ANALYSIS OF SOLVENT RESIDUES IN PHARMACEUTICAL BULK DRUGS BY WALL-COATED OPEN TUBULAR GAS CHROMATOGRAPHY

DAVID W. FOUST and MICHAEL S. BERGREN*

The Upjohn Company, Control Division, Kalamazoo, MI 49001 (U.S.A.)

(First received June 9th, 1988; revised manuscript received February 10th, 1989)

SUMMARY

A simple general method for the determination of solvent residues in drugs is described. The procedure is based on wide-bore wall coated open tubular (WCOT) gas chromatographic analysis of bulk drug solutions. The use of wide-bore WCOT columns with chemically crosslinked methyl silicone stationary phases offers improvements in specificity and sensitivity over earlier packed-column methods. The factors that influence method accuracy are discussed, including a consideration of instrumental and matrix contributions to the linearity and bias of the method. Some problems with interferences peculiar to benzyl alcohol are reported.

INTRODUCTION

The analysis of solvent residues is receiving greater emphasis in the evaluation of bulk pharmaceuticals. High-purity bulk drugs are produced by the pharmaceutical manufacturer using carefully tailored final process recrystallizations. As a result, solvents are a minor but ubiquitous component of these materials. The role of solvent residues in the toxicology, stability, and pharmaceutical properties of the finished dosage form is insignificant if the solvent content is controlled in the bulk drug, raw materials, packaging components and production systems. A general method applicable to all of the possible solvents and bulk drugs is attractive. The reliance on a single method would eliminate the confusion and inefficiencies that result from using a number of comparable, but instrumentally distinct, methods in routine application.

Several procedures based on packed-column separations have been reported[1-4]. Most of these employ porous polymer packings or packings based on graphitised carbon supports. The procedure of Haky and Stickney[3] is notable because of the simplicity of sample preparation and ease of adaptability to standard sampling equipment. The need for a general organic volatiles procedure in the U.S. Pharmacopeia has been noted[5], and recently, a procedure based on the Haky and Stickney method[3] has been proposed for adoption in that compendium[6].

The importance of evaluating solvent residues in research pharmaceuticals, as distinct from marketed pharmaceuticals, should not be underemphasized. Because of the high attrition rate for research compounds in the pharmaceutical industry, mar-

keted pharmaceuticals represent only a fraction of the compounds that require analytical evaluation. Large numbers of experimental drugs are continually being introduced. These drugs are the objects of laboratory study as well as clinical study. Modifications to the process chemistry may result in changes in the types or amounts of solvents retained in the bulk drug. The need exists for a quantitative solvent screen, which is capable of providing reliable information on the type and quantity of solvent residue present. In this application, the selectivity, peak capacity, and reproducibility of retention times have increased importance. The ability to interface the method to structurally informative detection schemes, such as mass spectrometry (MS) or infrared spectroscopy, is an important advantage.

Unfortunately, the variety of available solvents and bulk drug matrices is so diverse that a truly general method would probably be complex and expensive to implement on a routine basis. Headspace sampling, high-efficiency capillary gas chromatography (GC), and selective detection schemes are needed in the widest variety of potential applications. Our experience in pharmaceutical analysis, however, suggests that the complexity of the most general method is dictated by a small percentage of cases. The solvents in most of the current market or research pharmaceuticals are amenable to analysis on a much simpler and less expensive system. Our goal has been the development of a procedure suitable for the analysis of solvent residues in 80–90% of the available bulk drugs. Our approach reflects an attempt to provide optimum performance in terms of separation power, precision, dynamic range and simplicity for the largest number of compounds.

Recent advances in GC have provided the basis for improvements in the routine GC evaluation of solvent residues. In particular, the availability and ease of use of wide-bore (0.53 mm) fused-silica wall-coated open tubular (WCOT) columns with thick chemically bonded phases has provided a bridge between packed-column GC and high-resolution capillary methods. These columns yield improvements in separation efficiency by a factor of 3–10 over packed columns. They have a large sample capacity, which eliminates the need for split injection techniques required by narrower-bore capillary columns. The difficulty of coupling autosampler systems with capillary methods has been cited by other investigators[3]. These problems are not significant for wide-bore column systems if direct injection methods are employed on commercially avialable instruments.

EXPERIMENTAL

Equipment and materials

The method was developed on a Hewlett-Packard 5890 gas chromatograph equipped with a Hewlett-Packard 7673A robotic autosampler (Hewlett-Packard, Avondale, PA, U.S.A.). The Hewlett-Packard split/splitless injector port was used in splitless mode with the standard splitless insert. Samples were injected in the direct mode. A continuous inlet purge of 140 ml/min of carrier gas was maintained, except for a 30-s sampling time during the injection. A Hewlett-Packard flame ionization detector was used with a capillary jet and 30 ml/min of nitrogen make-up gas. Signals were digitised with a Hewlett-Packard 3392A integrator, and the digital data was processed on an in-house VAX computer based chromatography analysis system.

The columns were 30 m × 0.53 mm I.D. fused-silica columns with a 5-μm thick

chemically crosslinked methyl silicone stationary phase. RTx-1 halfmil columns (Restek, Port Matilda, PA, U.S.A.) or DB-1 Megabore columns (J&W Scientific, Rancho Cordova, CA, U.S.A.) were used interchangeably. The analytical columns were coupled to a 5 m × 0.53 mm I.D. phenyl methyl silicone deactivated retention gap (Restek Corp.) acting as a guard column. The columns were coupled with a butt connector with Vespel SP-211 ferrules (Supelco, Bellefonte, PA, U.S.A.). Carrier gas was purified with a heated scrubber (Supelco) to remove oxygen.

Benzyl alcohol was obtained from Aldrich (Milwaukee, WI, U.S.A.) as a 99% purity grade or as puriss grade from Fluka (Ronkonkoma, NY, U.S.A.). All other solvents were obtained from the Aldrich, Burdick & Jackson Labs. (Muskegon, MI, U.S.A.), Eastman Kodak (Rochester, NY, U.S.A.), and U.S. Industrial Chemicals (Houston, TX, U.S.A.) in high purity (98 + %) grades and used without further purification. Drug samples were obtained from in house sources at the Upjohn Co.

Sample preparation and analysis

Samples were prepared by dissolving about 10 mg of the drug, accurately weighed, per gram of benzyl alcohol and shaking to effect dissolution. Standards consisted of accurately prepared solutions of the appropriate solvents in benzyl alcohol. Where necessary, dilutions of concentrated standard solutions were calculated by weight. Typical concentrations for standard solutions were 0.02–0.05 mg solvent per gram of benzyl alcohol. These values correspond to solvent levels of 0.2–0.5% by weight in bulk drug for bulk drug samples of nominal 10 mg/g concentration. To avoid the loss of volatile components, headspace exchanges were minimized during the preparation of samples and standards.

Volumes of 0.5 μl of sample and standard preparations were alternately injected onto the GC system. Helium was used as the carrier gas, back-pressure regulated at 3 p.s.i. and with a linear velocity of *ca.* 35 cm/s. The injector and detector temperature were 180 and 260°C, respectively. The oven program was: 35°C (5 min hold); 8°C/min ramp to 175°C (0 min hold); ballistic ramp to 260°C (16 min hold). Quantitative determinations were accomplished by the external standard method.

RESULTS

Specificity

The chromatographic specificity is illustrated by the separation of 27 different process solvents shown in Fig. 1. With the exception of a few co-eluting solvents, the solvents of interest are distributed uniformly throughout the chromatographic profile. The time available for analysis, prior to the elution of benzaldehyde, is about 20 min. The peaks are symmetric with uniform widths of about 0.1 min throughout the chromatogram under the conditions employed. If Gaussian peaks are assumed, and a separation of 4σ is used as a criterion for resolution, a rough estimate of the peak capacity of the system is 110–120.

The reproducibility of retention times is illustrated in Table I, where representative results were taken from the ten injections of a fourteen-component standard. These injections were interspersed with drug samples in a sequence of chromatographic runs that spanned 55 h. The standard deviations (S.D.) are limited by the two significant digits in retention times for the data reported in the table. The repro-
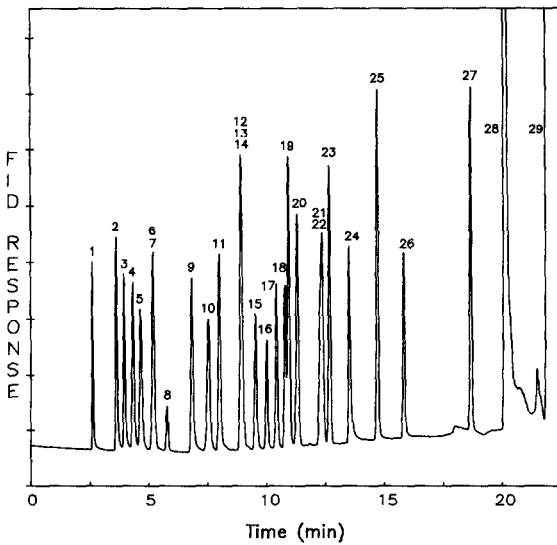
Fig. 1. Separation of a mixture of 27 different common process solvents. FID = Flame ionization detection. Peaks: 1 = methanol; 2 = ethanol; 3 = acetonitrile; 4 = acetone; 5 = isopropanol; 6 = diethyl ether; 7 = pentane; 8 = dichloromethane; 9 = n-propanol; 10 = methyl tert.-butyl ether; 11 = methyl ethyl ketone; 12 = ethyl acetate; 13 = hexane; 14 = chloroform; 15 = tetrahydrofuran; 16 = ethylene dichloride; 17 = n-butyl chloride; 18 = n-butanol; 19 = benzene; 20 = cyclohexane; 21 = isooctane; 22 = dioxane; 23 = heptane; 24 = pyridine; 25 = toluene; 26 = n-butyl acetate; 27 = o-xylene; 28 = benzaldehyde; 29 = benzyl alcohol.

ducibility of retention times between injections permits reliable identification of most components.

The slight variations in retention times from column to column and run to run are due to small differences in carrier flow and phase ratio. These variations can be

TABLE I

REPRODUCIBILITY OF RETENTION TIMES FOR SELECTED SOLVENTS

Results represent the average of ten determinations.

Solvent	Retention time (min)	S.D. (min)
Methanol	2.29	0.005
Ethanol	3.15	0.005
Acetone	3.75	0.005
Dichloromethane	5.02	0.005
Methyl tert.-butyl ether	6.71	0.005
Ethyl acetate	8.08	0.005
Tetrahydrofuran	8.69	0.005
n-Butyl chloride	9.58	0.004
Benzene	10.08	0.004
Dioxane	11.40	0.003
Pyridine	12.63	0.008
Toluene	13.82	0.000
n-Butyl acetate	14.96	0.000
o-Xylene	17.73	0.003

reduced by calculating the capacity factor of the solvent relative to the capacity factor of an arbitrarily chosen standard. The resulting relative capacity factors are reported in Table II for a number of solvents with toluene as a retention standard. Toluene is a convenient choice, because it is a common minor constituent of benzyl alcohol. Within our limited experience, the numbers in Table II usually agree with the measured values in a specific experimental configuration within ± 0.04.

Accuracy

The accuracy of the method cannot be assessed for general combinations of drugs and solvents. In any given case, the chromatographic system and the specific analytical matrix influence the signal for a specific solvent. In evaluating the limitations on experimental accuracy however, a number of practical points can be considered independently; the linearity and the bias of the method can be assessed at various levels of generality. In particular, the instrumental contributions to non-linearity and bias are important determinants of method performance.

A method that is linear over several decades of dynamic range is useful for quantitative solvent screening, because a complete standard curve is not essential for reasonably accurate assessment of solvent content at low (0.001–0.05%) as well as high (0.05–5.0%) levels. In practice, the most accurate determinations are necessary at levels where general quantitative limits on solvents are set. The typical levels of interest for most of the less toxic solvents are in the 0.05–1.0% range. Linearity has been examined for each of the 27 solvents shown in Fig. 1 over the range of 0.01–5.0%. Solutions were prepared for several nominal percentages of solvent in bulk drug: 0.01, 0.02, 0.05, 0.1, 0.2, 0.4, 0.6, 0.8, 1.0, 2.0 and 5.0%. These standards were prepared by dilution of the most concentrated sample containing the equivalent of 5% solvent in bulk drug. Dilutions were calculated by weight, and care was taken to

TABLE II

RETENTION OF SEVERAL SOLVENTS EXPRESSED AS THE CAPACITY FACTOR RELATIVE TO TOLUENE

Results represent an average over two separate determinations on different columns.

Solvent	Capacity factor (relative to toluene)	Solvent	Capacity factor (relative to toluene)
Methanol	0.062	Tetrahydrofuran	0.588
Ethanol	0.134	Dichloroethane	0.626
Acetonitrile	0.158	Butyl chloride	0.659
Acetone	0.185	n-Butanol	0.688
2-Propanol	0.208	Benzene	0.700
Diethyl ether	0.248	Cyclohexane	0.730
Pentane	0.248	Dioxane	0.806
Dichloromethane	0.294	Isooctane	0.813
n-Propanol	0.374	Heptane	0.839
Methyl *tert.*-butyl ether	0.429	Pyridine	0.904
Methyl ethyl ketone	0.464	Toluene	1.000
Ethyl acetate	0.539	n-Butyl acetate	1.091
Hexane	0.540	Dimethylsulfoxide	1.288
Chloroform	0.548	o-Xylene	1.317

avoid headspace losses. (In our first attempts, failure to minimize headspace exchanges during preparation resulted in significant curvature in the response plots. The problem was most pronounced for the volatile non-polar solvents like pentane and hexane.) Solvents were divided into three groups to avoid mutual interferences to peak integration within groups. Samples were injected in duplicate.

Linear regression was used to evaluate linearity throughout the 0.2–1.0% range, a range of concentrations used routinely for external standards. Five points between 0.2 and 1.0% inclusive were included. For each solvent, the linear fit to the data has a correlation coefficient of 0.999 of greater, and the absolute value of the intercept corresponds to the signal produced by 0.01% of the solvent or less.

Response linearity over the full range of concentrations from 0.01 to 5.0% cannot be evaluated adequately by simple linear regression. A plot of the specific response (area response per unit weight) as a function of concentration is given in Fig. 2. The response for each solvent is scaled relative to the value at the 5% level. The specific response at the 5.0% concentration has been set to 1.00 for each solvent to present the data on a single plot. The contribution of limited experimental precision to the spread of data points in Fig. 2 has not been determined. Pyridine has a concentration dependent peakshape, which is not typical of the other solvents investigated. Peaks for pyridine at concentrations below 0.05% were difficult to integrate, and the corresponding data are not included in the plot. For the remainder of the solvents, if standards at the high end of the response range are employed, the instrumental contribution to the inaccuracy of estimates at the low end is not worse than about 25% of the actual value. At the 0.1% level, the deviations are less than 10% of the actual
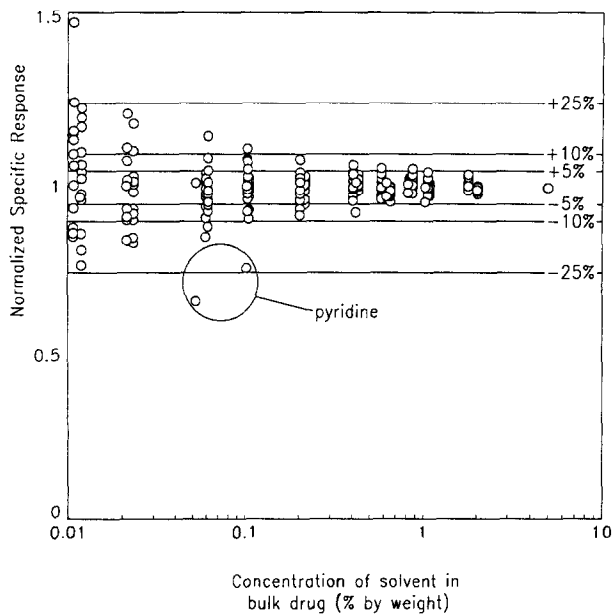

Fig. 2. Specific response for the 27 solvents of Fig. 1 as a function of solution concentration. Responses for each solvent are normalized to the response observed for that solvent at the 5% concentration. Data for pyridine are not included below 0.05%.

value. This performance is satisfactory for most applications. Instrumental contributions to inaccuracy can be reduced at low levels by preparation of standards appropriate to the concentration range.

In addition to instrumental non-linearities, sample dependent bias can also contribute to the loss of accuracy. Two major sources of bias can be identified. The first of these is bias from matrix contributions to the solvent profile. The matrix contributions include non-solvent organic volatiles, volatile thermal decomposition products, and volatile products arising from the interaction between components of the bulk drug and the benzyl alcohol in the injection port. Peaks that originate from these matrix components make a positive contribution to the solvent profile. The bias from these peaks can be particularly important if they are interpreted as true solvent peaks in a general solvent screen.

The absence of this positive matrix bias can be demonstrated for a given compound by verifying the absence of solvent peaks in the presence of the remaining matrix components. In many cases a simple sequence of experiments will suffice to establish the absence of this type of bias. First the residual solvent profile of the bulk drug is determined. A number of solvent responses may be observed. A sample of the drug is dissolved in a solvent that was not observed in the initial screen. The sample is dried under a stream of nitrogen or under vacuum, and the solvent profile of the sample is redetermined. If the solvents observed in the original determination are not present, or if the levels of these solvents are insignificant, they are probably not derived from matrix interferences.

This approach may not be effective if there are significant changes in the matrix composition during the dissolution and drying steps. Nevertheless, it is a simple scheme for establishing an additional measure of confidence in the ability to screen a given compound for a wide variety of solvents. An example of the chromatography from a typical initial screen is shown in Fig. 3a, where acetone is observed at 1.2% in an antibiotic drug. After dissolving the drug in methanol and drying under vacuum, the sample was reanalyzed. The results, shown in Fig. 3b, show that the methanol is observed, but the acetone in the original sample is now absent. Acetone is a true solvent response and not an interference from matrix decomposition products. More importantly, the major components of the matrix do not produce chromatographic peaks that interfere with the analysis for any solvents.

Bias can also result from the interaction between solvents and other components of the sample solution in the injection port. This interaction will decrease the response for the solvent and result in reduced recovery. If the solvent is converted to other volatile products, a positive bias for other volatiles may result. The hydrolysis of ethyl acetate, for example, would yield ethanol and acetic acid peaks. The injection port temperature (180°C) is high enough to preclude most of the physical losses, such as occlusion or adsorption of volatile solvents on a solid matrix, but low enough to suppress many problems with chemical reactivity. Our experience with an earlier packed column method at injection port temperatures greater than 250°C revealed a higher incidence of problems with volatile drug decomposition products.

In specific instances, however, solvents may be partially consumed by reactions within the injection port, or otherwise retained by matrix residue. If the solvent and bulk drug are specified, the bias can be evaluated from standard recovery experiments in the range of interest. Haky and Stickney[3] have adopted a standard additions
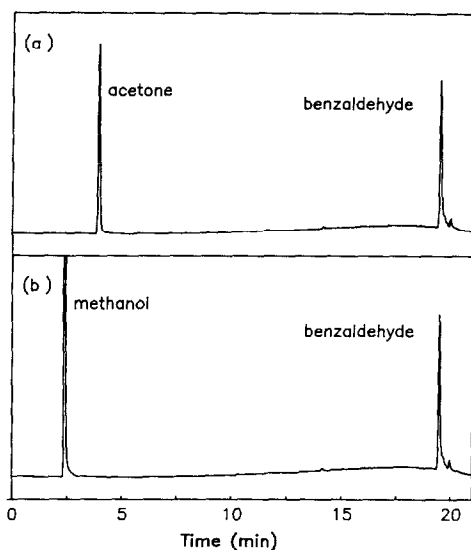
Fig. 3. Results of a typical experiment to evaluate matrix contributions to the solvent profile. (a) Acetone is observed at a level of 1.2% in an antibiotic. (b) The acetone response is eliminated after the drug is dissolved in methanol and taken to dryness.

approach to the analysis of solvent residues to account for proportional bias. For a number of specific examples they conclude that, even in the instances where statistically significant bias can be demonstrated, the bias is unimportant relative to the magnitude of the result.

Benzyl alcohol may contain contaminants that contribute to the solvent response in samples and standards, making blank corrections essential. Fortunately, benzyl alcohol is routinely available in high-purity grades. Aside from benzaldehyde and other oxidation products, the most common impurities observed in commercial high-purity benzyl alcohol are toluene and methanol at levels corresponding to about 0.01% of these solvents in bulk drug for the nominal sample preparation. Blank runs are made routinely to evaluate the contribution of contaminants. Fig. 4 is a typical example.

A small but significant matrix bias that is peculiar to benzyl alcohol has been observed for several drugs. A response for benzene is obtained for a number of salts, including some sodium salts, hydrochlorides, and mesylates that do not contain benzene. Benzene has been confirmed by GC–MS for these materials, and the absence of benzene in the benzyl alcohol diluent has been confirmed. The maximum quantity observed in any particular instance is as high as 0.07% of benzene in drug. A worst case example is shown in Fig. 5. Benzene is not observed when alternate diluents, such as dimethyl formamide, are used, and the benzene response is reduced at lower injection port temperatures. The benzene peak can be eliminated by using benzyl alcohol with very low levels (< 0.005%) of benzaldehyde and associated air oxidation products such as perbenzoic acid and benzoic acid. Commercial benzyl alcohol with these specifications is suitable for routine use. As an alternative, the treatment of benzyl alcohol with a small amount of sodium borohydride followed by reduced
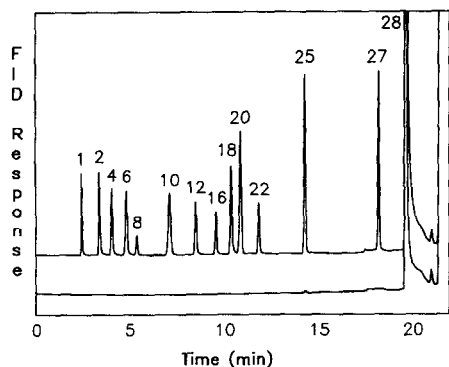
Fig. 4. Lower trace: typical chromatographic trace of benzyl alcohol blank. Upper trace: chromatography of several solvent standards at a level equivalent to 0.20% in bulk druk. Numbers as in Fig. 1.

pressure distillation is a satisfactory means of preparing benzyl alcohol with a low concentration of oxidation products.

Precision and limits of detection

The incompatibility of autosampling equipment with high-precision modes of sample introduction in capillary systems has been viewed as a major obstacle to the use of open-tubular chromatography in solvent residue analysis. With the wide-bore
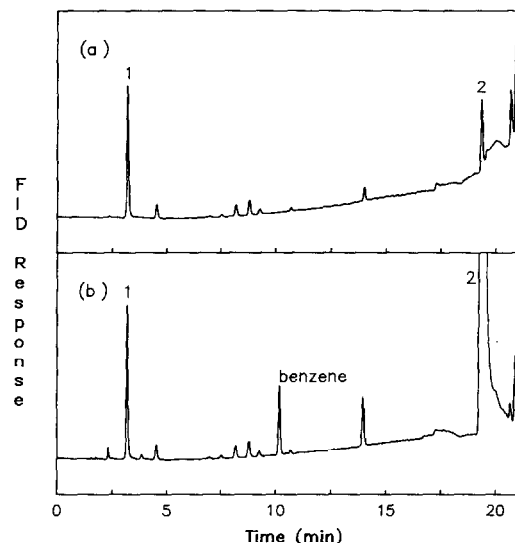

Fig. 5. Chromatography from the residual solvent determination of a bulk drug (hydrochloride salt) that interacts with benzyl alcohol contaminants to form benzene. (a) Sample prepared with benzyl alcohol that has been treated to eliminate benzaldehyde and other air oxidation products. (b) Sample prepared with commercial benzyl alcohol containing typical levels of benzaldehyde and other air oxidation products. Peaks: 1 = ethanol (0.24%); 2 = benzaldehyde.

thick film columns, injections can be made in the direct mode, and acceptable precision can be obtained with autosamplers for injections as small as 0.5 μl. The results in Table III were obtained from multiple injections of standard solutions prepared at levels of 0.02, 0.2 and 2.0% of solvent in drug. Based on the 2.0% data, the sampling precision is better than about 0.5%. The poorest precision is observed at the 0.02% level for components with low specific responses, such as chloroform. Signal-to-noise limitations become important at this level. The precision is not improved by extending the sampling time from 30 to 60 s.

Examples of the reproducibility of typical evaluations based on multiple sample preparations are given in Table IV. The reproducibility between preparations is as good as the precision between injections as long as the sample homogeneity is not a limiting factor.

Approximate limits of detection have been determined for our experimental configuration based on a signal-to-noise ratio of six. Results of this determination are given in Table V. The solvents in the table have been chosen to represent a wide range of elution times and specific responses. The chromatography of some representative solvents at the 100-ppm level and at the 5-ppm level is shown in Fig. 6. Acceptable integration of the peaks at the 5-ppm level is possible. The achievement of trace level limits of detection was not, however, an objective of this study. Lower limits can be achieved, if necessary, by injecting larger volumes of more concentrated drug solutions.

Ruggedness

Potential problems with system ruggedness have prompted some workers to develop methods based on headspace analysis. Specifically, Guimbard *et al.*[4], cite the

TABLE III

PRECISION [R.S.D. (%)] OF PEAK AREA DETERMINATION AT THE 0.02, 0.2 AND 2.0% LEVELS AVERAGED OVER SIX INJECTIONS

Solvent	Standard concentration			Solvent	Standard concentration		
	0.02%	*0.2%*	*2.0%*		*0.02%*	*0.2%*	*2.0%*
Acetone	1.3	1.0	0.4	Heptane	4.2	1.0	0.8
Acetonitrile	0.9	0.4	1.3	Hexane	1.4	0.4	0.2
Benzene	0.3	0.3	0.2	Isooctane	3.6	0.8	0.9
n-Butanol	2.7	1.3	0.5	Methanol	1.7	0.8	0.7
n-Butyl acetate	4.5	2.5	0.3	Methyl *tert.*-butyl ether	0.6	0.7	0.2
Butyl chloride	4.9	0.7	0.3	Methyl ethyl ketone	0.8	0.7	0.3
Chloroform	9.8	1.8	2.4	Pentane	0.7	0.4	0.2
Cyclohexane	4.0	0.5	0.2	2-Propanol	0.4	0.2	0.9
Dichloroethane	5.2	1.6	0.2	*n*-Propanol	0.8	0.5	0.2
Dichloromethane	1.3	1.0	0.3	Pyridine	10.5	1.9	0.9
Diethyl ether	0.6	0.3	0.5	Tetrahydrofuran	1.3	0.5	0.2
Dioxane	2.9	1.8	0.6	Toluene	3.7	0.8	0.2
Ethanol	0.4	1.2	0.9	*o*-Xylene	4.5	0.5	0.2
Ethyl acetate	2.4	1.1	0.3				

TABLE IV

REPRODUCIBILITY FOR DETERMINATIONS OF RESIDUAL SOLVENTS IN BULK DRUGS

Statistics are calculated for single injections of each of six sample preparations for each drug. The mean and standard deviation (S.D.) are given as percent by weight of the drug. ST1, ST2 = Steroids; CNS1, CNS2 = CNS agents; AB1, AB2 = antibiotics.

Drug	Solvent	Mean (%)	S.D. (%)
ST1	Acetone	0.105	0.001
	Isooctane	0.033	0.001
AB1	Acetone	1.076	0.06
ST2	n-Butanol	0.080	0.014
AB2	Acetone	0.021	0.002
	Diethyl ether	0.070	0.001
	Ethyl acetate	0.517	0.003
CNS1	Methanol	0.085	0.003
	Diethyl ether	0.0479	0.0004
CNS2	n-Butyl acetate	0.011	0.001

contamination of the column with drug as a major deterrent to the direct analysis of drug solutions. There are four factors which lessen the severity of this problem on our system: (1) most of the contamination is confined to the inlet liner where its influence on column performance is reduced, (2) a 5-m retention gap acts as a guard column to protect the analytical column from the build-up of non-volatile residue, (3) the injected drug load is small (*ca.* 5 μg), and (4) the inlet purge vents most of the products that slowly vaporize in the injection port. The injection volume is typically lower by a factor of ten than the volumes recommended for packed-column procedures with the same drug concentration[3]. The higher sensitivity of open-tubular column chromatography relative to packed-column systems permits smaller sample sizes to be employed without sacrificing detection limits.

Overall, we have experienced very few problems with system contamination over several months of operation. Single-run sequences as long as 55 h have included as many as ten different drug samples. No significant changes in retention times, peak shapes or peak areas have been observed for injections of multicomponent standards spaced throughout these runs. The data in Table I were taken from one of these

TABLE V

LIMITS OF DETECTION FOR REPRESENTATIVE SOLVENTS AT A NOMINAL DRUG CONCENTRATION OF 10 mg BULK DRUG PER GRAM OF BENZYL ALCOHOL

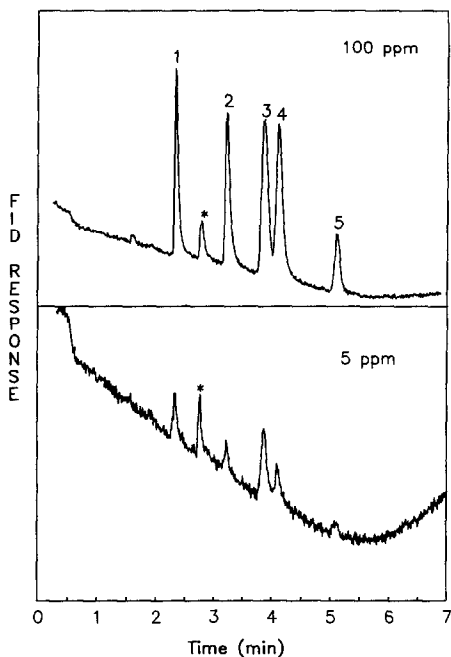| Solvent	Detection limit (ppm in bulk drug)	Solvent	Detection limit (ppm in bulk drug)
Methanol	3	Ethyl acetate	5
Ethanol	3	Tetrahydrofuran	4
Acetone	4	n-Butanol	3
2-Propanol	4	Isooctane	4
Dichloromethane	11		

Fig. 6. Chromatography of several solvents near the limit of detection. Peaks: 1 = methanol; 2 = ethanol; 3 = acetone; 4 = isopropanol; 5 = dichloromethane. The asterisk indicates blank interference.

sequences. The inlet liners are changed regularly, but the guard column has not shown evidence of contamination after analyzing over 200 drug samples. (The guard column is shortened occasionally when columns are removed and replaced in the oven, so it is difficult to determine how long it will last before the contamination becomes severe enough to influence the chromatography.)

CONCLUSIONS

Wide-bore WCOT column GC can be coupled with the generalized sample preparation procedure proposed by Haky and Stickney[3] to provide an effective method for the analysis of solvent residues in drugs. If the direct mode of injection is employed, automation of the procedure yields analytical precision that is comparable to that obtained from automated packed-column methods. The efficiency of the chromatographic system provides a high usable peak capacity for a short analysis time relative to packed-column alternatives. The method is particularly useful for screening a variety of common solvents in bulk drugs.

We have not encountered any instrumental limitations to method accuracy under normal use over the range of 0.01 to 5.0% of solvent in drug. Levels as low as 10 ppm have been determined reliably without modifications to the procedure. The contribution of non-solvent components of the matrix can usually be assessed for each drug by a straightforward sequence of experiments. In our laboratories, this sequence provides the minimal validation data necessary prior to implementing the

method for routine analysis. Recovery experiments are used to provide additional validation data if poor recovery is suspected. Benzene can be produced in the injection port by the interaction between some drugs and common contaminants of benzyl alcohol. Because benzene is rarely used as a process solvent in the pharmaceutical industry, a positive response for benzene should always be evaluated carefully to determine whether the appearance of benzene is an artifact of the procedure.

ACKNOWLEDGEMENTS

REFERENCES

1 C. Bicchi and A. Bertolino, *Farmaco, Ed. Prat.*, 37 (1982) 88–97.
2 F. Matsui, E. G. Lovering, J. R. Watson, D. B. Black and R. W. Sears, *J. Pharm. Sci.*, 73 (1984) 1664–1666.
3 J. E. Haky and T. M. Stickney, *J. Chromatogr.*, 321 (1985) 137–144.
4 J. P. Guimbard, M. Person and J. P. Vergnaud, *J. Chromatogr.*, 403 (1987) 109–121.
5 J. C. Sheridan, J. P. Hetcher, D. W. Hughes and B. B. Hubert, *Pharmacopoeial Forum*, July–August (1986) 1635–1636.
6 *Pharmacopoeial Forum*, March–April (1988) 3600–3604.