

Analysis of Volatile Impurities in Anhydrous Ethanol and Ethanol for Disinfection in Accordance with the Purity Test set by the Pharmacopoeias (JP, USP, EP)

Ethanol has antimicrobial properties and is sold as a disinfectant product at optimized concentrations. Quality control of the alcohol as a medical product is carried out through verification testing procedures as stipulated in each monograph of the Pharmacopoeias. Guided by the International Council for Harmonization on Technical Requirements for Pharmaceuticals for Human Use (ICH), the Japanese (JP), United States (USP) and European (EP) pharmacopoeias share roughly the same verification testing procedures for anhydrous ethanol and ethanol for disinfection. The Chinese Pharmacopoeia (ChP) also adopts a similar testing method.

Methanol, acetaldehyde, acetal and benzene are among the volatile impurities to be monitored. An instrument is required to detect benzene down to the specified 2 vol ppm limit or lower and also obtain a good resolution between acetaldehyde and methanol. This article presents the analysis of volatile impurities in accordance with the purity test (3) of the Japanese pharmacopoeia.

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■ **Testing Method**

The sample solution and standard solutions (1) – (4) *1 were prepared in accordance with Supplement I to the Japanese Pharmacopoeia Seventeenth Edition. For ethanol for disinfection, purified water was added to 83 mL of anhydrous ethanol*2 to make up to a total volume of 100 mL.

■ **Analysis Conditions**

Table 1 lists the instrument configurations and the analysis conditions used in this experiment.

Table 1 Instrument Configuration and Analysis Conditions

Model	: Nexis™ GC-2030/AOC-20i Plus
Column	: ZB-624 (30 m, 0.32 mm I.D., df=1.8 μm)
Column Temp.	: 40 °C (12 min)-10 °C/min-240 °C (10 min) Total : 42 min
Detector	: FID
Carrier Gas Control	: Constant linear velocity
Carrier Gas	: He, 35 cm/sec
Injection Temp.	: 200 °C
Detector Temp.	: 280 °C
Injection Mode	: Split *2
Split Ratio	: 1:20
Injection Volume	: 1 μL

*2: The insert for splitless use for GC-17A (P/N : 221-41544) was used. The insert was packed with 10 mg of deactivated glass wool (P/N: 221-48600).

■ **System Suitability Test**

When 1 μL of the standard solution (2) is injected into GC under the conditions shown in Table 1, acetaldehyde and methanol should elute with acetaldehyde ahead of methanol and their resolution needs to be no less than 1.5. In this experiment, the resolution of acetaldehyde and methanol was greater than 1.5 (Fig. 1 and Fig. 2). The calculation for the resolution was performed as per the JP, USP and EP Pharmacopoeias.

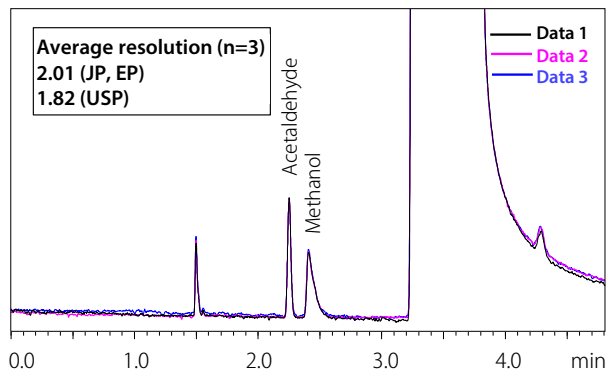


Fig. 1 Chromatogram of Standard Solution (2) for Anhydrous Ethanol (Overlaid Data from Three Continuous Analyses)

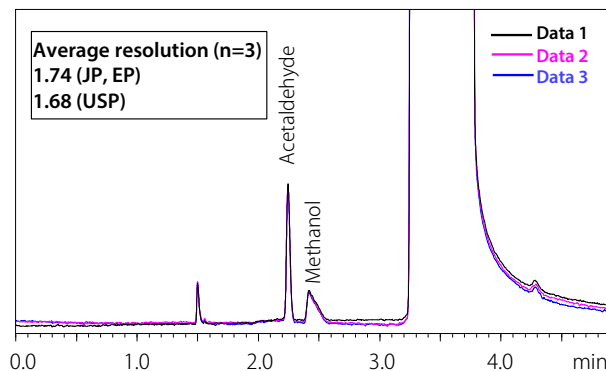


Fig. 2 Chromatogram of Standard Solution (2) for Ethanol for Disinfection (Overlaid Data from Three Continuous Analyses)

*1: This article uses the JP nomenclature. The USP and EP counterparts are as listed below.

	JP	USP	EP
Sample	Sample solution A	Sample solution A	Test solution(a)
Sample Solution	Sample solution B	Sample solution B	Test solution(b)
Standard Solution (1)	Standard solution A	Standard solution A	Reference solution(a)
Standard Solution (2)	Standard solution B	Standard solution B	Reference solution(b)
Standard Solution (3)	Standard solution C	Standard solution C	Reference solution(c)
Standard Solution (4)	Standard solution D	Standard solution D	Reference solution(d)

*2: FUJIFILM Wako Pure Chemical Corporation's Japanese Pharmacopoeia-grade ethanol (99.5)

Analysis of Volatile Impurities

Methanol, acetaldehyde, acetal and benzene are analyzed to verify that the volumes of these impurities will not exceed those specified. The chromatograms of the samples (i.e. anhydrous ethanol and ethanol for disinfection), the sample solution and standard solutions (1) – (4) are shown in Fig.3 and Fig. 4. The peak areas and volumes of the volatile impurities are listed in Table 2. The data obtained were confirmed to meet the three purity criteria listed below.

1. The peak area of methanol obtained with the sample be no greater than 1/2 times that of methanol with the standard solution (1).
2. When calculating the amounts of the volatile impurities, the total amount of acetaldehyde and acetal (equation 1) be no more than 10 vol ppm as acetaldehyde and the amount of benzene (equation 2) be no more than 2 vol ppm.
3. The total area of all other impurities peak with the sample solution be no larger than the peak area of 4-methylpentan-2-ol*1.

$$\text{Total amount of acetaldehyde and acetal (vol ppm)} = \frac{10 \times A_E}{A_T - A_E} + \frac{30 \times C_E \times 44.05}{(C_T - C_E) \times 118.2} \quad \text{(Equation 1) }^{*2}$$

$$\text{Amount of benzene (vol ppm)} = \frac{2B_E}{B_T - B_E} \quad \text{(Equation 2)}$$

*1: Peaks with areas less than 3 % of that of 4-methyl-2-pentanol should not be included. In this experiment, no target peaks were detected in the sample solution.

*2: For abbreviations of A_E , B_E , C_E , A_T , C_T and B_T , see refer to Table 2.

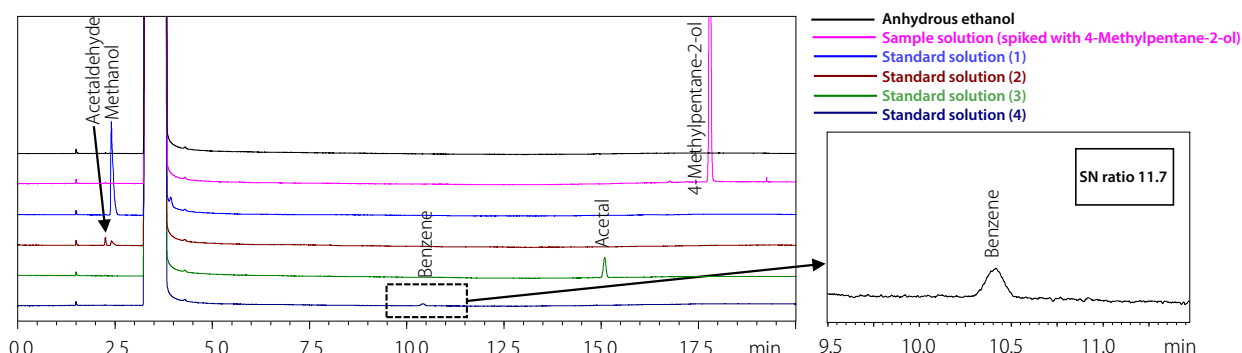


Fig. 3 Chromatograms of Anhydrous Ethanol, Sample Solution and Standard Solutions (1) – (4)

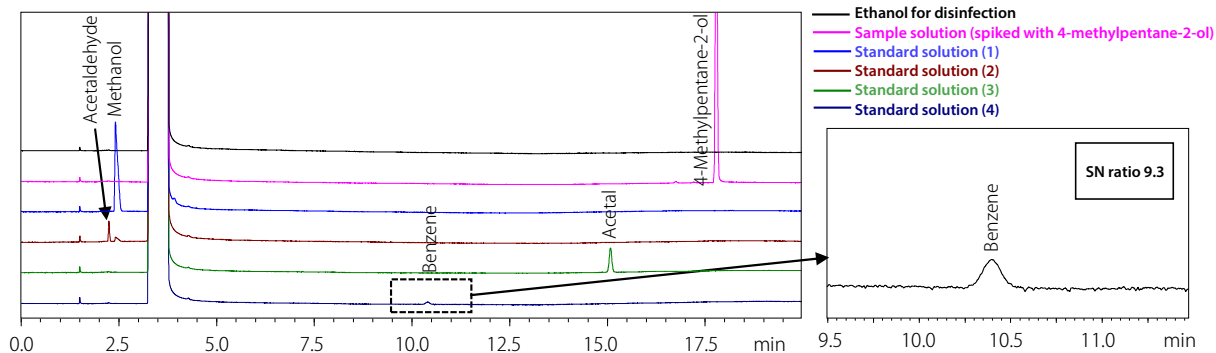


Fig. 4 Chromatograms of Ethanol for disinfection, Sample Solution and Standard Solutions (1) – (4)

Table 2 Average Areas and Amounts of Volatile Impurities (n=3)

Sample name	Sample			
	Peak area of methanol	Peak area of acetaldehyde	Peak area of acetal	Peak area of benzene
Anhydrous ethanol	0	107	0	0
Ethanol for disinfection	0	107	0	0
Diluted sample name	Standard solution (1)	Standard solution (2)	Standard solution (3)	Standard solution (4)
	Peak area of methanol	Peak area of acetaldehyde	Peak area of acetal	Peak area of benzene
Anhydrous ethanol	37050	1559	9418	1206
Ethanol for disinfection	34838	3108	8863	1115
Sample name	Total amount of acetaldehyde and acetal (vol ppm)			Amount of benzene (vol ppm)
Anhydrous ethanol	0.73			0
Ethanol for disinfection	0.36			0

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Conclusion

System suitability test and analysis of volatile impurities were carried out in accordance with the purity test of ethanol in the JP (USP, EP) using Nexis™ GC-2030 gas chromatograph.

The results met the criteria set for testing anhydrous ethanol and ethanol for disinfection.

Nexis™ GC-2030 equipped with highly sensitive FID-2030 had enough sensitivity to detect even the most demanding volatile impurity like benzene.



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