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Developing One Universal Method for Residual Solvents Using the New Teledyne Tekmar HT3™ Headspace Sample Introduction System

Application Note

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Introduction

A variety of solvents are used in the manufacturing of pharmaceutical products, substances, and excipients. In an effort to protect the health of the patient, pharmaceutical companies are adopting methodologies that will reduce the toxicity of the residual solvents. The International Conference on Harmonization (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use has published guidelines on a list of 3 separate classes of residual solvents and their daily exposure limits [(1)].

Class 1. These residual solvents are know carcinogens or environmental hazards and are avoided whenever possible in pharmaceutical manufacturing.

Class 2. This class causes some reversible or irreversible toxicity but is less toxic than class 1. These solvents are limited in their use in pharmaceutical manufacturing.

Class 3. These residual solvents have a low toxic potential or have no health-related exposure limits.

Difficulties have occurred in finding a matrix in which all of the residual solvents can be successfully analyzed. The diversity of pharmaceutical matrices has produced many analytical methods for the analysis of residual solvents. The multitude of methods has created a significant cost and complexity barrier to establishing residual solvent compliance on a global basis. Recently, a universal analytical method was developed using 1,3-dimethyl-2-imidazolidinone (DMI) as the sample matrix for the dissolution of the drug compounds with the use of static headspace for sample introduction into a Gas Chromatograph (GC).

DMI provides good solubility characteristics for a broad range of drug compounds. DMI is thermally stable and can be obtained at high purities (example 99.5%). DMI has the capability to dissolve both organic and inorganic compounds. The solubility characteristics allow for many drug substances and residual solvents to be evaluated using one method instead of numerous methods.

The static headspace sample introduction technique allows residual solvents in DMI to diffuse into a gas phase within a sealed vial until equilibrium is reached. The gas phase is then transferred to the GC for analysis. Because the sample transferred to the GC is in a gas phase, there is minimal interference from drug substance and drug product excipients.

Experimental

This study was created to test the Residual Solvent Method using the new Teledyne Tekmar HT3 Headspace Autosampler. A working standard of each of the residual solvent compounds (listed below in table 1) was prepared in DMI and dilutions were made from the working standard. The dilutions were also made in DMI, and 5 mL of the dilution was added to a 22 mL headspace vial and analyzed on the HT3.

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Table 1. Compounds of interest

Compound	Class
Methanol	2
Ethanol	3
1,1-dichloroethene	1
Acetone	3
2-propanol	3
Acetonitrile	2
Dichloromethane	2
MTBE	3
Hexane	2
1-propanol	3
Nitromethane	2
cis 1,2-dichloroethene	2
Ethyl Acetate	3
2-butanol	3
Tetrahydrofuran	3
Chloroform	2
1,1,1-trichloroethane	1
Cyclohexane	2
Carbon Tetrachloride	1
1,2-dimethoxyethane	2
2-methoxyethanol	2
Benzene	1

Compound (Cont'd)	Class
Isopropyl acetate	3
1,2-dichloroethane	1
Heptane	3
Methylcyclohexane	2
1,4-dioxane	2
2-ethoxyethanol	2
MIBK	3
Pyridine	2
Toluene	2
1-pentanol	3
1,1,2-trichloroethene	2
2-hexanone	2
N,N-dimethylformamide	2
Chlorobenzene	2
Ethylbenzene	Unlisted
M&P-xylene	2
O-xylene	2
DMSO	3
N,N-dimethylacetamide	2
N-methylpyrolidone	2
1,2,3,4-tetrahydronaphthalene	2

A DMI method was developed using a Teledyne Tekmar 7000/7050 Headspace Analyzer[(2)]. Because of the high boiling point of DMI (226°C), the platen temperature was set to 140°C and the loop and transfer line temperatures were set to 250°C. This prevented DMI condensation in the sample pathway. The high temperature pathway creates one robust method that may be applied to a variety of residual solvents.

The Teledyne Tekmar HT3 sample pathway can also be heated to 250°C, creating the same robust Residual Solvent Method. When trying to analyze very low-level compounds, one-way to increase the sensitivity of the instrument is to lower the pressure variation between the sample in the vial and the loop pressure during the loop fill. This is achieved by decreasing the loop oven temperature and is demonstrated with the following equation:

PV = nRT ***(n is the number of moles and R is a constant)***

When solving for n, the equation reads:

$$n = (PV)/(RT)$$

When temperature decreases, the number of moles increases, thus increasing the concentration in the loop during loop fill.

A study was performed to compare the response of a 500ppm standard analyzed with the loop and transfer line at 150°C and later with the loop and transfer line at 250°C. Each standard was followed by a DMI blank to check for carryover in the system.

Table 2. Increased response at lower loop and transfer line temperatures

Compounds	Loop and Transfer Line 150°C Response	DMI Blank	% Carryover	Loop and Transfer Line 250°C Response	DMI Blank	% Carryover	Response % Increase
Methanol	37428821	0	0.00	31602802	0	0.00	18.44
Ethanol	60496855	127506	0.21	51477460	195669	0.38	17.52
1,1-dichloroethene	146266963	249768	0.17	124221891	136743	0.11	17.75
Acetone	128950086	379998	0.29	113611218	288667	0.25	13.50
2-propanol	123864456	285510	0.23	107634457	400499	0.37	15.08
Acetonitrile	99738317	168866	0.17	84572229	225541	0.27	17.93
Dichloromethane	100116002	219926	0.22	84952517	175636	0.21	17.85
MTBE	448599481	1381203	0.31	405138499	765309	0.19	10.73
Hexane	296809076	739011	0.25	264143795	440635	0.17	12.37
1-propanol	49768951	126649	0.25	41471181	140680	0.34	20.01
Nitromethane	23926135	38455	0.16	20120601	36170	0.18	18.91
cis 1,2-dichloroethene	82951201	181240	0.22	68914618	195450	0.28	20.37
Ethyl Acetate	162970598	466118	0.29	141542704	363171	0.26	15.14
2-butanol	67881066	199842	0.29	63281250	194402	0.31	7.27
Tetrahydrofuran	120253666	374060	0.31	107240318	264726	0.25	12.13
Chloroform	108551292	257654	0.24	93374146	265658	0.28	16.25
1,1,1-trichloroethane	167125081	415680	0.25	139561136	180912	0.13	19.75
Cyclohexane	232738843	608091	0.26	212514770	332346	0.16	9.52
Carbon Tetrachloride	28002685	61759	0.22	22807110	27746	0.12	22.78
1,2-dimethoxyethane	196259318	527104	0.27	175849952	563708	0.32	11.61
2-methoxyethanol	13717792	42514	0.31	11919599	40232	0.34	15.09
Benzene	225997677	822303	0.36	208422879	769830	0.37	8.43
Isopropyl acetate	157088665	724275	0.46	147901515	564550	0.38	6.21
1,2-dichloroethane	39828820	105556	0.27	34569227	113837	0.33	15.21
Heptane	196352212	626730	0.32	159900840	311968	0.20	22.80
Methylcyclohexane	233827711	703584	0.30	209381582	342592	0.16	11.68
1,4-dioxane	35194756	81769	0.23	32122890	85022	0.26	9.56
2-ethoxyethanol	6587795	0	0.00	6471020	0	0.00	1.80
MIBK	66815803	222528	0.33	66387370	203930	0.31	0.65
Pyridine	40755754	336775	0.83	39942334	151077	0.38	2.04
Toluene	186926902	526122	0.28	148251404	554036	0.37	26.09
1-pentanol	4818955	0	0.00	5127409	0	0.00	-6.02
1,1,2-trichloroethene	27159466	79596	0.29	21113031	50834	0.24	28.64
2-hexanone	67647992	199348	0.29	48916132	127406	0.26	38.29

Compounds (Cont'd)	Loop and Transfer Line 150°C Response	DMI Blank	% Carryover	Loop and Transfer Line 250°C Response	DMI Blank	% Carryover	Response % Increase
N,N-dimethylformamide	16969528	0	0.00	14561948	376983	2.59	16.53
Chlorobenzene	58185111	243257	0.42	55227644	144770	0.26	5.36
Ethylbenzene	111649180	531562	0.48	110354805	368706	0.33	1.17
M&P-xylene	164326245	739773	0.45	144305990	498897	0.35	13.87
O-xylene	95364902	331935	0.35	74912238	193718	0.26	27.30
DMSO	2843307	0	0.00	4619660	0	0.00	-38.45
N,N-dimethylacetamide	9164649	0	0.00	9658759	0	0.00	-5.12
N-methylpyrolidone	1435828	0	0.00	3566261	2074	0.06	-59.74
1,2,3,4-tetrahydronaphthalene	7212788	0	0.00	6979435	0	0.00	3.34

Practically all compounds had higher recoveries with the loop and transfer line temperatures at 150°C than 250°C. The four compounds that did not show an increase in response had higher acceptable ICH concentration limits so the response was not as critical. The percent carryover at the 150°C temperature for all compounds was less than 0.5%. Tables 3 and 4 list the HT3 and GC parameters used in the application.

Table 3. HT3 Parameters

Variable	Value
GC cycle time	45 min
Valve oven temp	**150°C**
Transfer line temp	**150°C**
Standby flow rate	50 mL/min
Platen/sample temp	140°C
Platen temp equil. time	0.50 min
Sample equil. Time	20.00 min
Mixer	On
Mixing time	2.00 min

Variable (Cont'd)	Value
Mixing level	Level 5
Mixer stabilize time	0.50 min
Pressurize	8 psig
Pressurize time	1.00 min
Pressure equil. time	0.50 min
Loop fill pressure	5 psig
Loop fill time	0.50 min
Loop fill equil. time	0.50 min
Inject time	2.00 min

The lower valve oven and transfer line temperatures increase response and increase sensitivity, however higher temperatures (250°C) reduce DMI condensation which keep the system clean and reduce maintenance.

Table 4. GC and MS parameters

Column	J&W 624 60m x 0.32, 1.8 micrometer film, constant column flow of 1.2 mL/minutes
Inlet	Split ratio 30:1, total flow of 39.7mL/minutes, inlet temperature of 250°C
Oven	Initial temperature 50°C, hold for 0 minutes, rate of 1.0 to 60°C, hold for 0 minutes, rate of 9.20 to 115°C, hold for 0 minutes, rate of 35 to 250°C, hold for 10 minutes
MS Detector	MS quad at 150°C, MS source at 230°C, low mass scan at 30, high mass scan at 500

The mass spectrometer detector was chosen for exact identification of all compounds and also to check for breakdown products of certain solvents.

Results

A curve was generated using standards of 2ppm, 5ppm, 10ppm, 20ppm, 50ppm, 100ppm, 200ppm, and 500ppm. The results are listed below (Table 5) including the r^2 value and the calculated MDL. The range varied for some compounds, either they were not detected at the low end, or at higher concentrations they were saturating the detector.

Table 5. Curve results

Compounds	r^2 Values	Curve range	MDL (ppm)	ICH Concentration Limit (ppm)
Methanol	0.999	5ppm-500ppm	1.85	3000
Ethanol	1.000	2ppm-500ppm	0.46	5000
1,1-dichloroethene*	0.995	2ppm-50ppm	0.28	8
Acetone	0.999	2ppm-200ppm	0.42	5000
2-propanol	1.000	2ppm-500ppm	0.38	5000
Acetonitrile	1.000	2ppm-500ppm	0.44	410
Dichloromethane	0.999	2ppm-500ppm	0.81	600
MTBE	0.996	2ppm-500ppm	0.85	5000
Hexane	0.996	2ppm-100ppm	0.72	290
1-propanol	1.000	2ppm-500ppm	0.86	5000
Nitromethane	1.000	2ppm-500ppm	0.65	50
cis 1,2-dichloroethene	1.000	2ppm-500ppm	0.73	1870
Ethyl Acetate	0.998	2ppm-500ppm	0.61	5000
2-butanol	1.000	2ppm-500ppm	0.74	5000
Tetrahydrofuran	0.995	10ppm-500ppm	0.21	5000
Chloroform	1.000	2ppm-500ppm	0.52	60
1,1,1-trichloroethane	0.999	2ppm-500ppm	0.75	1500
Cyclohexane	0.996	2ppm-200ppm	0.55	3880
Carbon Tetrachloride*	0.997	2ppm-100ppm	0.33	4
1,2-dimethoxyethane	0.997	2ppm-500ppm	0.32	100
2-methoxyethanol	1.000	2ppm-500ppm	0.47	50

Compounds (Cont'd)	r^2 Values	Curve range	MDL (ppm)	ICH Concentration Limit (ppm)
Benzene	0.999	2ppm-500ppm	0.38	2
Isopropyl acetate	0.999	2ppm-200ppm	0.35	5000
1,2-dichloroethane	0.999	2ppm-500ppm	0.56	5
Heptane	0.996	2ppm-100ppm	0.34	5000
Methylcyclohexane	0.998	2ppm-200ppm	0.45	1180
1,4-dioxane	1.000	2ppm-500ppm	0.67	380
2-ethoxyethanol	0.996	2ppm-200ppm	1.11	160
MIBK	0.999	2ppm-500ppm	0.50	5000
Pyridine	0.998	2ppm-500ppm	1.47	200
Toluene	0.999	2ppm-200ppm	0.61	890
1-pentanol	0.996	10ppm-200ppm	1.34	5000
1,1,2-trichloroethene	0.999	2ppm-500ppm	0.72	80
2-hexanone	0.999	2ppm-500ppm	0.83	50
N,N-dimethylformamide	1.000	2ppm-500ppm	1.35	880
Chlorobenzene	1.000	2ppm-500ppm	0.84	360
Ethylbenzene	0.997	2ppm-500ppm	0.66	unlisted
M&P-xylene	0.999	2ppm-200ppm	0.45	2170
O-xylene	0.999	2ppm-500ppm	0.56	2170
DMSO	0.995	10ppm-500ppm	0.46	5000
N,N-dimethylacetamide	1.000	2ppm-500ppm	0.76	1090
N-methylpyrolidone	1.000	10ppm-500ppm	1.83	530
1,2,3,4-tetrahydronaphthalene	1.000	10ppm-500ppm	1.89	100

*1,1-dichloroethene and Carbon Tetrachloride could not be successfully analyzed because of interference with the DMI. 1,1-dichloroethene was not recovering below 20ppm; however, the curve was linear above 20ppm. Carbon Tetrachloride was breaking down almost completely in DMI to form Chloroform. The two solvents were diluted in water and the platen temperature was decreased to 85°C. Both compounds were linear down to 2ppb.

Figure 1. Example chromatogram of a 500 ppm standard in DMI, the last peak at 23 minutes is the DMI solvent peak.

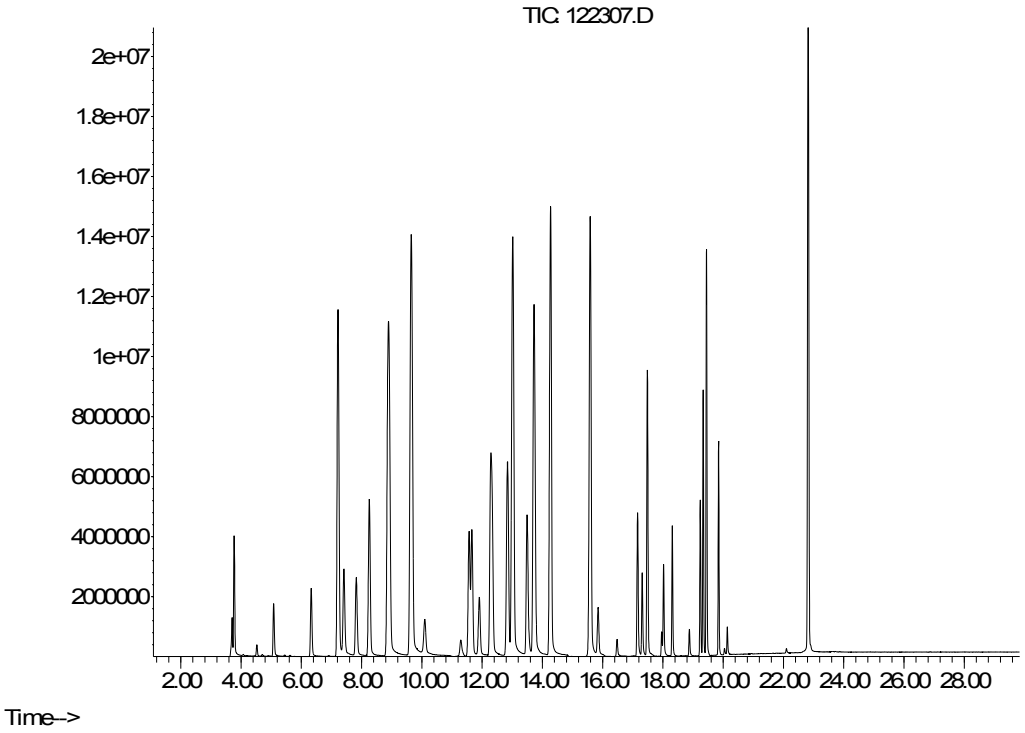
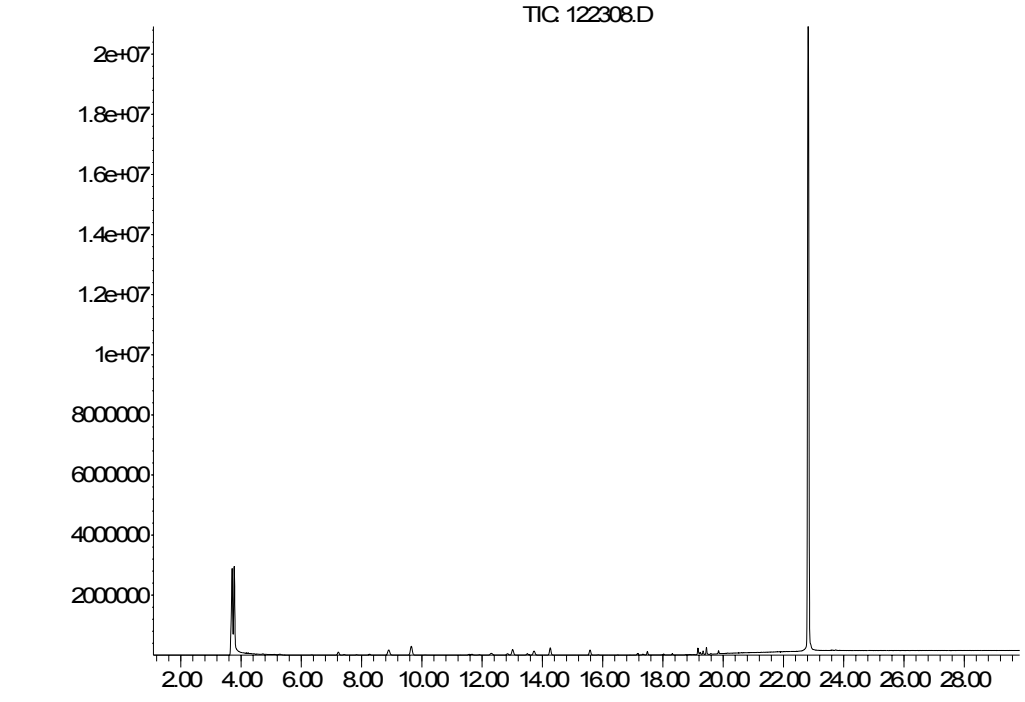


Figure 2. Example chromatogram of a DMI blank after a 500ppm standard in DMI. The largest carryover is N,N-dimethylformamide at 1.4%.



Conclusion

Residual Solvent analysis can be complicated when using multiple methods. DMI works as an excellent dissolution matrix along with the new Teledyne Tekmar HT3 Headspace Autosampler. Because the entire sample pathway can be precisely heated to 250°C, one robust method could be used for the analysis of Residual Solvents. However, for lower detection limits the loop temperature can be decreased to 150°C, increasing the concentration in the loop during the loop fill mode. The above parameters provide MDL's below the residual solvents listed in ICH with acceptable reproducibility and linearity.

Static Headspace has proven to be the best technique for DMI analysis. Headspace provides a cleaner alternative to methods that involve direct injects. The cleaner the analysis, the less GC maintenance that is required, saving downtime and money. The HT3 offers several new features to maximize productivity such as automatic vial pressure and loop control, which ensures identical loop-fill conditions each time. With the new HT3 Headspace Autosampler and DMI as a universal solvent, one robust method may be applied to a variety of residual solvents.

References

(1) "International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (Impurities: Guideline for Residual Solvents)." Recommended for Adoption at Step 4 of the ICH Process on 17 July 1997 by the ICH Steering Committee.

(2) Wallace, Brian and Kancler, Julie. "One Universal Method for Residual Solvents in Pharmaceuticals Using a High Temperature Static Headspace Sample Introduction System", Application Note (Teledyne Tekmar), Document # 7000-021. March 2004.