Recovery Test

The recovery test was repeated 5 times, and the percent recovery and repeatability were calculated (Table 1). The average recovery for glycidol was poor at 59.7 %, but the recovery of the haloalcohols was at least 84.2 %. Favorable results were obtained, with repeatability (%RSD) of 4.3 % max. for 5 repetitions.

Table 1 Percent Recovery and Repeatability Results

Compound Name	Percent Recovery (%)					Average Recovery (%)	Repeatability %RSD
	No. 1	No. 2	No. 3	No. 4	No. 5		
2-Chloroethanol-TMS	94.6	89.0	89.1	87.0	91.6	90.2	3.2
2-Bromoethanol-TMS	102.7	98.3	99.9	98.4	104.1	100.7	2.6
Glycidol-TMS	60.9	61.7	61.9	56.4	57.4	59.7	4.3
2-Iodoethanol-TMS	84.1	85.3	82.7	82.5	86.4	84.2	2.0

Reference

[1] Frank David, Karine Jacq, Pat Sandra, Andrew Baker and Matthew S. Klee: Analysis of potential genotoxic impurities in pharmaceuticals by two-dimensional gas chromatography with Deans switching and independent column temperature control using a low-thermal-mass oven module, Anal Bioanal Chem, 396, 1291-1300 (2010)

First Edition: Nov, 2012

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