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Review

Residual Solvent Testing: A Review of Gas-Chromatographic and Alternative Techniques

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The purpose of this brief review is to describe and discuss some of the current analytic procedures including gas-chromatographic and alternative techniques for residual solvent testing. Residual solvents, or organic volatile impurities, are a potential toxic risk for pharmaceutic products and have been a concern of manufacturers for many years. Residual solvents have had official limits in the United States as set in *USP XXV* and by the FDA in 1997 and have been monitored by most pharmaceutical manufacturers extensively for more than two decades in both bulk and finished products. The chief method of analysis for residual solvents is gas chromatography, which is generally considered the preferred methodology. Sample introduction techniques include both static and dynamic headspace analysis, solid-phase microextraction, and direct injection of solution containing bulk drug substance or drug product into the gas chromatograph. Also, some alternative methodologies for residual solvent testing are discussed in this review. In conclusion, gas chromatograph–based procedures will continue to dominate residual solvent testing because of its specificity for identification of the solvent, but the use of alternative sample introduction techniques into a gas chromatograph will continue to expand in the near future.

KEY WORDS: review; residual solvents; gas chromatography; headspace analysis; solid-phase microextraction.

INTRODUCTION

Residual solvents in pharmaceuticals are volatile organic chemicals that are used in and are produced during the synthesis of drug substances or can be in excipients used in the production of drug formulations. These residual volatiles are remains from processing agents. Many of these volatile organic chemicals generally can not be completely removed by standard manufacturing processes or techniques and are left behind, preferably at low levels. Residual solvent analysis of bulk drug substance and finished pharmaceutic products is necessary for a number of reasons. High levels of residual organic solvents represent a risk to human health because of their toxicity. Residual organic solvents also play a role in the physicochemical properties of the bulk drug substance. Crystallinity of the bulk drug substance can be affected. Differences in the crystal structure of the bulk drug may lead to changes in dissolution properties and problems with formulation of the finished product. Finally, residual organic solvents can create odor problems and color changes in the finished product and, thus, can lead to consumer complaints. Often, the main purpose for residual solvent testing is in its use as a monitoring check for further drying of bulk pharmaceuticals or as a final check of a finished product.

In the recent past, guidelines for organic residual solvents have generally been vague and not up to date. The USP set official limits in *USP XXV* (1), but it is far from complete considering the number of organic solvents actually used within pharmaceutic manufacturing. The USP lists benzene, chloroform, 1,4-dioxane, methylene chloride, and 1,1,1-trichloroethane and has stated limits ranging from 2 to 600 parts per million (ppm). Residual solvent testing beyond loss on drying (LOD) has been seriously pursued for nearly 20 years, and residual solvent test methods have been published before that time period (2,3). Internationally, there has been a demand for the establishment of standard guidelines. The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) (4) has made much progress in recent years with residual solvent guidelines and limits (5). Essentially, this body has consistently proposed that limits on organic solvents be set at levels that can be justified by existing safety and toxicity data. This body has also kept proposed limits within the level achievable by normal manufacturing processes and within current analytic capabilities.

Before 1997, the guidelines and regulatory authorities seemed to be generally behind the actual testing done within the pharmaceutical industry, but that situation was finally improved in the United States by the FDA. In 1997, the FDA issued their guidance "Q3C Impurities: Residual Solvents" (6,7). This document was designated as a "guidance" rather than a narrower "guideline," and it was based on the recommendations of the ICH (4). The acceptable amounts listed by

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the FDA guidance were derived only for patient safety considerations. Residual solvents were classified in three categories and are listed in Table I. Class 1 solvents are the most toxic, and those in class 2 are considered a lesser risk. Finally, class 3 solvents are the lowest risk category. The class 1 solvents are benzene, carbon tetrachloride, 1,2-dichloroethane, 1,1-dichloroethane and 1,1,1-trichloroethane. The concentration limits for the first four class 1 solvents listed are between 2 and 8 ppm, and the limit is 1500 ppm for trichloroethane, which is considered an environmentally hazardous chemical. Class 1 solvents should be avoided in the manufacturing of pharmaceuticals. Class 2 solvents should be limited and specifically tested for in products and have distinct toxicity or tetraogenicity. The class 3 solvents are considered to have low toxic potential and include such chemicals as acetic acid and ethyl acetate. Class 3 solvents require only nonspecific GMP-based testing and are limited to 5000 ppm or 0.5% (w/w).

THE TYPES OF RESIDUAL SOLVENT ANALYSIS

Residual solvent testing can be conducted by a number of analytic techniques. Gas chromatograph–based test procedures are the most popular and are chemically specific for residual solvents. Gas chromatographic procedures can be classified into a number of categories; the main three are direct injection, headspace analysis, and solid-phase microextraction (SPME). Numerous miscellaneous analytic techniques exist, including gravimetric analysis [i.e., loss on drying (LOD)] and some spectrometric and spectroscopic procedures. All of these residual solvent analysis techniques are covered in more detail in this review

GAS CHROMATOGRAPHY

The most popular, and the most appropriate, specific solvent analysis is testing by gas chromatography (GC). GC has the ability to separate component solvents, thus identifying them, and it is capable of low detection limits when the appropriate detector is used. A benchtop mass spectrometer (MS) can be used for a detector and adds an additional level of identification capability; this approach is often used in forensic applications of residual solvent testing in pharmaceuticals (8). Generally, for known solvent determinations, the flame ionization detector (FID) is more than adequate for validated specific residual solvent test methods. The FID was introduced by McWilliam and Dewar in 1958 (9), and it has become the most widely used detector for GC because of its low detection limits, wide linear dynamic range, and general reliability and utility, especially for trace organic compounds (10). In a review of residual solvent testing of pharmaceutical products, Witschi and Doelker (11) reported that more than 80% of the literature citations of gas chromatographic procedures used the FID. Common detectors used for gas chromatography and residual solvent testing are shown in Table II along with general performance characteristics. Capillary GC columns, which have high resolution and low detection limits, are used most often for trace organic volatile analysis (10).

Gas chromatographic testing can be categorized into

Table I. The Classes of Solvents in Pharmaceutic Products and Their Suggested Limits[a]

Class 1		Class 2		Class 3	
Solvent	Limit (ppm)	Solvent	Limit (ppm)	Solvent	Limit (%w/w)
Benzene	2	Acetonitrile	410	Acetic acid	0.5
Carbon tetrachloride	4	Chlorobenzene	360	Acetone	0.5
1,2-Dichloroethane	5	Chloroform	60	Anisole	0.5
1,1-Dichloroethene	8	Cyclohexane	3880	1-Butanol	0.5
1,1,1-Trichloroethane	1500	1,2-Dichloroethene	1870	2-Butanol	0.5
		Dichloromethane	600	Butyl acetate	0.5
		1,2-Dimethoxyethane	100	*t*-Butylmethyl ether	0.5
		N,N-Dimethylacetamide	1090	Cumene	0.5
		N,N-Dimethylformamide	880	Dimethylsulfoxide	0.5
		1,4-Dioxane	380	Ethyl acetate	0.5
		2-Ethoxyethanol	160	Ethyl ether	0.5
		Ethylene glycol	620	Ethyl formate	0.5
		Formamide	220	Formic acid	0.5
		Hexane	290	Heptane	0.5
		Methanol	3000	Isobutyl acetate	0.5
		2-Methoxyethanol	50	Isopropyl acetate	0.5
		Methylbutyl ketone	50	Methyl acetate	0.5
		Methylcyclohexane	1180	3-Methyl-1-butanol	0.5
		N-Methylpyrrolidone	4840	Methyl ethyl ketone	0.5
		Nitromethane	50	Methylisobutyl ketone	0.5
		Pyridine	200	2-Methyl-1-propanol	0.5
		Sulfolane	160	Pentane	0.5
		Tetralin	100	1-Pentanol	0.5
		Toluene	890	1-Propanol	0.5
		1,1,2-Trichloroethene	80	2-Propanol	0.5
		Xylene	2170	Propyl acetate	0.5
				Tetrahydrofuran	0.5

[a] The information in the table is from reference 6.

Table II. Summary of Common Gas Chromatographic Detectors and Their Characteristics[a]

Detector	Type	Approximate detection limit	Selectivity	Dynamic linear range
Flame ionization detector (FID)	Universal (organic/carbon compound)	2×10^{-12} g/s	None, universal	Greater than 10^7
^{63}Ni electron capture detector (ECD)	Selective (halogens and other electron-withdrawing groups)	Highly variable, as low as 5×10^{-15} g	None	10^4
Photoionization detector (PID)	Universal	2×10^{-13} g/s	Based on ionization energy	Greater than 10^7
Thermal conductivity detector (TCD)	Universal	4×10^{-10} g/ml	None	Greater than 10^5
Mass spectrometer (MS)	Universal or selective	Variable, as low as 25 fg	Variable, can be use for selective ions	10^5

[a] Information in the table is from reference 10.

three main procedures according to the means of introducing the sample into the instrument, and each is discussed in detail in the following sections of this review. A direct gas chromatographic procedure is one in which a portion of the actual drug substance or formulation is injected into a GC system. The drug substance is usually dissolved in an appropriate solvent and loaded into a syringe and injected. Headspace analysis, on the other hand, is an indirect testing procedure. The analysis is conducted when a volume of gas above the drug substance or formulation is collected and analyzed by a gas chromatograph. Finally, solid-phase microextraction (SPME) is making much progress in recent years for residual solvent testing. In SPME, a silica fiber coated with a sorbent is used to collect and concentrate the volatile solvents. The volatiles are then thermally desorbed in the inlet of the gas chromatograph and analyzed.

Direct Injection Gas Chromatography

Residual solvent analysis by direct injection into a gas chromatograph is often preferred because of its simplicity and reliability (11). A standard autosampler can be used, and no addition equipment or expense is necessary. Generally, a bulk drug substance or a finished product is either dissolved in or extracted with a solvent. Then, this solvent is injected into the gas chromatograph for analysis. Sample dissolution or extraction solvents have included water, dimethylformamide (DMF), dimethylsufoxide (DMSO), and benzyl alcohol. Water has the advantage of having no solvent peak when the flame ionization detector (FID) is used. DMF, DMSO, and benzyl alcohol generally have higher boiling points than those of the volatile analytes. This allows the elution of the solvent peak after the analyte residual solvent peaks.

A drug matrix effect has been claimed to be a possible problem with the direct injection technique. Kersten (12) evaluated the direct injection method using neutral, weakly acidic, and weakly basic drug substances; recovery of spiked common volatiles was not affected by any of the drug matrices studied. There is another major disadvantage with the direct injection technique for residual solvent analysis. The sample matrices may contain nonvolatile or corrosive substances, which could either remain on the head of the column or reduce its operational lifetime (11,13). Interactions inside the GC injection port between solvents and other components in the matrix could cause a number of problems. Solvent interaction could reduce the response for an analyte peak, or, conversely, the generation of any volatiles would give false responses for other volatiles (13). Benzene was reported to be the product of any interaction involving drug salts and benzyl alcohol as the dilution solvent inside a heated injection port (14). The GC injection port temperature must be high enough to ensure complete vaporization of the solvents but low enough to avoid problems of sample reactivity or decomposition, which may generate volatiles or peaks that could interfere with the true residual solvent analytes. Generally, injector temperatures of 200°C or lower have shown no interaction with components in the sample solution matrix (13).

Many general residual solvent procedures using direct-injection GC have been reported over the years in the literature and are very common. Li *et al.* (15) developed a method for the separation of methanol, methylene chloride, hexane, ethyl acetate, THF, iso-octane, 1,4-dioxane, toluene, and DMF using a cyanopropylphenyl/dimethyl polysiloxane capillary column. Detection limits varied between 3 and 30 ppm for the nine solvents studied intended for water-insoluble pharmaceuticals dissolved in DMSO. Smith and Waters (13) separated ten commonly used solvents using a capillary wide-bore column.

Headspace Analysis

The preferred methodology of residual solvent analysis used by me and others (8) is by headspace sampling. In many cases, pharmaceutic samples contain nonvolatile or degradable substances that can remain on a GC column and reduce its lifetime or, worse yet, create interfering peaks from volatiles during thermal degradation. In most cases, the samples require the separation of the volatile residual solvents before GC analysis. This can be performed by headspace analysis or

solid-phase microextraction, which is discussed in a subsequent section.

Two types of headspace-sampling techniques are available: dynamic headspace analysis (sometimes referred to trap-and-purge analysis) and static headspace analysis. These techniques have been described, compared, and reviewed extensively in the literature (16–21) and are briefly illustrated in Fig. 1. Hachenburg and Schmidt (16) wrote the definitive text on headspace analysis in 1977. Dynamic headspace analysis has the general advantage of low detection limits, whereas the static headspace analysis has the main advantages of ease of use and automation as a result of the commercial offering of systems from major manufacturers such as Tekmar-Dohrmann (Mason, Ohio) and Agilent Technologies (Palo Alto, California).

In dynamic headspace analysis, a continuous flow of gas is swept over the surface of a sample matrix. Volatiles from the sample matrix are conveyed into a trap where the volatile residual solvents are accumulated prior to analysis (see Fig. 1). The trap usually consists of a column containing a sorbent such as Tenex®, Chromosorb®, Porapak®, or Amberlite® XAD resins. Tenax is most used because of its thermal stability. A thermal desorption cycle of the trap is initiated, and a carrier gas takes the analytes into a gas chromatograph for the analysis. Cold trapping followed by thermal vaporization is another technique of dynamic headspace anaylsis.

Dynamic headspace analysis is particularly suited for the determination of volatile residual solvents at very low concentrations. Because the "total" amount of a volatile substance is extracted, trapped, and analyzed at one time, lower detection limits are obtained. Detection limits have been reported in picogram-per-milliliter levels for dynamic headspace vs. nanogram-per-milliliter levels for static headspace analysis (22). Dynamic headspace analysis also has the advantage of avoiding an equilibrium between the gas and sample matrix, as is required with static headspace and solid-phase microextraction techniques. One disadvantage of the dynamic approach is the problem of artifact volatiles collecting in the trap. This is common for the trap-and-purge technique and can be controlled by complete desorption of the trap. One advantage of dynamic headspace analysis is that a dissolution solvent peak can be avoided in the chromatogram (23). Applications of dynamic headspace testing for residual solvents in pharmaceuticals have included toluene and benzene (23).

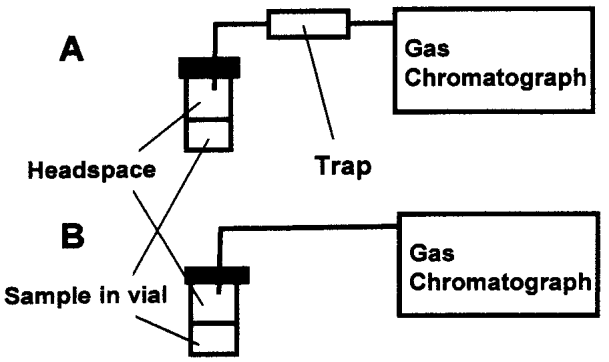

Fig. 1. Dynamic vs. static headspace sampling. (A) Dynamic headspace sampling uses a trap to concentrate volatile residual solvents before analysis by a gas chromatograph. (B) Static headspace sampling takes a volume of gas from the headspace above the heated sample vial directly to a gas chromatograph for analysis.

Static headspace analysis is probably the most widely used technique for residual solvent analysis in pharmaceuticals. In the static headspace procedure, a liquid or sometimes a solid sample is placed into a sealed vial. This vial is heated until a thermodynamic equilibrium between the sample and the gas phase is reached. A volume of the headspace gas is sampled and injected into the gas chromatograph for analysis. This method is preferred when the liquid or solid pharmaceutical samples are soluble (or extractable) in solvents such as water, benzyl alcohol, DMF, or DMSO (8,11).

In instances in which partition coefficients and the equilibrium time are not known for static headspace analysis, the repeated gas-extraction method proposed by McAuliffe (24) can be used. Kolb also used this technique but referred to it as multiple-headspace extraction and also used it on solid samples (25,26). This technique has generally fallen out of use. Sampling a heated headspace vial at various times to determine the equilibrium time is the simplest experiment. For the drug substance vigabatrin dissolved in water, an equilibrium time of 30 min was determined by B'Hymer (27). Figure 2 shows a chromatogram of a spiked vigabatrin sample obtained with static headspace sampling. Methanol, ethanol, acetone, isopropanol, methylene chloride, 1-propanol (internal standard), 1,2-dichoroethane (internal standard), *n*-butanol, and toluene were separated and quantified by this procedure.

The main disadvantage of static headspace analysis over dynamic headspace is in lower sensitivity. Sensitivity can be increased by salting-out, pH control, or increasing the equilibrium temperature during sample heating (16–20,28,29). Salting-out is simply adding an inorganic salt to a liquid sample matrix. The activity or partitioning of volatiles into the

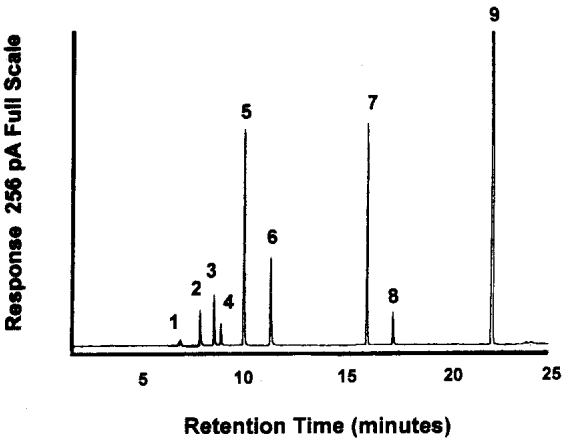

Fig. 2. Gas chromatogram of a vigabatrin drug substance sample spiked with possible residual solvents. Peaks: 1 = methanol; 2 = ethanol; 3 = acetone; 4 = isopropanol; 5 = methylene chloride; 6 = 1-propanol (internal standard); 7 = 1,2 dichloroethane (internal standard); 8 = butanol; 9 = toluene. Static headspace sampling was used with the following conditions: Hewlett-Packard/Dani Model 19395A with 1.0-ml sample loop with a bath temperature of 60°C and a valve temperature of 70°C. Equilibrium time was 30 min. The Hewlett-Packard Model 5880 gas chromatograph was equipped with a 60 m × 0.32 mm Supelco SPB-1 column with a 1.0-μm film. Initial column temperature was 35°C for 12 min, then increased at a rate of 10°C/min to a final temperature of 175°C. A flame ionization detector (FID) was used. (Reprinted from reference 27 with permission from Elsevier Science, copyright 1988.)

headspace is increased, thus increasing the method's sensitivity. When water is chosen as the dissolution medium and static headspace sampling is used, nonpolar analytes typically are enriched, while polar analytes typically are depleted. Dennis *et al.* (30) showed enrichment up to a factor of 50 for trace nonpolar solvents in water, while polar analyte concentrations in the headspace of polar compounds dropped by a factor of four. Multiple internal standards may be necessary to match trace solvents of similar polarity and partitioning in the headspace. Another possible problem with static headspace sampling is in the purity of the dissolution solvent. A small impurity in the dissolution solvent may give a large interference peak in the gas chromatogram of a test sample.

Automated static headspace systems have been offered by several major manufacturers for many years, including Tekmar-Dohrmann and Agilent Technologies. Static headspace analysis has been used and reported in the literature often. B'Hymer (27), as reported before, developed a residual solvent test method for vigabatrin bulk drug substance using static headspace sampling. Finished products have also been studied using static headspace analysis. Kumar and Egoville (31) developed a method for the determination of isopropanol and toluene extracted from a hormone dermal patch. Hong and Altorfer (32) reported an unusual methodology using small quantities of liquid solution in a headspace vial, described as "microsized." A volume of 100 μl of 1,3-dimethyl-2-imidazolidinone (DMI) containing only 5 to 30 mg of drug was found to shorten headspace equilibrium times from 45 to 60 min down to 5 to 10 min. Many other methods have been reported in the literature and have been reviewed extensively (11).

Solid-Phase Microextraction

Solid-phase microextraction (SPME), as does dynamic headspace analysis, has the advantage of concentrating the analytes, thus lowering detection limits for residual solvent analysis. In SPME, a small amount of extracting phase, a stationary phase (described as the solid 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. When the equilibrium time is reached, continued exposure of the SPME fiber for a longer time does not lead to accumulation of any additional analyte. The fiber is usually attached to a sampling device, which is essentially a syringe. The SPME fiber is attached to the plunger and is extended during sampling and withdrawn into the syringe before insertion into a GC. The fiber is extended into the inlet of a gas chromatograph, and the volatile analytes are thermally desorbed from the extracting phase of the fiber and swept onto the gas chromatographic column for analysis.

In general, two different types of SPME extractions can be performed. As shown in Fig. 3, "direct extraction" or "immersion" involves bringing the SPME fiber in contact with the sample matrix. The analytes are transported directly from the liquid sample matrix to the extracting phase. For pharmaceutic residual solvent analysis, the second type of SPME, the headspace mode, is usually used (see Fig. 3). In this mode, the volatile analytes need to be transported through the barrier of air above the sample before they can reach the SPME extracting phase. This mode serves to protect the fiber coating from damage by high-molecular-mass and other nonvolatile interferences present within the sample matrix (33). SPME has been demonstrated to extract a wide range of organic compounds from various matrices (34,35). Headspace SPME has been demonstrated to be more sensitive than immersion SPME for polar residual solvents (36). In recent years, headspace solid-phase microextraction has gained a sturdy reputation as a valid alternative to headspace GC because of the simplicity of execution of the procedure and the low cost of hardware (37).

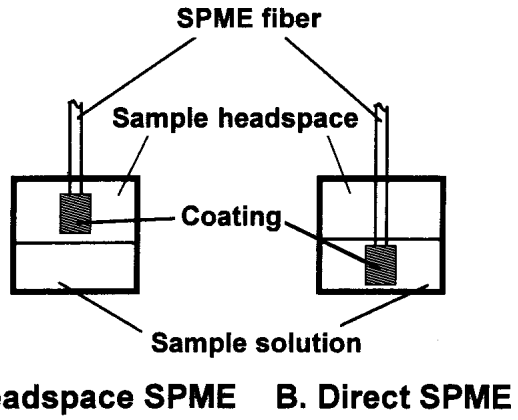

Fig. 3. Modes of solid-phase microextraction (SPME) operation. (A) Headspace SPME in which the fiber coating is exposed only to the headspace above the sample. (B) Direct or "immersion" SPME in which the coating is exposed to the sample solution.

Camarasu *et al.* (22) conducted an extensive comparison test of two SPME injection techniques and static headspace analysis. Gas-tight SPME, where only a small volume of headspace gas is removed from the sample matrix, and "headspace injection" SPME, where a larger volume of headspace gas is removed from sample matrix along with the SPME fiber (see Fig. 4), were both used in this study. Gas-tight SPME was found to be the most sensitive of the techniques in this study and was attributed to its inherent selectivity. Dichloromethane and acetonitrile were demonstrated to have detection limits more than half that of the headspace SPME technique. Volatile residual solvents were shown to have detection limits

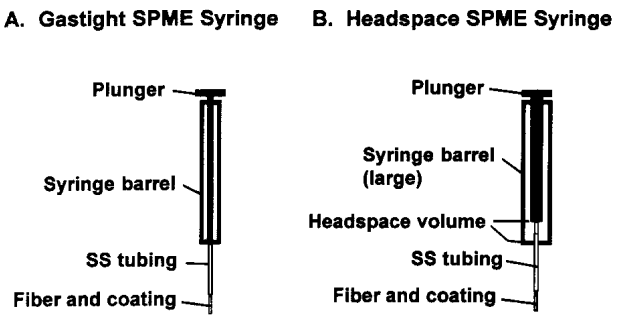

Fig. 4. Injection modes of solid-phase microextraction (SPME) using a manual syringe. (A) "Gas-tight" SPME samples a small volume of the sample headspace by using a small syringe. Most of the volatile sample is collected on the coated SPME fiber. (B) Headspace SPME syringe collects a larger volume of the sample's headspace along with the coated fiber.

nearly two orders of magnitude lower when gas-tight SPME was used than when the static headspace conditions were used as in this study. Results of this study are shown in Table III.

In a reported study by Coran *et al.* (37), residual cyclohexane and toluene levels in ketoprofen drug substance and capsules were determined by headspace SPME using a gas chromatograph and an mass spectrometric (MS) detector. Good procedural internal standards are necessary for quantitative results using SPME. Deuterated homologs of cyclohexane and toluene were used as internal standards in the Coran study (37) because of the similarity of affinity to the stationary phase of the SPME fiber.

Utilization of SPME is increasing with the availability of commercial devices. Supelco (Avondale, Pennsylvania) has offered a manual syringe since 1993. It has been reported that Varian (Palo Alto, California) has developed a SPME autosampler on their model 8000 GC autosampler in 1998 (22), and Varian has recently introduced SPME capability in their Combi PAL autosampling system (38). Any autosampler design would take advantage of the fact that SPME sampling is analogous to the operation of a common syringe. Also, SPME fibers can be cleaned easily and are ready for reuse after thermal desorption (22,39), making adaptation to automation simple. These improvements will make SPME more viable for routine residual solvent analysis of pharmaceutic products.

Method Validation Considerations

Validation of gas chromatographic methods can be complicated when nondirect sample solution injection procedures are used. General validation guidelines have been reviewed in literature (40) and are not covered in any more depth within this manuscript. Direct sample injection into a gas chromatograph usually offers the simplest case in method validation. Precision is based only on the injection technique, and linearity of response is generally understood. The linear response of the column and the detection system is either known or easily determined by experimentation. Static headspace often adds additional injection-to-injection variability, even after the optimal heating equilibrium time has been determined. Dynamic headspace analysis adds another level of complexity. Trap equilibrium time and sample capacity, as well as problems from artifact peaks from the trap, can make method development and validation more difficult. These aspects of headspace sampling have been cited in the literature (16) and should be considered in the development of such methods. Solid-phase microextraction fibers have their own equilibrium sampling time to determine as well as sample capacity and linearity factors to be determined and considered within the method validation process. These can be problems the analyst must deal with in method validation, but the increasing number of published residual solvent methods in the literature clearly demonstrate that nondirect solution injection GC methods can be properly developed and validated. Variations of the static-headspace procedure I have reported (27) were used to develop several validated residual solvent methods. Camarasu *et al.* (22) reported extensive validation data in a study of headspace and SPME procedures; this study is a useful reference for any analyst trying to validate either a headspace or SPME method.

Table III. Detection Limit Comparison of Methods Developed by Camarasu *et al.* (22) (ng ml^{-1})

Residual solvent	Headspace SPME (PDMS/DVB)	Gastight SPME (PDMS/DVB)	Static headspace
Acetonitrile	0.1	0.05	2
Dichloromethane	0.01	0.005	0.5
Chloroform	0.01	0.007	7
Trichloroethylene	0.01	0.01	7
1,2-Dichloroethane	0.01	0.02	7
Benzene	0.01	0.01	0.1
1,4-Dioxane	2	2	20
Pyridine	0.5	0.7	30

Note: PDMS/DVB is a polydimethylsilozane/divinylbenzene SPME fiber.

Miscellaneous Residual Solvent Methods

Many alternatives to gas chromatography have been used to determine the level of residual solvent in pharmaceutic products. Many of these procedures are either nonspecific—that is, the solvents are not identified—or they have high detection limits. The oldest and simplest method for determining the quantity of volatile residue is measuring the weight loss of a sample during heating. Loss on drying (LOD) suffers from the main disadvantage of being nonspecific. Two other disadvantages are that atmospheric humidity can cast doubt on the experimental results and that a large quantity of material must be used for the test. Usually, 1 g or more of material is used for a typical LOD test to achieve a detection limit of 0.1% (w/w) or less (41–44). More advanced instrumentation available from many manufacturers, including Perkin-Elmer, Mettler, and Dupont, can be used to perform thermogravimetric analysis (TGA). A detection limit of approximately 100 ppm can be obtained using only a few milligrams of sample (42). Benoit *et al.* (43) used TGA, differential thermal analysis (DTA), and differential scanning calorimetry (DSC) of progesterone-loaded poly(D,L-lactide) microsphere samples to determine the level of residual methylene chloride. DSC and TGA were used by C. Dubernet (44) for the determination of residual chloroform in ethyl cellulose raw material and microspheres. List and Laun (45) used thermogravimetric analysis to determine the level of residual isopropanol in Eudragit® L films. Thermogravimetric instruments are capable of observing the solvent entrapped within a drug substance, formulation, or film preparation.

Spectroscopic and spectrometric methods have generally lacked the low detection limits needed for toxic residual solvents, although the detection limits would be applicable for ICH class 2 and 3 solvents. In the case of infrared spectroscopy (IR), a detection limit above 100 ppm and lack of accuracy at low concentrations of residual solvent have been reported (46). Osawa and Aiba (47) used infrared spectroscopy to determine the levels of THF, dichlorobenzene, and methylene chloride in polymer samples by measuring the characteristic solvent bands in the spectra. Avdovich *et al.* (48) determined the levels of residual benzene, toluene, acetone, and ethyl ether in cocaine samples using Nuclear Magnetic Resonance (NMR) spectrometry. This NMR study also found methylene chloride and ethyl acetate in some samples of cocaine, two solvents previously not detected in cocaine samples. Unfortunately, the NMR has higher detection limits

than gas-chromatographic methods; the Avdovich study (48) reported quantification of benzene as low as 100 ppm. Again, this detection limit is not adequate for ICH class 1 and some class 2 solvents. Finally, in another study, Thomasin *et al.* (49) obtained a detection limit of 5000 ppm by IR and 100 ppm by proton NMR when analyzing residual silicone oil in poly(lactic acid) and poly(lactic acid–co-glycolic acid) microspheres.

In the case of chlorinated residual solvents, the solvent level can be estimated from the chlorine content in the sample. Mumper and Jay (50) found an excellent correlation between NMR spectrometric estimates of chloroform and the results of Schoniger flask combustion analysis for chlorine. Benoit *et al.* (43) used chlorine analysis to estimate the level of entrapped methylene chloride in progesterone-loaded poly(D,L-lactide) microspheres; their data matched the estimated level of residual solvent determined by thermal analysis. Numerous other miscellaneous methods have been reported and reviewed in the literature (11).

CONCLUSIONS AND FUTURE TRENDS

Residual solvents from the processes in the manufacture of pharmaceuticals are a problem and must be removed. Gravimetric analysis is simple but lacks specificity to identify the volatile analyte. Spectroscopic and spectrometric tests have generally lacked sensitivity. Gas-chromatographic analysis is the ideal methodology for residual solvent analysis. Although direct injection sampling for GC analysis offers the least expensive option in terms of equipment, problems arising from the direct injection of materials into the injection port and column head can makes this technique less useful in many cases. Static headspace analysis gives a high level of automation from the instrumentation currently available and has a low impact on GC column life.

Two new trends in gas chromatographic testing appear to be taking shape. Microsized headspace, as used by Hong and Altorfer (32), may become more widely used in the near future. They found that a small liquid sample size produced a linear and sensitive response using short headspace heating equilibrium times. Solid-phase microextraction (SPME) will certainly be used more now that more automated sampling systems are available from major instrument manufacturers. SPME offers a high sensitivity similar to that of dynamic headspace, without many of the problems or expense of a dynamic headspace sampling system.

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