SHIMADZU
Excellence in Science

Application News

Nexis™ GC-2030 Gas Chromatograph-FID with HS-20 NX Headspace autosampler.

High Throughput HS-GC Method for Residual Solvent Analysis in Valsartan API

Hemant Kesarkar, Sanket Chiplunkar, Prashant Hase, Durvesh Sawant, Aseem Wagle, Rahul Dwivedi, Pratap Rasam, Jitendra Kelkar and Dheeraj Handique
Shimadzu Analytical (India) Pvt. Ltd.

User Benefits

- HS-20 NX features a short transfer line along with continuous isolation gas flow minimizes carryover and enhances precision.
- Active overlapping function, reduces sample analysis cycle time which boosts productivity.
- Multiple solvent analysis in a single method.

■ Introduction

Overview : According to Guidelines by International Conference on Harmonization (ICH) [1], all residual solvents should be removed to the extent possible, to meet product specifications, good manufacturing practices, or other quality-based requirements. Testing for residual solvents in raw materials is highly recommended as this solvent may be carried through the process and remain in the finished product. Early in the process, control is usually more effective during initial manufacturing stages compared to remediation which may results in even rejection of final product.

Residual Solvent : Residual solvents in pharmaceuticals are defined as organic volatile chemicals that are used or produced in the manufacturing of drug substances or excipients, or in the preparation of drug products. Residual solvent analysis in pharmaceutical products is necessary not only because they represent a potential risk for human health, due to their toxicity and their undesirable side effects, but also because they may affect the physicochemical properties of pharmaceutical products. Therefore, it is a mandatory requirement for health authorities in the world to accurately determine the levels of residual solvents that are present in APIs or finished products.
The ICH guideline Q3C(R9)[2] classifies the regularly used solvents into three different classes based on their toxicity :

- Class 1 solvents should be avoided due to their known carcinogenic effect on human. Hence, their use should not be employed in the manufacture of drug substances, excipients and drug products.
- Class 2 solvents should be limited in the drug products because of their inherent toxicity.
- Class 3 solvents are regarded as less toxic and of a lower risk to human health but those also have specified control threshold.

Analysis of Residual solvents :
Gas chromatography is the technique of choice used for the analysis of the residual solvents. Several methods are available for this analysis in pharmacopeial references such as USP, BP, PhEur which are based on headspace technique.

Requirement of high throughput GC method :
Multiple method are required to analyze all the classified solvents in ICH. Also, these methods are having longer run time which decreases productivity. Further, huge amounts of solvents are consumed during sample and standard preparations. By using high throughput method, maximum number of residual solvents can be analyzed in a single method. Various combinations of residual solvents can be analyzed by preparing standard of desired residual solvents. This method can be optimized for the critically separated residual solvent pair at the time of actual analysis. Hence, it proves to be time efficient and cost effective.

Use of Nexis GC-2030 with HS-20 NX for the high throughput method :
Shimadzu's Nexis GC with HS-20 NX headspace autosampler provides unique features which helps in rapid chromatographic analysis such as high head pressure capacity enabling fast GC analysis. Also, vial overlapping function decreases cycle time, thereby boosting productivity. Figure 1 depicts the benefit of overlapping function.

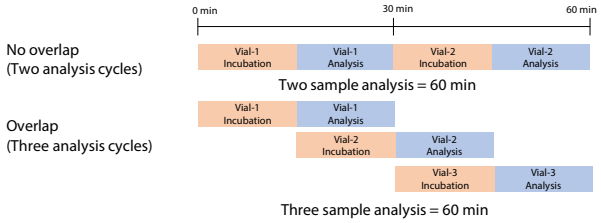

Figure 1 : Difference between the analysis time with and without overlapping function

Automatic leak check function helps in investigating any error in the analysis. Furthermore, patented vial delivery technology improves stability of the oven temperature, and continuous isolation gas flows with temperature controlled short transfer line minimizes carryover. Figure 2 depict design of isolation gas flow and effect of short transfer line on the carryover for the compound with high boiling point such as Dimethyl sulfoxide.

The isolation gas flow prevents sample diffusion from the vent channel, which has been a problem with conventional headspace samplers. (patent pending)

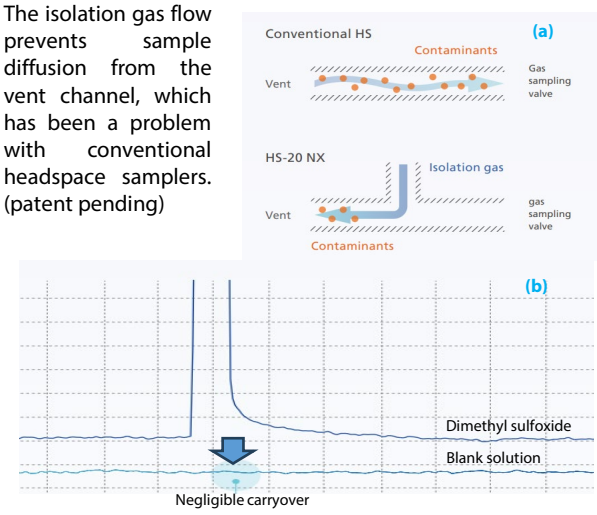

Figure 2 : (a) Image for isolation gas flow and (b) Representative carryover data for Dimethyl sulfoxide

Also, continuous running of GC system leads to high consumption of utilities, such as carrier gas and power consumption. Active time management and carrier gas saver function in the energy efficient Nexis GC-2030 NX (Figure 3) with LabSolutions software helps to save the time as well as analysis cost by minimizing utilities.

Figure 3 : Nexis™ GC-2030 with HS-20 NX

■ Experimental

Standards of solvents which are mentioned in result summary table (Table 2) were procured and used for the analysis. Limits which are available in the ICH Q3C(R9) guideline were considered for classified solvents. However, non-classified solvents were analyzed considering limit as 5000 ppm.

During method development, a mixture of 40 solvents was prepared in N-Methyl-2-Pyrrolidone (NMP) and analyzed by Nexis GC-2030 using SH-Rxi-624 (20 m, 0.18 mm I.D. 1 µm df).

Five-point linearity standards were prepared from 10% to 150% concentration of specified limit. LOQ precision as well as system precision was performed by injecting six injections of LOQ and 100% linearity level.

For accuracy study and method precision, Valsartan API sample was used. Spiked recovery was performed at the LOQ and 100% Linearity Level.

■ Method

Method for the analysis was developed and optimized in order to achieve best possible resolution, and quantification at trace level in short run time. Analytical conditions and method parameters were as mentioned below.

Instrument Parameters	: Nexis GC-2030
Column	: SH-Rxi-624 20 m, 0.18 mm ID, 1 µm df (PN - 227-36259-01)
Injection Port Temperature	: 250 °C
Carrier Gas	: Nitrogen
Flow Control Mode	: Linear Velocity
Linear Velocity	: 22.1 cm/sec
Split ratio	: 100
Purge Flow	: 3 mL/min
Oven Temperature Program	: 42 °C (3.55 min), 5.10 °C/min to 72 °C (1.20 min), 33.70 °C/min to 240 °C (1.38 min)
Detector	: FID
Detector Temp.	: 250 °C
Diluent	: NMP

Instrument Parameters	: HS-20 NX headspace sampler
Oven Temperature	: 130 °C
Sample Line	: 140 °C
Transfer Line	: 150 °C
Pressurizing Gas Pressure	: 80 kPa
Pressuring Time	: 1 min
Shaking Level	: 3
Multi injection count	: 1
Equilibration Time	: 15 min
Load Time	: 0.5 min
Injection Time	: 1.0 min

■ Linearity Solutions

Linearity standard stock solution were prepared in NMP. Concentration for all solvents was equal to the 10x to their limit in ICH Q3C(R9)[2]. For example, limit of methanol is 5000 ppm, hence concentration of methanol in the linearity standard stock solution was 50000 ppm.

Similarly, solutions of all solvents were prepared as mentioned in Table 1. Linearity level standard solutions having 10%, 30%, 50%, 100% and 150% concentration to the working level were prepared and injected in triplicate. LOQ level standard and working level (i.e 100%) standard were injected in six replicate to check precision. LOQ for all the solvents was 10% concentration to the limit except Dimethyl sulfoxide and Dimethyl acetamide. However, for these two solvents four Linearity Levels were considered (i.e 30% to 150%) and LOQ was 30% to the limit level.

■ Sample Preparation

Transferred 100 mg Valsartan API Sample into 20 mL head space vial and added 1mL NMP. Vortexed for 5 min and submitted for analysis.

■ Spike Sample Preparation

Transferred 100 mg Valsartan Sample into 20 mL head space vial and added 1mL respective standard solutions. Vortexed for 5 min and submitted for analysis.

Table 1 : Linearity standard solution preparations

Linearity Levels	Volume taken from Linearity standard stock solution (mL)	Final dilution (mL)	Concentration w.r.to ICH-Q3C limit (%)
Level – 1	0.2	20 mL	10
Level – 2	0.6		30
Level – 3	1		50
Level – 4	2		100
Level – 5	3		150

Where, Level-1 and level-4 are LOQ level and working level, respectively.

■ Result and discussion:

Figure 4 depicts calibrations curves of representative solvents and Figure 5 depicts typical chromatogram at LOQ level standard injection. Suitability criteria such as correlation coefficient, signal to noise ratio, repeatability at LOQ level as well as working level for all the solvents were evaluated. All the parameters found to be satisfactory. Refer summary of results reported in the Table 2.

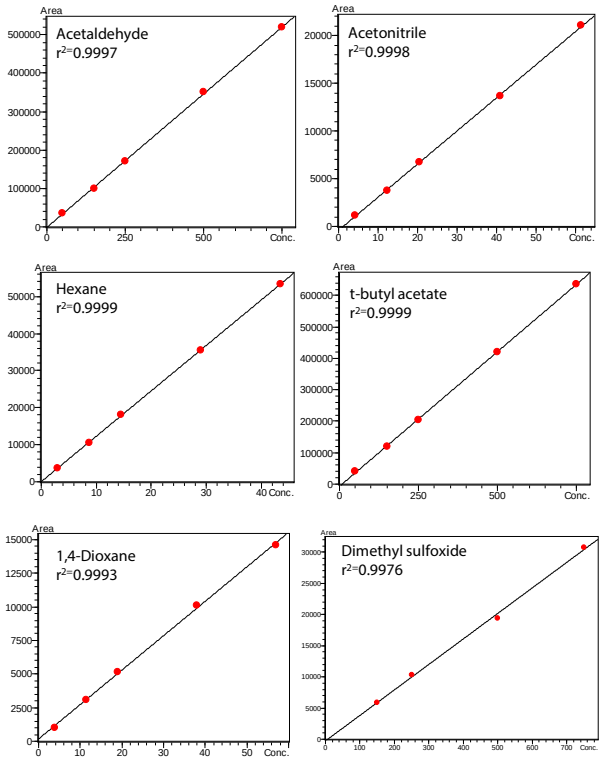

Figure 4: Calibration curve for Acetaldehyde, Acetonitrile, Hexane, t-butyl acetate, 1,4 dioxane and Dimethyl sulfoxide

Table 2 : Results summary Table

Peak. No.	Name	RT (min)	LOQ conc. (ppm)	Precision at LOQ (%RSD)	Working Level conc. (ppm)	Precision at Working Level (%RSD)	Correlation coefficient (r^2)	Resolution	Linearity Range (ppm)
1	Acetaldehyde	2.3	500	3.4	5000	0.6	0.999	-	500 - 7500
2	Methanol	2.4	300	1.3	3000	0.8	0.999	2.0	300 – 4500
3	Isopentane	2.8	500	1.3	5000	3.6	0.999	7.5	500 – 7500
4	Pentane	3.1	500	1.7	5000	3.0	0.999	5.9	500 – 7500
5	Ethanol	3.1	500	1.4	5000	1.1	0.999	1.4	500 – 7500
6	Acetone	3.7	500	1.1	5000	0.4	0.999	9.3	500 – 7500
7	Isopropyl alcohol	3.9	500	1.7	5000	1.2	0.999	3.2	500 – 7500
8	Acetonitrile	4.1	41	3.3	410	1.7	0.999	2.7	41 – 615
9	Methyl acetate	4.2	500	1.4	5000	0.5	0.999	0.7	500 – 7500
10	Dichloromethane	4.4	60	3.6	600	1.2	0.999	3.0	60 - 900
11	Cyclopentane	4.5	500	1.6	5000	1.0	0.999	1.2	500 – 7500
12	t-Butyl methyl ether	4.8	500	1.8	5000	0.5	0.999	4.5	500 – 7500
13	n-Hexane	5.2	29	3.2	290	0.8	0.999	6.3	29 – 435
14	1-Propanol	5.6	500	1.9	500	2.2	0.999	5.3	500 – 7500
15	Methyl cyclopentane	6.3	500	1.6	500	0.7	0.999	9.1	500 – 7500
16	Methyl ethyl ketone	6.4	500	1.2	500	1.3	0.999	2.3	500 – 7500
17	Ethyl acetate	6.5	500	1.5	500	0.9	0.999	1.3	500 – 7500
18	Tetrahydrofuran	6.9	72	9.7	720	0.8	0.999	5.0	72 – 1080
19	Cyclohexane	7.5	388	1.6	3880	0.4	0.999	7.1	388 - 5820
20	Iso-butanol	7.9	500	3.4	5000	2.8	0.999	5.8	500 – 7500
21	Iso-propyl Acetate	8.2	500	1.5	5000	0.7	0.999	2.3	500 – 7500
22	Methyl tetrahydrofuran	8.3	500	1.8	5000	0.6	0.999	1.7	500 – 7500
23	n-Heptane	8.6	500	1.3	5000	0.4	0.999	4.1	500 – 7500
24	1-Butanol	9.3	500	3.7	5000	2.8	0.999	7.9	500 – 7500
25	t-Butyl acetate	9.6	500	1.1	5000	0.6	0.999	4.6	500 – 7500
26	1,4-Dioxane	10.1	38	4.7	3880	1.3	0.999	5.4	38 – 570
27	Cyclo-pentyl methyl ether	11.6	150	0.9	1500	0.8	0.999	22.3	150 – 2250
28	Isoamyl alcohol	11.8	500	5.2	5000	4.0	0.999	3.0	500 – 7500
29	Toluene	11.9	899	2.0	8900	2.0	0.999	1.4	899 – 1335
30	1-Pentanol	12.4	500	6.3	5000	5.3	0.999	10.7	500 – 7500
31	Tetrachloroethelene	12.5	500	1.3	5000	0.8	0.999	1.4	500 – 7500
32	2-Hexanone	12.7	5	3.3	50	3.6	0.990	3.8	5 – 75
33	n-Butyl acetate	12.8	500	1.5	5000	1.6	0.999	3.0	500 – 7500
34	Cyclopentanone	12.9	500	5.0	5000	2.6	0.999	1.5	500 – 7500
35	Dimethyl formamide	13.1	88	10.1	880	5.5	0.999	4.6	88 – 1320
36	Ethyl benzene	13.5	217	2.2	2170	1.9	0.999	7.2	217 – 3255
37	p-Xylene	13.6	217	3.1	2170	2.0	0.999	2.8	217 – 3255
38	o-Xylene	13.9	217	2.6	2170	2.3	0.999	7.3	217 – 3255
39	Dimethyl sulfoxide	14.1	1500	5.5	5000	6.7	0.997	3.4	1500 – 7500
40	Dimethyl acetamide	14.1	327	13.4	1090	9.2	0.999	1.1	327 – 1635

All Concentration are reported with respect to sample preparation.

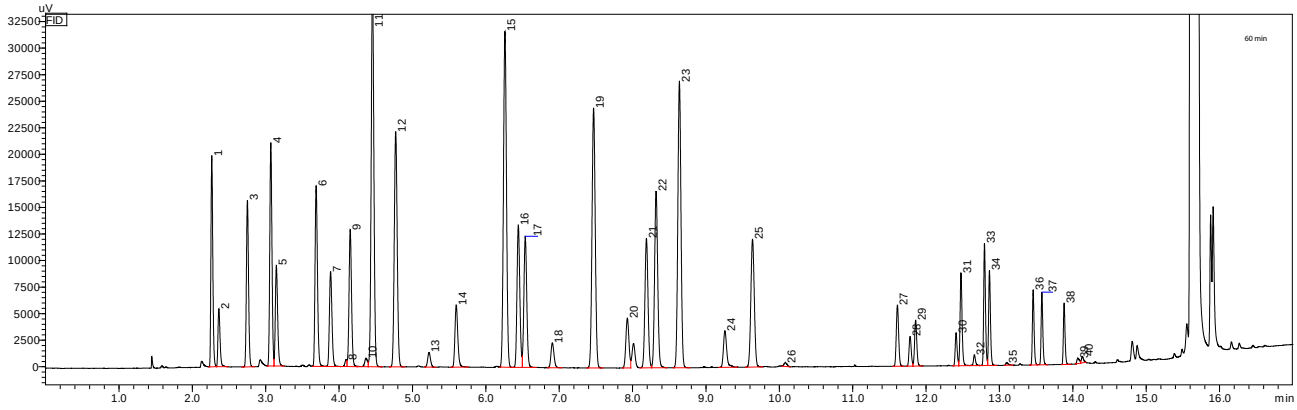

Figure 5 : Representative Chromatogram of LOQ Level

■ Critical Solvents Pair

As per pharmacopeial guidance, resolution should be greater than 1.5. Here, solvent pairs which shows resolution less than 1.5 are considered as critical pairs and reported in Table 3. During development, multiple trials were performed to get better resolution. Finally, below reported resolution was the optimum. Although, the resolution is less than the expected, other parameters are complying with criteria of method validation study. Further, there is scope for method optimization to get the better resolution as on need basis.

Table 3 : Critical Solvent Pairs

Sr. no.	Solvent Pairs	Retention Time	Resolution
1	Acetonitrile and Methyl acetate	4.15	0.7
2	Dichloromethane and Cyclopentane	4.46	1.2
3	Methyl ethyl ketone and Ethyl acetate	6.54	1.3
4	Isoamyl alcohol and Toluene	11.87	1.4
5	1-Pentanol and Tetrachloroethylene	12.48	1.3
6	Dimethyl sulfoxide and Dimethyl acetamide	14.10	1.1

Method validation was performed the with respect to few of the critical parameter. Below are the observation for the same.

- Relative Standard Deviation of area observed in six replicate injections of LOQ and working level (i.e 100% Level) was found to be less than 15%.
- Correlation coefficient of calibration curve was found to be above 0.99
- Resolution was above 1.5 for almost all the solvents except the critical solvent pairs.
- Accuracy study was performed in terms of spike and recovery. In which LOQ and working level concentration of analyte were spiked in the test sample. Recovery for both the spike level was within 80% to 120%.

■ Conclusion

Shimadzu's Nexis GC-2030 along with HS–20 NX headspace system is suitable for drug discovery and pharmaceutical applications, allowing testing of wide range of residual solvents from low to high boilers in a single method with a short run time.

■ References

1. ICH Q2(R2): Validation of analytical procedures
2. ICH Q3C (R9): Guidelines for residual solvents

06-SAIP-GC-040-EN First Edition: Dec. 2024

SHIMADZU

Shimadzu Corporation
www.shimadzu.com/an/

Shimadzu Analytical (India) Pvt. Ltd.
www.shimadzu.in