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Quality Control in Pharmaceuticals: Residual Solvents Testing and Analysis

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1. Introduction

Organic solvents are constantly present in the pharmaceutical production processes. They are usually used at any step of the synthesis pathway during the drug product formulation process. Organic solvents play an important role in the pharmaceutical industry, and appropriate selection of the solvents for the synthesis of drug substance may enhance the yield, or determine characteristics such as crystal form, purity, and solubility. Because of some physical and chemical property, the solvents are not completely removed by practical manufacturing techniques. Usually some small amounts of solvents may remain in the final drug product. They are called as residual solvents. Thus, residual solvents in pharmaceuticals are defined as organic volatile chemicals that are used or produced in the manufacture of drug substances or excipients, or in the preparation of drug products (International Conference on Harmonisation of Technical Requirement for Registration of Pharmaceuticals for Human Use [ICH], 2009). Since there is no therapeutic benefit from residual solvents, all residual solvents should be removed to the extent possible to meet product specifications, good manufacturing practices, or other quality-based requirements. If the presence of residual solvents in pharmaceuticals exceeds tolerance limits as suggested by safety data, they may be harmful to the human health and to the environment. That's the reason that residual solvents testing become one of the important parts of quality control in pharmaceuticals. This chapter will review the regulation of residual solvents and methods for residual solvents testing and analysis. Special emphasis will be given to the recent progress of residual solvents analysis and systematic study on residual solvents analysis in pharmaceuticals.

2. Regulation of residual solvents testing

The toxicity of residual solvents was recognized by the regulatory agency in the world in 90's. The United States Pharmacopeia was the first one that adopted residual solvent testing in 22 th edition 3 rd supplement in 1990 (The United States Pharmacopoeia [USP], 1990) British Pharmacopeia (1993 edition supplement) (British Pharmacopoeia [BP], 1996), European Pharmacopeia (3 rd edition) (European Pharmacopoeia [EP], 1997) and Chinese Pharmacopeia (1995 edition) (Pharmacopoeia of the People's Republic of China [ChP], 1995) subsequently adopted residual solvent testing, but only 6-8 residual solvents were controlled at that time. (Table 1)

Organic volatile impurities	Limit (ppm)			
	USP 22 edition 3rd supplement	BP(1993) supplement	EP 3rd	ChP 1995 edition
Benzene	100	100	100	100
Chloroform	50	50	50	50
1,4-Dioxane	100	100	100	100
Ethylene oxide	10	-	-	10
Dichloromethane	100	100	100	100
Trichloroethene	100	100	100	100
Acetonitrile	-	50	50	-
Pyridine	-	100	100	100
Toluene	-	-	-	100

Table 1. Categories and limits of residual solvents initially controlled in each pharmacopoeia

At that time, each pharmacopeia used various guidelines for residual solvents control in pharmaceutical products with different categories and acceptance limits. Moreover, only 6-8 residual solvents were controlled, which was far behind from the categories that were really used in pharmaceutical industry. Internationally, a standard guideline for control of residual solvents is needed to be established. Efforts were made to harmonize the guideline for residual solvents by ICH. On 17 July 1997, the Q3C parent guideline on residual solvent guidelines and limits was approved by the Steering Committee under Step 4 and recommended for adoption the three ICH regulatory bodies. 69 organic solvents that are commonly used in pharmaceutical industry were classified in 4 categories by ICH guideline (Table 2). Solvents in Class 1 are known carcinogens and should not be employed in the manufacture of drug substances, excipients, and drug products because of their unacceptable toxicity or their deleterious environmental effect. However, if their use is unavoidable in order to produce a drug product with a significant therapeutic advance, then their levels should be restricted as shown in Table 2, unless otherwise justified. The limits of Class l solvents are usually between 2-8 ppm except 1,1,1-trichloroethane is 1500 ppm, which is an environmental hazard. Class 2 solvents are nongenotoxic animal carcinogens. Solvents of this class should be limited in pharmaceutical products because of their inherent toxicity. The concentration limits of these solvents are in the range of 50 ~ 3880 ppm. Class 3 solvents have less toxic and lower risk to human health. Class 3 includes no solvent known as a human health hazard at levels normally accepted in pharmaceuticals. However, there are no long-term toxicity or carcinogenicity studies for many of the solvents in Class 3. They are less toxic in acute or short-term studies and negative in genotoxicity studies. The concentration limits of these solvents are 5000 ppm. Class 4 solvents are the solvents that may also be of interest to manufacturers of excipients, drug substances, or drug products. However, no adequate toxicological data was found. Manufacturers should supply justification for residual levels of these solvents in pharmaceutical products.

Solvent	Concentration limit (ppm)
Class 1 solvents (solvents to be avoided)	
Benzene	2
Carbon tetrachloride	4
1,2-Dicloroethane	5
1,1-Dichloroethene	8
1,1,1-Trichloroethane	1500
Class 2 solvents (solvents to be limited)	
Acetonitrile	410
Chlorobenzene	360
Chloroform	60
Cyclohexane	3880
1,2-Dichloroethene	1870
Dichloromethane	600
1,2-Dimethoxyethane	100
N,N-Dimethylacetamide	1090
N,N-Dimethylformamide	880
1,4-Dioxane	380
2-Ethoxyethanol	160
Ethyleneglycol	62
Formamide	220
Hexane	290
Methanol	3000
2-Methoxyethanol	50
Methylbutyl ketone	50
Methylcyclohexane	1180
N-Methylpyrrolidone	4840
Nitromethane	50
Pyridine	200
Sulfolane	160
Tetralin	100
Toluene	890
1,1,2-Trichloroethene	80
Xylene	2170
Class 3 solvents (solvents which should be limited by GMP or other qualitybased requirements)	
Acetic acid	5000
Acetone	5000
Anisole	5000
1-Butanol	5000
2-Butanol	5000
Butyl acetate	5000
tert-Butylmethyl ether	5000
Cumene	5000
Dimethyl sulfoxide	5000

Solvent	Concentration limit (ppm)
Ethanol	5000
Ethyl acetate	5000
Ethyl ether	5000
Ethyl formate	5000
Formic acid	5000
Heptane	5000
Isobutyl acetate	5000
Isopropyl acetate	5000
Methyl acetate	5000
3-Methyl-1-butanol	5000
Methylethyl ketone	5000
Methylisobutyl ketone	5000
2-Methyl-1-propanol	5000
Pentane	5000
1-Pentanol	5000
1-Propanol	5000
2-Propanol	5000
Propyl acetate	5000
Tetrahydrofuran	5000
Class 4 solvents (solvents for which no adequate toxicological data was found)	
1,1-Diethoxypropane	Methylisopropyl ketone
1,1-Dimethoxymethane	Methyltetrahydrofuran
2,2-Dimethoxypropane	Petroleum ether
Isooctane	Trichloroacetic acid
Isopropyl ether	Trifluoroacetic acid

Table 2. List of solvents included in the guideline of ICH

After the ICH guideline regarding residual solvents in pharmaceuticals became official in 1997, consequently, pharmacopeias of different countries have adopted it and have revised their general methods to reflect it. EP (3rd edition) was the first one that accepted ICH guideline with the same categories and limits of residual solvents. In general chapter: Identification and control of residual solvents, general methods for residual solvent determination were described. Gas chromatography (GC) with headspace injection is proposed in both systems. Two procedures (systems), A and B, are presented, and System A is preferred whilst System B is employed normally for confirmation of identity (EP, 1999). Japanese Pharmacopoeia accepted ICH guideline in 14th edition (Japanese Pharmacopoeia [JP], 2001). ICH guideline was accepted by Chp in 2005 edition (Chp, 2005). Three methods were used to screening and analysis residual solvents in pharmaceuticals: Isothermal temperature HS-GC method, Programmed temperature HS-GC method, and direct injection method. Until USP 28, residual solvents testing was finally updated to comply with ICH guideline. Current official methods for residual solvent determination are described in <467> chapter Organic Volatile Impurities. Three procedures (A, B, C) for water-soluble and water-insoluble articles, are available. Procedures A and B are useful to identify and quantify residual solvents, when the information regarding which solvents are likely to be present in the material is not

available. In cases when we have information about residues of solvents that may be expected in the tested material, only procedure C is needed for quantification of the amount of residual solvents (USP, 2005).

3. Methods for residual solvents analysis

In the early stage, one of the simplest methods for determining the content of volatile residues consists in measuring the weight loss of a sample during heating. However, this method suffers the great disadvantages of being totally non-specific (multicomponent solvent blends cannot be analysed and there will always be a doubt on humidity contamination) and of needing several grams of product to achieve a detection limit of about 0.1% (Benoit, 1986; Dubernet, 1990; Guimbard, 1991). Nevertheless, when carried out by thermogravimetry, the limit can be lowered to 100 ppm using only a few milligrams of substance (Guimbard, 1991). Infrared spectroscopy (IR) (Osawa & Aiba, 1982) and Fourier Transform Infrared Spectrometry (FTIR) (Vachon & Nairn, 1995) were used to determine residual Tetrahydrofuran (THF), dichloroethane and methylene chloride in polymer samples by measuring the characteristic solvent bands in the spectra. The most common limiting factors in these methods are possible interferences of solvent and matrix peaks and, in the case of IR, the high detection limit (above 100 ppm) and a lack of accuracy at low concentrations (Weitkamp & Barth, 1976). Avdovich et al. determined benzene, toluene, acetone, methyl ethyl ketone and ethyl ether (in a few samples also methylene chloride and ethyl acetate) in cocaine samples by NMR, which allowed a quantification down to 100 ppm, with possibly detection or identification problems in the case of ethyl ether and methyl ethyl ketone at these low levels (Avdovich, 1991). However, these detection limits are too high to satisfy the requirements relating to residual solvents determination, especially for the most toxic solvents.

The methods mentioned above were replaced by GC. GC is the natural choice for residual solvent analysis. Firstly, because of its excellent separation ability, according to the chromatographic conditions and the column and, secondly, because of its low detection limits and the possibility of analysing liquid or solid samples of a complex nature. Modern capillary-column GC can separate a large number of volatile components, permitting identification through retention characteristics and detection at ppm levels using a broad range of detectors. The most popular detectors are: the flame ionization detector (FID), which is a rather universal detector for organic volatile compounds; and, the electron capture detector (ECD), which is especially suited to detection of halogenated compounds. However, FID is by far the most preferred for release-related tasks because of its low detection limits, wide linear dynamic range, robustness, ease of operation, and general reliability and utility, especially for trace organic compounds. There are three type of GC classed by different sample preparation procedures: direct-injection GC, headspace (HS) GC and solid-phase microextraction (SPME) GC. Application of these three GCs in residual solvent analysis will be reviewed below.

3.1 Direct-injection GC

Residual solvent determination using direct-injection sample preparation is the oldest technique, and, historically, it was preferred because of its simplicity, reliability, ease of operation and throughput (Witschi & Doelker, 1997). The drug substance or the formulation is dissolved in or extracted with a high-boiling-point solvent, such as water,

dimethylsulfoxide (DMSO), dimethylformamide (DMF), dimethylacetamide (DMA), benzyl alcohol (BA) or ethylene glycol. Using high-boiling-point solvents has the advantage that the diluent solvent peak will elute later, thus not interfering with the earlier eluting analyte peaks. However, it has the big disadvantage that non-volatile components, such as the drug substance or the formulation components, are also injected, and that leads to injector contamination, column contamination and deterioration, together with unavoidable matrix effects. Furthermore, as the matrix is also injected onto the column, this must be eluted prior to beginning the next injection, and that has the effect of prolonging the analytical run. From Witschi and Doelker (Witschi & Doelker, 1997) and Hymer's (Hymer, 2003) reviews, the data in the literature on direct injection applications was summarized up to 2003. It was evident from the trend that, in more recent times, based on the number of publications, the interest of industry-research groups has shifted to other sample-preparation techniques, such as static headspace and sorbent-based approaches.

3.2 Headspace GC

Two types of HS sampling are available: dynamic HS analysis (also called purge-and-trap); and static HS analysis. The theory of static headspace is thoroughly described in three books, by Hachenberg and Schmidt (Hachenberg & Schmidt, 1977), Loffe and Vitenberg (Loffe & Vitenberg, 1984), and Kolb and Ettre (Kolb & Ettre, 2006). It was summarized by Snow and Bullock as below (Snow & Bullock, 2010). In HS extraction, the vapor phase directly above and in contact with a liquid or solid sample in a sealed container is sampled and an aliquot is transferred to a GC for separation on a column, detection and quantitation. The ability to determine the amount of a substance within a liquid or solid sample by analyzing the headspace vapor above it in a closed vessel derives from three critical fundamental principles: Dalton's Law, Raoult's Law and Henry's Law. Generally, static HS sampling is the most widely used technique for residual solvent determination in pharmaceuticals. This fact comes from some of the advantages of this technique, mainly that only volatile substances and dissolution medium can be injected onto the column. Also HS systems are fully automated, in addition, a sample preparation is easy, and the sensitivity of analysis is sufficient for the majority of solvents mentioned in ICH guidelines. Static HS sampling is based on thermostatic partitioning of volatile compounds in a sealed vial between the sample diluent and the gas phase. Sample diluent is a critical factor affecting HS-GC method sample load, sensitivity, equilibration temperature and time. A good sample diluent for analyzing residual solvents in pharmaceutical products should have a high capability for dissolving a large amount of samples, a high boiling point and a good stability. There are a number of commonly used sample diluents for HS analysis, such as water, DMSO, DMF, DMA, BA, 1,3-dimethyl-2-imidazolidinone (DMI), and mixtures of water-DMF or water-DMSO. For water-soluble samples, water is the choice of diluent. The influence of the matrix medium used for the determination of residual solvents in pharmaceuticals was investigated by Urakami et al (Urakami et al, 2004). A guide for the choice of a matrix medium suitable for the determination of residual solvents was proposed. Water, DMSO, DMF, DMA, BA, DMI were studied as matrix media, and seventeen solvents were used as target analytes. The peak shapes of each analytes were not affected by the matrix medium, whereas the peak intensities for all solvents were strongly affected by the matrix medium. Otero et al established a static HS GC method for quantitative determination of residual solvents in a drug substance according to European Pharmacopoeia general procedure. A water-dimethylformamide mixture is proposed as sample solvent to obtain good sensitivity and recovery (Otero et al,

2004). Recently, ion liquid was used as matrix medium in HS analysis in residual solvent analysis. Liu et al used a new solvent room temperature ionic liquid (1-butyl-3-methylimidazolium teterafluoroborate) as matrix medium in static HS to determine residual solvents in pharmaceutical. Six residual solvents were analyzed and better sensitivities were gained with it as diluent comparing with DMSO (Liu & Jiang, 2007). Laus et al reported that 1-n-Butyl-3-methylimidazolium dimethyl phosphate (BMIM DMP) was identified as the most suitable ionic liquid as solvent for the HS-GC analysis of solvents with very low vapor pressure such as dimethylsulfoxide, N-methylpyrrolidone, sulfolane, tetralin, and ethylene glycol (Laus et al, 2009). The main drawback of static HS is the lower detection limit compared to dynamic HS. Partition Coefficient (K) is the key factor that affects the sensitivity of HS analysis, which represented the concentration ratio of a volatile in the liquid and gas phase at a defined temperature and pressure at equilibrium stage. Substance with low partition coefficient (K < 10-100) is easier to go to the gas phase, and is considered to suitable for HS analysis. Several methods are available for reducing the partition coefficient of volatiles, in particular in aqueous systems, and thus to improve the HS sensitivity, such as salting-out, pH adjustment or increasing the equilibration temperature of the sample. Dynamic headspace sampling technique involves the passing of carrier gas through a liquid sample, followed by trapping of the volatile analytes on a sorbent and desorption onto a GC. A major advantage of this technique is that a thermodynamic equilibrium is not necessarily needed, and the sensitivity of the method is increased by enrichment of the anlaytes on the trap. Consequently, limit of detection reported for dynamic headspace are lower (pg/ml) than those obtained with static headspace (ng/ml) (Arthur & Pawliszyn, 1990). Therefore, the automation of the instrument and reproducibility of the results are not as good as static headspace, so the application of purge and trap in residual solvent analysis was not popular.
Dynamic headspace analysis is particular suited for the determination of volatile residual solvents at very low concentrations. Recently, Lakatos reported that four Class 1 solvents were analyzed in a water-soluble drug using dynamic headspace technique. The results show that the Purge and trap technique is more sensitive than the static headspace. Repeatability, accuracy and the linearity were examined, and these characteristics of the method were proved to be suitable for residual solvent analysis. It was found that the Purge and trap could be an alternative sample preparation method besides the static headspace method (Lakatos, 2008).

3.3 Solid-phase microextraction GC

SPME, in which a small amount of extracting phase, a stationary phase is coated on a support. Commonly, a fused silica fiber is used. The extracting phase is placed in contact with the sample matrix for a predetermined amount of time. If the time is long enough, a concentration equilibrium of the volatile analyte is established between the sample matrix and the extraction phase, then the analytes adsorbed on the fiber are thermally desorbed in the injector of the GC. In general, two types of SPME extractions can be performed. The first type, “Direct extraction” or “immersion” involves bringing the SPME fiber in contact with the sample matrix. The second type of SPME is headspace SPME, in which, the volatile analytes need to be transported through the barrier of air above the sample before they can reach the SPME extracting phase. It helps to protect the fiber coating from damage by high molecular-mass and other non-volatile interferers present in the sample matrix. Since the headspace SPME was developed in 1993 and has experienced the strongest growth in research interest over the past decade. Advantages of SPME include simplicity of execution,

low cost of the instrument and less solvent consume. Headspace SPME attracted more attention in residual solvent testing area due to it can avoid the interference from the non-volatile pharmaceuticals. Camarasu et al used two types of SPME methods to determine residual solvents in pharmaceuticals. Three fibers with different polymer films were compared and the polydimethylsiloxane/divinylbenzene coated fiber was found to be the most sensitive one for the analyzed analytes. Bewteen the investigated sample preparation techniques, gastight-SPME proved to be the most sensitive one. Headspace SPME is more precise. Compared with the static headspace technique, SPME method showed superior results (Camarasu et al, 1998). Another paper from Camarasu reported that an SPME method has been developed and optimized for the polar residual solvents determination in pharmaceutical products. The headspace SPME from aqueous solutions was found to be ten times more sensitive than Immersion SPME and Headspace SPME from organic solutions (Camarasu, 2000)

3.4 Recent progress

A new method for direct determination of residual solvents in solid drug product using multiple headspace sing-drop microextraction (MHS-SDME) was reported by Yu et al. The MHS-SDME technique is based on extrapolation to an exhaustive extraction of consecutive extractions from the same sample which eliminates the matrix effect on the quantitative analysis of solid samples. Factors affecting the performance of MHS-SDME including extraction solvent, microdrop volume, extraction time, sample amount, thermostatting temperature and incubation time were studied. Experimentally, a model drug powder was chosen and the amounts of residues of two solvents, methanol and ethanol were investigated. Quantitative results of the proposed method showed good agreement with the traditional dissolution method. Compared with the conventional method for determination of residual solvents, the MHS-SDME technique can eliminate possible memory effects with less organic solvents. The results also indicated that MHS-SDME had a great potential for the quantitative determination of residual solvents directly from the solid drug products due to its low cost, ease of operation, sensitivity, reliability and environmental protection (Yu et al, 2010).

A novel on-line solvent drying technique has been described that is capable of simultaneously measuring the solvent end point in vapor phase and maintaining high accuracy with precision. The technique used non-contact infrared sensor for monitoring the solvent vapors during the pharmaceutical solvent drying process. The data presented demonstrated that on-line combined with non-contact sensor method had high degree of precision and accuracy for monitoring the end point of the solvent drying (Tewari et al, 2010).

4. Systematic study of analysis residual solvents in pharmaceuticals-database

Analysis of residual solvent is known to be one of the most challenging analytical tasks in pharmaceutical analysis and control. The challenge is due to the different manufacturer produce the same pharmaceutical products using different manufacturing processes. Unknown peaks are often detected during routine quality control testing using GC. When this happened, the only thing we can do is to try different solvent standards to find out which has the same retention time with the unknown peak. It is a time consuming work, sometimes the unknown peak is not a residual solvent, but an interference peak. To address this problem, a systematic study was conducted by our laboratory; three databases were

established for fast screening, confirmation and method optimization in the analysis of residual solvents in pharmaceuticals. These three databases were published separately (Liu & Hu, 2006, 2007, 2009) and were combined here for a better understanding purpose since they are three parts of the intact database for residual solvent analysis.

4.1 Screening database

4.1.1 Establishment of screening database

When analysis residual solvent using GC, unknown peaks often show up. It is hard to tell the unknown peak is another residual solvent or interference peak. Moreover, some organic solvents controlled by ICH have the same retention time on a GC column. To solve these problems, a database for preliminary screening of residual solvents in pharmaceuticals has been established using the parallel dual-column system. The basic principle is that different compounds may have the same retention times on one column, but it is highly unlikely that different compounds will have the same retention times on another column with opposite polarities. So if an organic solvent is present in both columns in the screening procedure, then it is a suspect residual solvent in pharmaceutical. The establishment and application of the screening database were described in one of article published by our lab (Liu & Hu, 2007). Two columns with different polarities, SPB-1 and HP-INNOWAX, connected with a 'Y' splitter, constituted the dual pathways system. Fifty-two solvents that suitable for static headspace analysis were studied according to the guidelines for residual solvents regulated by ICH on this system. The retention times of 52 organic solvents in both systems were recorded under the above conditions. The dead time was determined using methane, and the adjusted retention times of each solvent were calculated. The relative retention times (RRTs) of each solvent in both systems were then calculated as follows, using methyl ethyl ketone (MEK) as the reference standard.

$$RRT = [t_R(\text{compound}) - t_0] / [t_R(\text{MEK}) - t_0] \quad (1)$$

Where t_R is the retention time of the compound, and t_0 is the retention time of methane. The RRT was selected as the basis of identification. The RRTs of the 52 organic solvents in both systems constituted the database (Table 3).

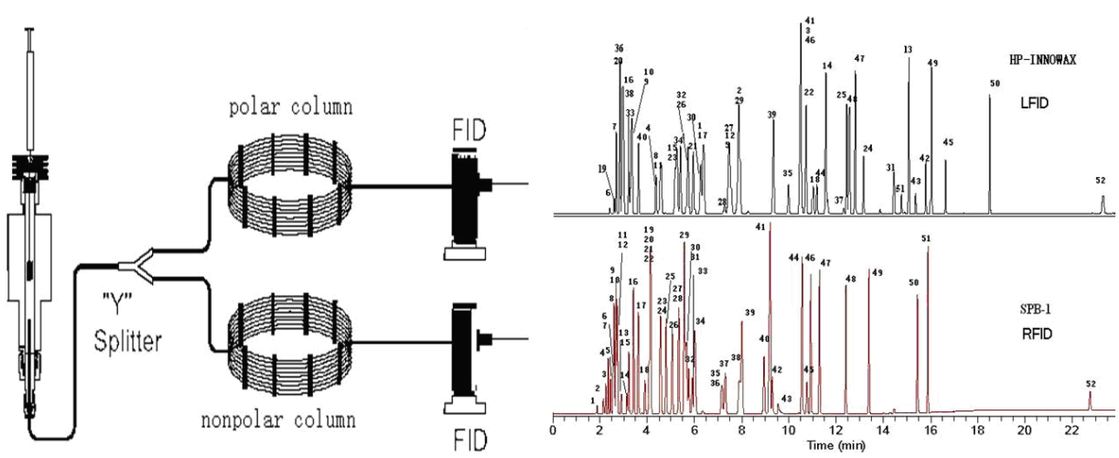


Fig. 1. Schematic diagram of parallel-column system and two chromatograms of all of 52 organic solvents obtained from the system in a single run

Non-polar system SPB - 1				Polar system HP - INNOWAX			
Order	**Organic solvent**	**t_R(min)**	**RRT**	**Order**	**Organic solvent**	**t_R(min)**	**RRT**
1	methanol	1.872	0.135	1	pentane	2.432	0.038
2	ethanol	2.155	0.274	2	hexane	2.607	0.081
3	acetonitrile	2.237	0.315	3	ethyl ether	2.675	0.098
4	acetone	2.345	0.368	4	isooctane	2.848	0.141
5	2-propanol	2.447	0.419	5	isopropyl ether	2.850	0.141
6	pentane	2.557	0.473	6	tert-butyl methyl ether	2.928	0.161
7	ethyl ether	2.568	0.479	7	heptane	2.987	0.175
8	ethyl formate	2.600	0.495	8	cyclohexane	3.232	0.236
9	1,1-dimethoxymethane	2.672	0.530	9	1,1-dichloroethene	3.277	0.247
10	1,1-dichloroethene	2.687	0.538	10	1, 1,1-dimethoxymethane	3.348	0.264
11	methyl acetate	2.730	0.559	11	methylcyclohexane	3.652	0.339
12	dichloromethane	2.733	0.560	12	acetone	4.378	0.518
13	nitromethane	2.903	0.644	13	ethyl formate	4.492	0.547
14	1-propanol	3.135	0.759	14	methyl acetate	4.562	0.564
15	1,2-dichloroethene	3.222	0.802	15	1,2-dichloroethene	5.190	0.719
16	tert-butyl methyl ether	3.407	0.894	16	tetrahydrofuran	5.217	0.725
17	methyl ethyl ketone	3.622	1.000	17	methyl tetrahydrofuran	5.378	0.765
18	2-butanol	3.892	1.134	18	1,1,1-trichloroethane	5.692	0.843
19	hexane	4.072	1.223	19	carbon tetrachloride	5.693	0.843
20	isopropyl ether	4.103	1.238	20	ethyl acetate	5.893	0.892
21	ethyl acetate	4.122	1.247	21	isopropyl acetate	6.250	0.980
22	chloroform	4.127	1.250	22	methyl ethyl ketone	6.330	1.000
23	tetrahydrofuran	4.537	1.453	23	methanol	6.358	1.007
24	2-methyl-1-propanol	4.560	1.464	24	1,2-dimethoxyethane	7.270	1.232
25	1,2-dichloroethane	4.788	1.577	25	2-propanol	7.390	1.262
26	1,1,1-trichloroethane	5.047	1.705	26	methyl isopropyl ketone	7.400	1.264
27	methyl isopropyl ketone	5.310	1.835	27	dichloromethane	7.470	1.281
28	1,2-dimethoxyethane	5.348	1.854	28	ethanol	7.802	1.363
29	benzene	5.563	1.960	29	benzene	7.827	1.369
30	isopropyl acetate	5.652	2.004	30	propyl acetate	9.355	1.746
31	1-butanol	5.718	2.037	31	1,1,2-trichloroethene	9.937	1.890
32	carbon tetrachloride	5.743	2.049	32	methyl isobutyl ketone	10.495	2.028
33	cyclohexane	5.903	2.128	33	acetonitrile	10.503	2.030
34	methyl tetrahydrofuran	5.997	2.175	34	isobutyl acetate	10.655	2.067
35	1,1,2-trichloroethene	7.143	2.741	35	chloroform	10.980	2.147
36	isooctane	7.278	2.808	36	2-butanol	11.182	2.197
37	1,4-dioxane	7.337	2.837	37	toluene	11.568	2.292
38	heptane	7.883	3.107	38	1-propanol	11.610	2.303
39	propyl acetate	7.997	3.164	39	1,4-dioxane	12.258	2.463
40	methylcyclohexane	8.933	3.627	40	1,2-dichloroethane	12.463	2.513
41	methyl isobutyl ketone	9.177	3.747	41	butyl acetate	12.540	2.532
42	3-methyl-1-butanol	9.270	3.793	42	methyl butyl ketone	12.800	2.596
43	pyridine	9.652	3.982	43	2-methyl-1-propanol	13.170	2.688
44	toluene	10.548	4.425	44	1-butanol	14.355	2.980
45	1-pentanol	10.737	4.519	45	cumene	15.030	3.147
46	isobutyl acetate	10.932	4.615	46	nitromethane	15.065	3.155
47	methyl butyl ketone	11.278	4.786	47	pyridine	15.357	3.227
48	butyl acetate	12.428	5.355	48	3-methyl-1-butanol	15.747	3.323
49	chlorobenzene	13.375	5.823	49	chlorobenzene	16.015	3.390
50	anisole	15.443	6.846	50	1-pentanol	16.618	3.538

Non-polar system SPB - 1				Polar system HP - INNOWAX			
Order	**Organic solvent**	**t_R(min)**	**RRT**	**Order**	**Organic solvent**	**t_R(min)**	**RRT**
51	cumene	15.887	7.066	51	anisole	18.523	4.008
52	tetralin	22.778	10.474	52	tetralin	23.303	5.188
	methane	1.600			methane	2.277	

Table 3. The relative retention times of 52 organic solvents on non-polar system and polar system

4.1.2 Applications of the database

4.1.2.1 Screening the residual solvents in parmacuticals in a single run

Amoxicillin sodium and clavulanate potassium (5:1), an antibacterial drug registered by a foreign company in China, was analyzed. The preliminary screening results (Table 4) were obtained simultaneously in a single run. According to Table 4, the solvents that appeared on both column systems simultaneously may be the residual solvents in the pharmaceuticals. The possible residual solvents were acetone, methyl acetate, ethyl acetate and 2-propanol in this case. All of these solvents were mentioned by the manufacturer, except for methyl acetate. It was confirmed by the reference standard. The confirmation database was used to give further identification of this peak, and the results indicated that the peak was indeed methyl acetate (4.2.3.1). Finally, the manufacturer admitted that methyl acetate was actually used in the manufacturing process, but for some reason it was not disclosed in the manufacturer's product information sheet. In addition, although only 4 out of the 8 impurities detected in Table 4 could be identified as residual solvents, it showed that the database could eliminate the interference of thermal degradation products or other volatile impurities (which were not the 52 residual solvents we concerned), which was one of the advantages of the database.

4.1.2.2 Eliminating the interference of co-elution

Potassium clavulanate and cellulose microcrystallistate (1:1), an enzyme inhibitor of β-lactamase, was registered by a foreign company in China. The content of methanol was reported much higher than the limit specified by the ICH in the routine residual solvent test. The database was used to check this result. The preliminary screening results are given in Table 5.

According to Table 5, the solvents that appeared on both column systems simultaneously may be the residual solvents in the pharmaceutical product. The possible residual solvents in the drugs were acetone and 2-propanol without methanol. If the peak whose RRT was 0.129 was judged only according to the results of SPB-1, it would definitely be identified as methanol, but on the HP-INNOWAX there was no peak with the RRT of methanol. Therefore, this peak was not methanol and was not included in the 52 residual solvents; it might be a degradation product from the headspace process. The database can eliminate the interference of co-elution and avoid false positive result.

4.2 Confirmation database

Mass spectrometry (MS) and FTIR are powerful tools for identification of organic compounds. GC is the most common technique for separation of volatile and semi-volatile mixtures. It is well accepted that when GC is coupled with spectral detection methods, such as FTIR or MS that the resulting combination is a powerful tool for the separation and

Column	Number	t_R(min)	RRT	Data in database	Possible residual solvents
SPB-1	1	2.352	0.369	0.368	acetone*
	2	2.445	0.416	0.419	2-propanol*
	3	2.727	0.556	0.538 0.559 0.560	1,1-dichloroethene methyl acetate* dichloromethane
	4	3.807	1.092	1.134	2-butanol
	5	4.135	1.255	1.223 1.238 1.247 1.250	hexane isopropyl ether ethyl acetate* chloroform
	6	5.863	2.113	2.037 2.049 2.128 2.175	1-butanol carbon tetrachloride cyclohexane methyl tetrahydrofuran
	7	8.697	3.520	3.627	methylcyclohexane
	8	17.988	8.133	no corresponding data	
HP-INNOWAX	1	3.080	0.197	no corresponding data	
	2	4.347	0.510	0.518	acetone*
	3	4.563	0.563	0.547 0.564	ethyl formate methyl acetate*
	4	5.913	0.897	0.892	ethyl acetate*
	5	6.308	0.995	0.980 1.000 1.007	isopropyl acetate methyl ethyl ketone methanol
	6	7.425	1.271	1.232 1.262 1.264	1,2-dimethoxyethane 2-propanol* methyl isopropyl ketone
	7	7.702	1.339	1.363 1.369	ethanol benzene
	8	16.808	5.590	no corresponding data	

Note: The organic solvents appeared in both columns were marked with *.

Table 4. The preliminary screening results of the SPB-1 column and the HP-INNOWAX column

Column	Number	t_R (min)	RRT	Data in database	Possible residual solvents
SPB-1	1	1.878	0.129	0.135	methanol
	2	2.363	0.368	0.368	acetone*
	3	2.458	0.415	0.419	2-propanol*
	4	4.832	1.588	1.577	1,2-dichloroethane
HP-IN NOWAX	1	3.037	0.194	no corresponding data	
	2	4.287	0.505	0.518	acetone*
	3	7.310	1.258	1.232	1,2-dimethoxyethane
				1.262	2-propanol*
				1.264	methyl isopropyl ketone
	4	11.543	2.311	2.292	toluene
				2.303	1-propanol

Note: The organic solvents appeared in both columns were marked with *.

Table 5. The preliminary screening results of the SPB-1 column and the HP-INNOWAX column

identification of components in complex mixtures. Gas chromatography-mass spectrometry (GC-MS) has superior detection limits and is widely used in qualitation of volatile organic compound. Gas chromatography-fourier transform infrared spectrometry (GC-FTIR) also has applications in the identification for compound. The combination application of mass spectra and FTIR spectra is a very powerful coupling because of the complementary nature of the data acquired, which will make the confirmation more confident. Another problem is that the residual solvents testing is trace analysis, usually the concentration of residual solvent in the drugs is very low. So it was hard to get good results using the commercial MS spectra library when the analytes at low concentration. To address this issue, 60 organic solvents introduced by ICH were studied using GC-MS and GC-FTIR. The standard mass spectra library, limit of detection (LOD) mass spectra library, standard vapor-phase infrared spectra library and limit of detection (LOD) vapor-phase infrared spectra library were obtained to establish a confirmation database for determining residual solvents in pharmaceuticals. The confirmation database can be used to identify the unknown residual solvents without using reference organic solvents.

4.2.1 Establishment of the confirmation database

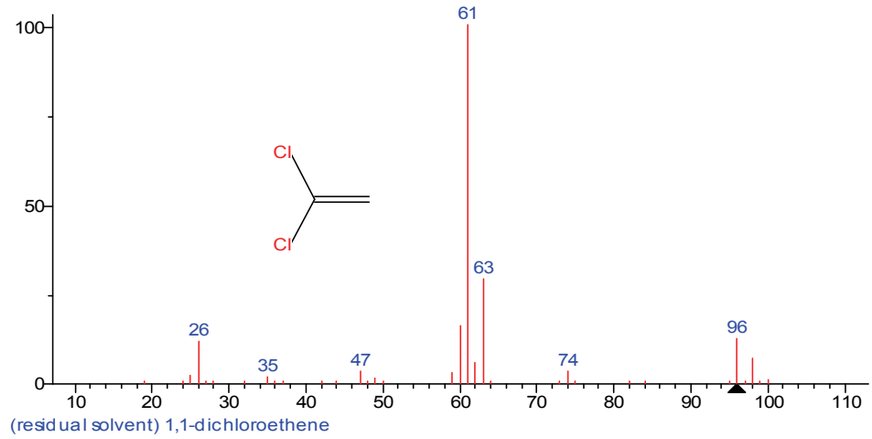
One microliter of each stock standard solution was injected into the GC-MS system and the mass spectra and the retention time of the organic solvents were recorded. The limit of detection was considered as the quantity of analyte that generated a response three times greater than the noise level at the retention time by diluting the stock standard solutions as required, and the mass spectra of organic solvents were recorded. The mass spectra library was established with Xcalibur software by exporting to the Library Brower a spectrum that had background subtracted and then attaching the chemical structure, compound name, molecular weight and molecular formula among other standard characteristics.

One microliter of each stock standard solution was injected into the GC-FTIR system and the vapor-phase infrared spectra and the retention time of organic solvents were recorded. The limit of detection was considered as the quantity of analyte that generated a response ten times greater than the noise lever at the retention time in the Gram-Schmidt chromatogram. This limit was achieved by diluting the stock standard solutions as required, and the vapor-phase infrared spectra of organic solvents were recorded. The vapor-phase infrared spectra

library was established with OPUS software by exporting to the library a spectrum that had background subtracted and attaching an information mask that included compound name, molecular weight, molecular formula, melting point, boiling point and other standard characteristics.

4.2.2 Mass spectra library and vapor-phase infrared spectra library can verify and complement each other

The advantages of mass spectra in compound identification include the ability to give the molecular weight of compound, the ability to distinguish homologues, and superior detection limits. The LODs of organic solvents are usually in the picogram range. The main limitations of mass spectra include the inability to give the intact information of compound and the inability to distinguish closely related isomers. The advantages of FTIR spectra in compound identification are that it can give information about the intact molecule, and similar structures such as isomers can be distinguished. The main limitation of infrared is lower sensitivity. Obviously, the combination application of mass spectra and FTIR spectra is a very powerful coupling because of the complementary nature of the data acquired. If mass spectra and infrared spectra give the same result, then the result can be considered accurate with greater confidence.



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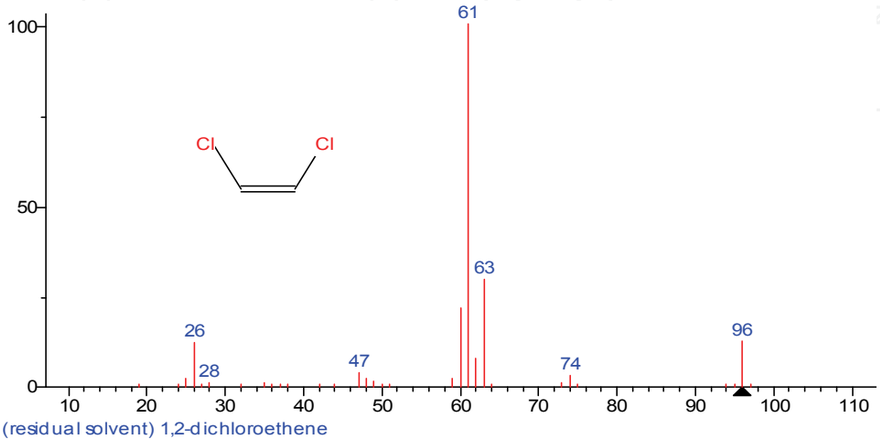

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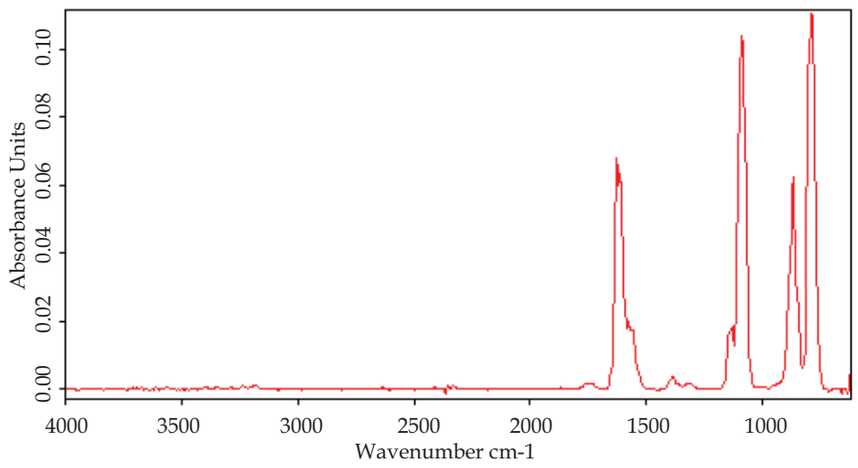

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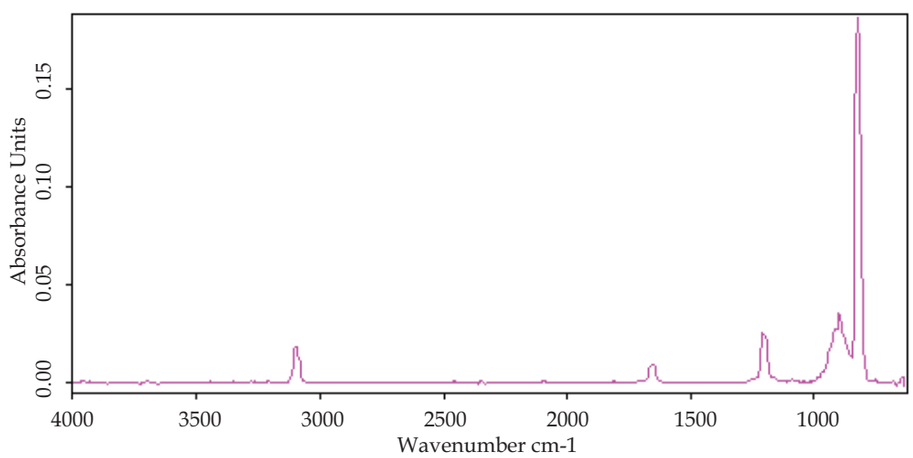


(b2)

Fig. 2. (a) Mass spectra of (1)1,1-Dichloroethene and (2)1,2-Dichloroethene. (b) Vapor-phase infrared spectra of (1)1,1-Dichloroethene and (2)1,2-Dichloroethene

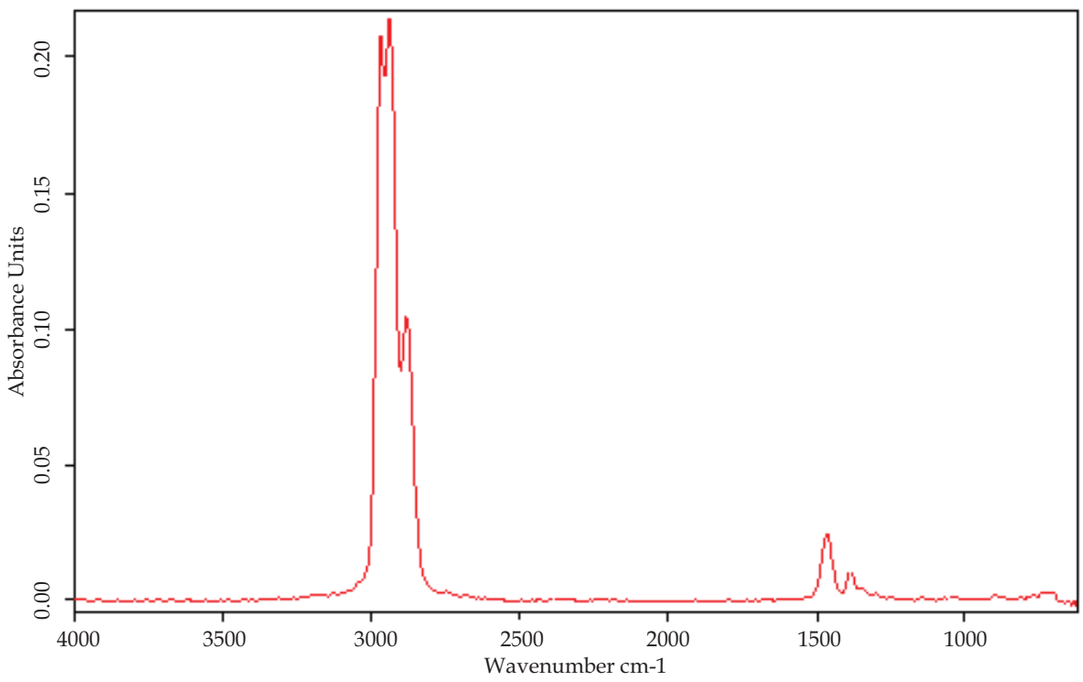
Of the 60 organic solvents were determined, 1,1-Dichloroethene and 1,2-Dichloroethene were isomers. They had very similar mass spectra (Fig. 2.a), and they were difficult to distinguish in the mass spectra library search. But their vapor-phase infrared spectra showed a significant difference (Fig. 2.b).

Isomers that had very similar mass spectra were suited for determination by a vapor-phase infrared spectra library; the normal alkanes(homologs) which had simple vapor-phase infrared spectra (Fig. 3.a) were suited for determination by mass spectra library (Fig. 3.b).

4.2.3 Applications of the confirmation database

4.2.3.1 Confirmation for the residual solvents that were preliminarily identified in pharmaceuticals

Amoxicillin sodium and clavulanate potassium (5:1), an antibacterial medicine registered by a foreign company, was analyzed by the screening database. According to the screening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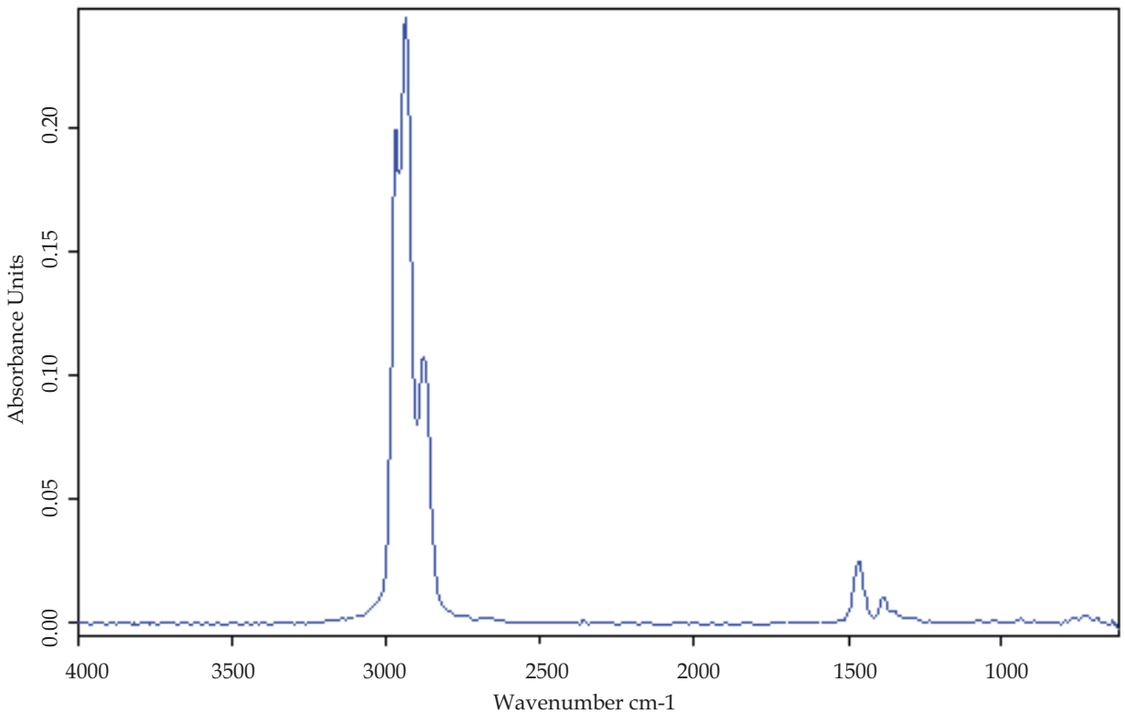
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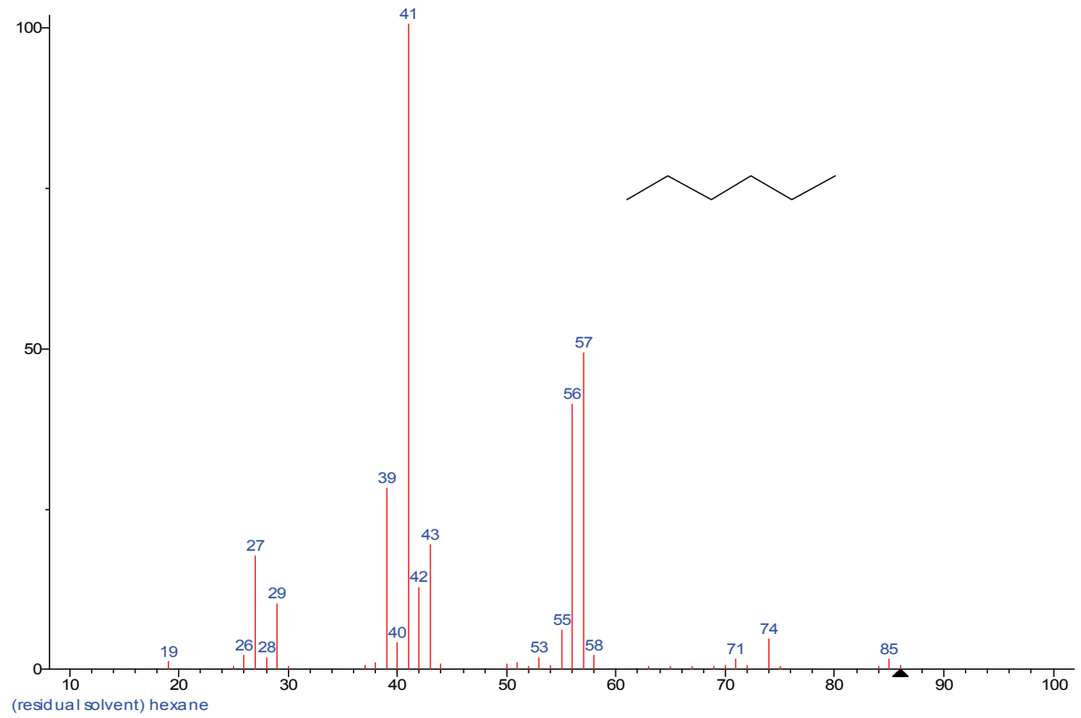

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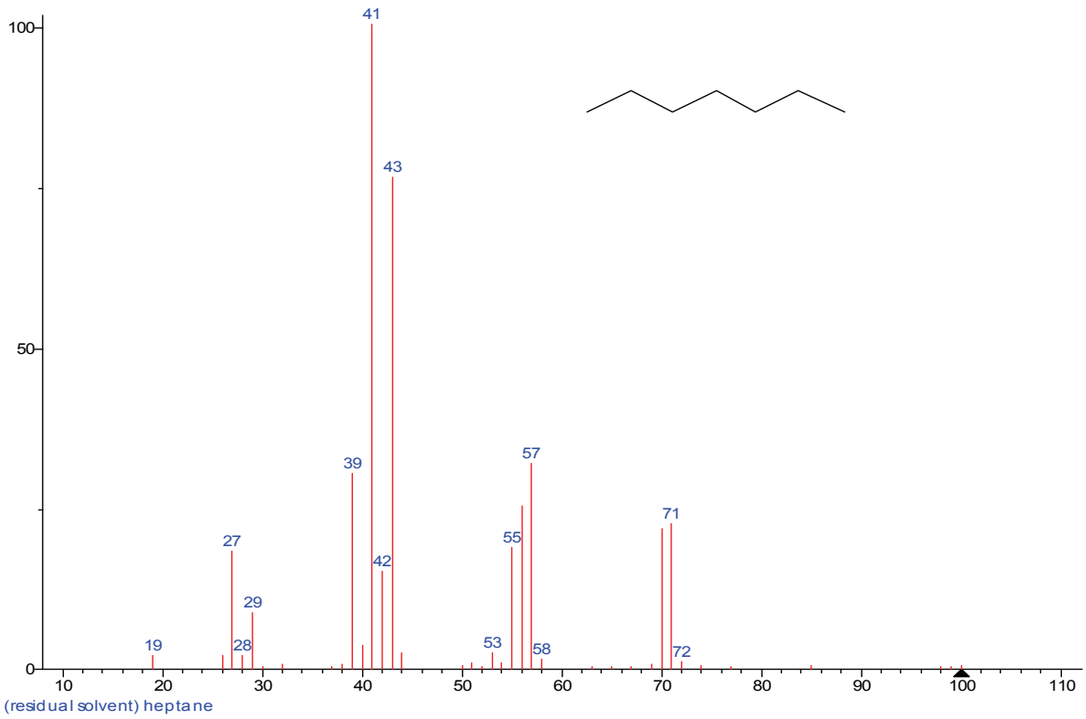


(b2)

Fig. 3. (a) Vapor-phase infrared spectra of (1) hexane and (2) heptane. (b) Mass spectra of (1) hexane and (2) heptane

results, acetone, isopropanol and methyl acetate were found in the product. Besides acetone and isopropanol were used in the synthesis, methyl acetate was not included. The confirmation database was used to confirm the screening results. According to the result from GC-MS, Ethyl acetate was the rank 1 compound according to the standard mass spectra library, and the similarity value was 913 (Fig. 4.a). The sample was analyzed by GC-FTIR using the standard vapor-phase infrared spectra library. Methyl acetate was also the rank 1 compound, and the similarity value was 983 (Fig. 4.b). The screening result was confirmed by the confirmation database, and methyl acetate was confirmed in the product.

4.3 Method optimization database

After the databases for screening and confirmation of residual solvents in pharmaceuticals were established, our next challenge is to focus on systematic method development and optimization, such as the fast selection of appropriate columns and optimization of chromatographic conditions. The solvation parameter model was applied in the development of a method for the analysis of residual solvents in pharmaceuticals. The interactions between organic solvents and six different stationary phases were studied using gas chromatography. The retention times of the organic solvents on these columns could be predicted under isothermal or temperature-programmed conditions using the established solvation parameter models. The predicted retention times helped in column selection and in optimizing chromatographic conditions during method development, and will form the basis for the development of a computer-aided method.

The solvation parameter model, first introduced by Abraham (Abraham, 1994a, 1994b, 1997), is a useful tool for delineating the contribution of defined intermolecular interactions to the retention of neutral molecules in separation systems based on a solute equilibrium between a gas mobile phase and a liquid stationary phase. The solvation parameter model in a form suitable for characterizing the retention properties of stationary phases in gas-liquid chromatography is shown below (Abraham, 2004):

$$SP = c + eE + sS + aA + bB + lL \quad (2)$$

Where SP, is the gas chromatography retention data for a series of solutes. c is the model intercept, the lower case letters (e, s, a, b, l) are the system constants representing the stationary phase contribution to intermolecular interactions. *l, for the* contribution from cavity formation and solute-stationary phase dispersion interactions; *e, for the capacity of the phase to interact with n-* and π-electrons present in the solute; *s, for the ability to interact with dipoles of the solute*; *a* and b for the facility to interact with basic or acid solutes through hydrogen-bond forces, respectively.

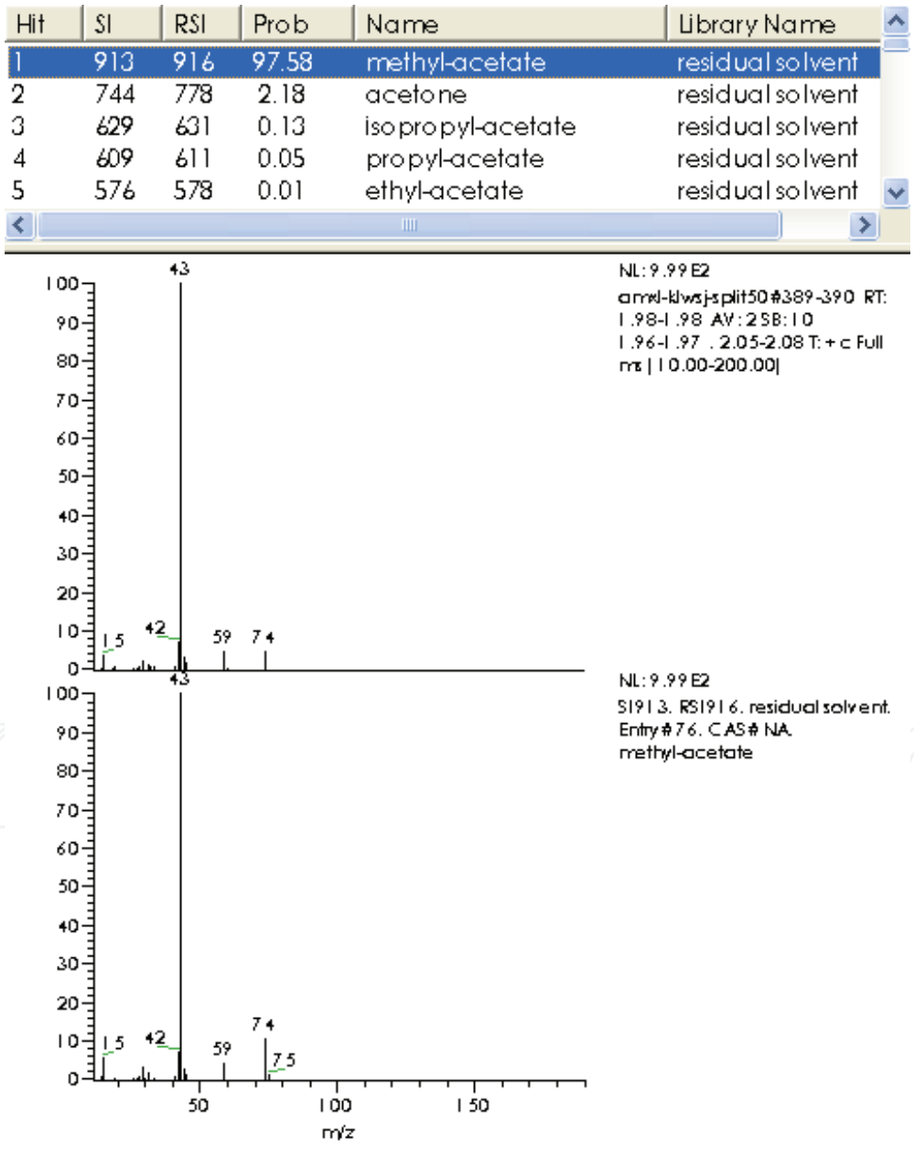
The capital letters (E, S, A, B, L) are the solute descriptors for the complementary interactions with the system constants of the stationary phase. L being the gas-hexadecane partition coefficient; E, the molar refraction excess; S, the effective dipolarity/polarizability of the solute; A, the hydrogen-bond effective acidity of the solute; B, the hydrogen-bond effective basicity of the solute.

4.3.1 Prediction of retention time under isothermal conditions

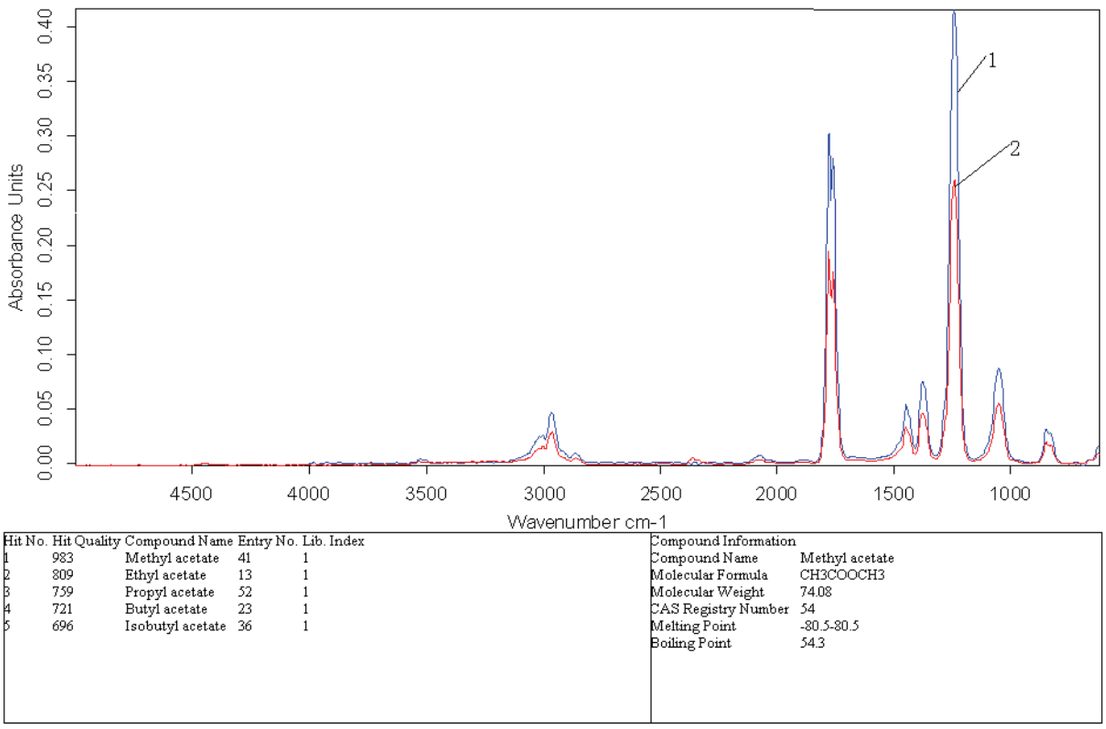
The chromatographic columns used in this work were: SPB-1 (100% dimethyl siloxane, 30.0 m×0.32 mm×1 µm); HP-5 (5% diphenyl, 95% dimethyl siloxane, 30.0 m×0.53 mm×1.5 µm, used in Table 2); HP-5 (5% diphenyl, 95% dimethyl siloxane, 30.0 m×0.32 mm×0.25 µm);

HP-35 (35% diphenyl, 65% dimethyl siloxane, 30.0 m×0.53 mm×1 μm); DB-624 (6% cyanopropylphenyl, 94% dimethyl siloxane, 30.0 m×0.53 mm×3 μm); AT-225 (50% cyanopropylphenyl, 50% dimethyl siloxane, 30.0 m×0.32 mm×0.25 μm); ZB-WAX (100% polyethylene glycol, 30.0 m×0.32 mm×1 μm). The retention times of 39 organic solvents were determined on six columns at 40°C, 60°C, 80°C and 100°C. The dead time was determined using methane, and the RRTs of each organic solvent on each column were calculated using Eq. (1).

The system constants of these columns were obtained using Eq.(2) by multiple linear regression analysis. *SP* in this case was RART. The solute descriptors were taken from the literature (Kiridena, 2001; Abraham, 1993; Poole, 2002)], and are listed in Table 6. Multiple linear regression and statistical calculations were performed using SPSS software.



(a)



Hit No.	Hit Quality	Compound Name	Entry No.	Lib. Index
1	983	Methyl acetate	41	1
2	809	Ethyl acetate	13	1
3	759	Propyl acetate	52	1
4	721	Butyl acetate	23	1
5	696	Isobutyl acetate	36	1

Compound Information	
Compound Name	Methyl acetate
Molecular Formula	CH3COOCH3
Molecular Weight	74.08
CAS Registry Number	54
Melting Point	-80.5-80.5
Boiling Point	54.3

(b)

Fig. 4. Search result from (a) the standard mass spectra library and (b) the standard vapor-phase infrared spectra library (1) Spectrum of methyl acetate in the standard vapor-phase infrared spectra library (2) Spectrum of the residual solvent to be determined

The procedure for predicting retention time under isothermal conditions included the following steps:

i. The column t_0 is determined using methane, and t_R is measured for the standard (MEK).
ii. The value of *LogRRT* is calculated using the solvation parameter model and the known system constants and solute descriptors (Abraham, 1999).
iii. The retention time of the residual solvent is calculated from Eq. (1).

4.3.2 Prediction of retention time under temperature-programmed conditions

According to Cavalli's theory (Cavalli & Guinchard, 1995, 1996), retention time under temperature-programmed conditions can be calculated using only a few sets of isothermal experiments. The hypothesis is that, in temperature-programmed gas chromatography, the column acts as a series of short elements undergoing a succession of isothermal stages. The retention factor of the solute (k) decreases with increased column temperature and the logarithm of retention factor ($ln\ k$) has a linear correlation with the reciprocal of column temperature *(T)*. A and B can easily be determined experimentally from the linear regression using the following formula:

$$\ln k = \ln\left(\frac{t_R}{t_0} - 1\right) = \frac{A}{T} + B \tag{3}$$

where T is the oven temperature, A and B are fitting coefficients.

	Organic solvents	Solute descriptors				
		E	*S*	*A*	*L*	*B*
1	1,1,1-Trichloroethane	0.369	0.41	0	2.733	0.09
2	1,1,2-Trichloroethene	0.524	0.4	0.08	2.997	0.03
3	1,1-Dichloroethene	0.362	0.34	0	2.11	0.05
4	1,1-Dimethoxymethane	0.099	0.46	0	1.894	0.52
5	1,2-Dichloroethene	0.425	0.41	0.09	2.278	0.05
6	1,2-Dimethoxyethane	0.116	0.67	0	2.654	0.68
7	1-Butanol	0.224	0.42	0.37	2.601	0.48
8	1-Propanol	0.236	0.42	0.37	2.031	0.48
9	2-Butanol	0.217	0.36	0.33	2.338	0.56
10	2-Methyl-1-propanol	0.217	0.39	0.37	2.413	0.48
11	2-Propanol	0.212	0.36	0.33	1.764	0.56
12	Acetone	0.179	0.7	0.04	1.696	0.49
13	Acetonitrile	0.237	0.9	0.07	1.739	0.32
14	Benzene	0.61	0.52	0	2.786	0.14
15	Carbon tetrachloride	0.458	0.38	0	2.823	0
16	Chloroform	0.425	0.49	0.15	2.48	0.02
17	Cyclohexane	0.305	0.1	0	2.964	0
18	Dichloromethane	0.387	0.57	0.1	2.019	0.05
19	Ethanol	0.246	0.42	0.37	1.485	0.48
20	Ethyl acetate	0.106	0.62	0	2.314	0.45
21	Ethyl ether	0.041	0.25	0	2.015	0.45
22	Ethyl formate	0.146	0.66	0	1.845	0.38
23	Heptane	0	0	0	3.173	0
24	Hexane	0	0	0	2.668	0
25	Isooctane	0	0	0	3.106	0
26	Isopropyl acetate	0.055	0.57	0	2.546	0.47
27	Isopropyl ether	0	0.19	0	2.482	0.45
28	Methanol	0.278	0.44	0.43	0.97	0.47
29	Methyl acetate	0.142	0.64	0	1.911	0.45
30	Methyl ethyl ketone	0.166	0.7	0	2.287	0.51
31	Methyl isobutyl ketone	0.111	0.65	0	3.089	0.51
32	Methyl isopropyl ketone	0.134	0.65	0	2.692	0.51
33	Methyl tetrahydrofuran	0.241	0.48	0	2.82	0.53
34	Methylcyclohexane	0.244	0.1	0	3.323	0
35	Nitromethane	0.313	0.95	0.06	1.892	0.31
36	Pentane	0	0	0	2.162	0
37	Propyl acetate	0.092	0.6	0	2.819	0.45
38	Tetrahydrofuran	0.289	0.52	0	2.636	0.48
39	Toluene	0.601	0.52	0	3.325	0.14

Table 6. Solute descriptors of organic solvents

The prediction of the retention times of residual solvents under temperature-programmed conditions involves three steps:

i. The retention times of four different temperatures within the range of the temperature-programmed conditions, such as 40°C, 60°C, 80°C and 100°C is predicted using the solvation parameter model.
ii. The values of A and B is calculated using Eq.(3) and the retention times obtained from step (i).
iii. The retention time of residual solvent under temperature-programmed conditions is calculated according to Cavelli's theory.

Column	T (°C)	System constant (b=0 in all cases)					Statistics		
		r	s	a	l	c	ρ	SE	F
SPB-1	40	-0.162	0.297	0.355	0.766	-1.916	0.992	0.050	511
	60	-0.108	0.254	0.270	0.692	-1.730	0.993	0.043	582
	80	-0.065	0.223	0.210	0.628	-1.570	0.994	0.036	685
	100	-0.024	0.190	0.162	0.569	-1.425	0.994	0.032	759
HP-5	40	-0.155	0.435	0.385	0.769	-2.021	0.993	0.045	602
	60	-0.094	0.373	0.301	0.696	-1.825	0.994	0.039	695
	80	-0.045	0.324	0.235	0.629	-1.649	0.995	0.033	785
	100	-0.009	0.276	0.185	0.572	-1.493	0.995	0.029	858
HP-35	40	-0.057	0.926	0.544	0.760	-2.359	0.993	0.045	600
	60	0.009	0.809	0.487	0.690	-2.134	0.994	0.038	678
	80	0.067	0.710	0.376	0.618	-1.912	0.995	0.032	810
	100	0.108	0.627	0.313	0.560	-1.713	0.995	0.029	849
DB-624	40	-0.245	0.689	0.815	0.765	-2.193	0.993	0.041	637
	60	-0.173	0.601	0.653	0.687	-1.967	0.994	0.035	710
	80	-0.114	0.529	0.531	0.621	-1.777	0.995	0.031	773
	100	-0.068	0.471	0.433	0.563	-1.611	0.994	0.029	758
AT-225	40	-0.178	1.680	1.878	0.707	-2.803	0.994	0.047	682
	60	-0.098	1.530	1.627	0.630	-2.533	0.994	0.044	657
	80	-0.040	1.397	1.415	0.564	-2.299	0.993	0.041	615
	100	0.009	1.293	1.254	0.512	-2.115	0.992	0.041	534
ZB-WAX	40	0.401	2.007	3.045	0.575	-2.712	0.991	0.080	448
	60	0.388	1.801	2.698	0.517	-2.448	0.992	0.068	504
	80	0.384	1.617	2.378	0.463	-2.205	0.992	0.058	542
	100	0.373	1.467	2.126	0.421	-2.011	0.992	0.052	558

ρ= Overall multiple linear regression correlation coefficient; SE= standard error in the estimate; F = Fischer statistic; n = 39 in all cases.

Table 7. System constants for six columns at different temperatures

4.3.3 Prediction of system constants at different temperatures

The system constants (Eq. (2)) were summarized in Table 7. The overall multiple linear regression coefficients (ρ) of the solvation parameter models were all above 0.990 which indicated that the solvation parameter models could predict the retention times of the organic solvents.

The relationship between system constant and temperature was also studied. The system constants were reversely correlated with temperatures as indicated in the following equation:

$$y = \frac{m}{T} + n \tag{4}$$

where y is a system constant, T is the column temperature, and m and n are coefficient obtained by linear regression (Table 8).

Column	System constant	m	n	r^2
SPB-1	r	-267.12	0.6928	0.9996
	s	205.75	-0.3614	0.9985
	a	374.78	-0.8481	0.9938
	l	382.6	-0.4565	1.0000
	c	-954.11	1.1333	1.0000
HP-5	r	-323.08	0.852	0.9981
	s	320.86	-0.5702	0.9995
	a	455.2	-1.0223	0.9935
	l	389.59	-0.4709	0.9999
	c	-1044.4	1.2913	0.9998
HP-35	r	-323.84	0.9799	0.9973
	s	582.54	-0.9376	0.9994
	a	452.13	-0.9015	0.9994
	l	392.27	-0.4915	0.9992
	c	-1260.1	1.6599	0.9992
DB-624	r	-345.47	0.8615	0.9979
	s	424.98	-0.6718	0.9984
	a	743.05	-1.5676	0.9963
	l	392.84	-0.4912	0.9998
	c	-1131.9	1.4272	0.9997
AT-225	r	-362.72	0.9853	0.9961
	s	756.94	-0.7413	0.9991
	a	1220.1	-2.029	0.9980
	l	380.94	-0.5121	0.9988
	c	-1344.5	1.4992	0.9990
ZB-WAX	r	53.664	0.2285	0.9892
	s	1054.7	-1.3651	0.9996
	a	1798.9	-2.7054	0.9995
	l	301.68	-0.3893	0.9994
	c	-1371.4	1.6713	0.9996

Table 8. Fitted regression coefficients for Eq. (4)

These coefficients were used to further predict the retention at any temperature in the studied range.

For instance, the system constants of SPB-1 column were predicted at 50°C using Eq. (4) as follows: r = -0.134, s = 0.276, a = 0.312, l = 0.728, and c = -1.821. Meanwhile the system constants of this column were determined under 50°C and r = -0.145, s = 0.282, a = 0.326, l = 0.734, and c = -1.837. The results showed that the differences between predicted and experimental values were very small, and the system constants can be well predicted at any temperature within the ranges of 40°C to 100°C.

4.3.4 Application in the process of method development

The control of 8 residual solvents (methanol, ethanol, dichloromethane, chloroform, hexane, benzene, methyl isobutyl ketone and toluene) was evaluated in rabeprazole sodium formulations. Methyl ethyl ketone was used as internal standard (IS). The solvation parameter models were used to select columns under isothermal conditions and to optimize chromatographic conditions under temperature-programmed conditions in the analysis of residual solvents in rabeprazole sodium.

4.3.4.1 Column selection under isothermal conditions

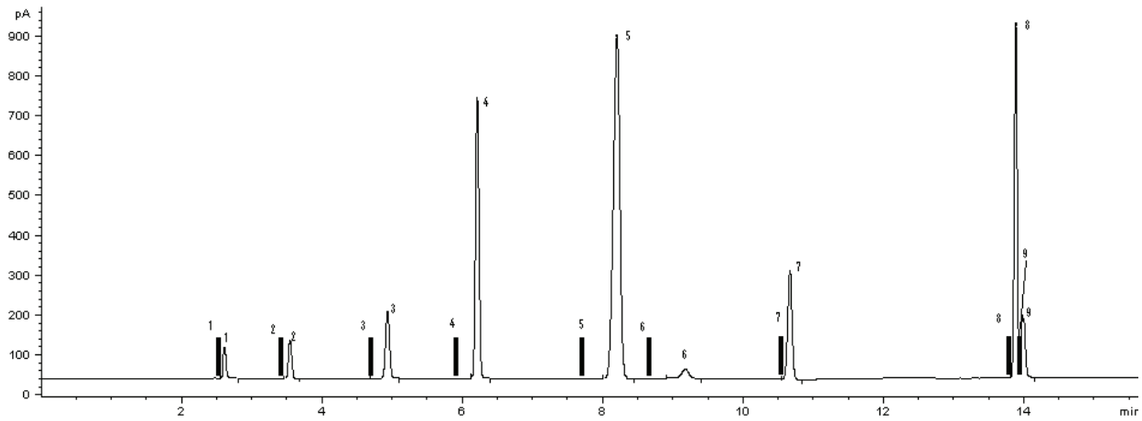
The retention times of these solvents were predicted on SPB-1 (non polar), ZB-WAX (polar) and DB-624 (moderately polar) columns at 40°C using the solvation parameter model. The optimum column was selected according to the results shown in Table 9. Hexane and chloroform could not be separated on the SPB-1 column. On the HP-INNOWAX column, the predicted retention time of methanol was close to that of methyl ethyl ketone, as were ethanol and benzene. On the DB-624 column, all the residual solvents could be separated according to the predicted retention times, therefore the DB-624 column was selected in this experiment. The residual solvents were determined on the DB-624 column, and the results were compared with the predicted results shown in Table 10. These findings indicated that the predicted results were consistent with the experimental results, and that the 8 residual solvents could be separated on this column.

Organic solvent	Predicted t_R (min)		
	SPB-1	ZB-WAX	DB-624
Methanol	1.838	5.098	2.551
Ethanol	2.157	5.320	3.606
Dichloromethane	2.800	4.398	5.179
Methyl ethyl ketone (IS)	3.704	5.142	8.172
Chloroform	4.228	6.832	9.167
Hexane	4.315	1.766	6.271
Benzene	5.398	5.336	10.836
Methyl isobutyl ketone	10.130	8.016	25.493
Toluene	11.457	9.161	27.114

Table 9. Predicted retention times of residual solvents in rabeprazole sodium on 3 different columns at 40°C using Eqs. (1) and (2)

Organic solvent	t_R (min)		
	Predicted	Experimental	Δt_R
Methanol	2.551	2.606	0.055
Ethanol	3.606	3.539	-0.067
Dichloromethane	5.179	4.928	-0.251
Hexane	6.271	6.296	0.025
Methyl ethyl ketone (IS)	8.172	8.199	0.027
Chloroform	9.167	9.190	0.023
Benzene	10.836	10.833	-0.003
Methyl isobutyl ketone	25.493	25.016	-0.477
Toluene	27.114	27.409	0.295

Table 10. Comparison between the predicted and experimental retention time of residual solvents in rabeprazole sodium on DB-624 column at 40°C using Eqs. (1) and (2)



1-Methanol; 2-Ethanol; 3-Dichloromethane; 4-Hexane; 5-Methyl ethyl ketone (IS); 6-Chloroform; 7-Benzene; 8-Methyl isobutyl ketone; 9-Toluene;
Note: Predicted retention times of each organic compound were indicated by the vertical bars inserted in the chromatogram

Fig. 5. Chromatogram of 8 organic solvents under temperature-programmed conditions on DB-624 column

4.3.4.2 Optimization of chromatographic conditions under temperature-programmed conditions

From Table 10, it can be seen that the separation of these 8 residual solvents on the DB-624 column at 40°C took approximately 30 min, and no peak was eluted between 10 and 25 min, therefore temperature-programmed conditions can be used to shorten the analysis time. The method for predicting retention time under temperature-programmed conditions can be used to optimize the chromatographic conditions. The retention times of the solvents under designated temperature-programmed conditions were first calculated, and according to the predicted retention times, separations among the solvents were evaluated. If some of the solvents could not be separated under that condition, the temperature program was revised and the retention times were recalculated. This process was repeated until optimal chromatographic conditions were found under which all the solvents could be separated. In this case, the temperature-programmed conditions were as follows: oven temperature was

maintained at 40°C for 10 min, and then raised to 120°C by a rate of 20°C/min for 2 min. These 8 residual solvents were determined under the optimized conditions, and the results were compared with the predicted results (Fig. 5). These findings indicated that the predicted results were consistent with the experimental results, and that the 8 residual solvents were separated within 15 min. The analysis time was decreased by 15 min compared to the analysis time under isothermal conditions. Therefore workload and time were dramatically decreased following the process of method optimization using the proposed approach.

5. Conclusion

Residual solvents from the processes in the manufacture of pharmaceuticals are a problem and must be removed. The ICH guideline is already accepted by different pharmacopeias. GC analysis is the ideal methodology for residual solvent analysis. Now the official method for sample preparation is still static headspace analysis, which gives a high level of automation from the instrumentation currently available and has a low impact on GC column life. Other methods such as SPME, MHS-SDME are useful alternative methods for residual solvents testing.

From the regulatory perspective, each pharmacopoeia focused on comprehensive analysis of residual solvents in pharmaceuticals. The official methods in USP and EP use two system and all the organic solvent reference standards to screening residual solvents. The established database for residual solvents analysis was adopted by ChP. Different from USP and EP, reference standards were not required for all organic solvents. Organic solvents having the same or similar retention times on one column usually have quite different retention times on the column with opposite polarity. The nature of the organic solvents can be identified using the two columns. The screening database was used to make a full-scale screening of the residual solvents in the pharmaceuticals. Only a few organic solvent reference standards were needed to confirm the screening result. If there are residual solvents that were not mentioned in the specification or production process, first class solvents or unknown solvents were found, that can be analyzed by GC-MS and GC-FTIR, using the confirmation database to make a confirmation. The dababase system can solve the difficult problem of unknown residual solvents determination, making it a powerful tool for determining residual solvents in pharmaceuticals.

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Wide Spectra of Quality Control

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Quality control is a standard which certainly has become a style of living. With the improvement of technology every day, we meet new and complicated devices and methods in different fields. Quality control explains the directed use of testing to measure the achievement of a specific standard. It is the process, procedures and authority used to accept or reject all components, drug product containers, closures, in-process materials, packaging material, labeling and drug products, and the authority to review production records to assure that no errors have occurred.The quality which is supposed to be achieved is not a concept which can be controlled by easy, numerical or other means, but it is the control over the intrinsic quality of a test facility and its studies. The aim of this book is to share useful and practical knowledge about quality control in several fields with the people who want to improve their knowledge.

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