ELSEVIER

Journal of Chromatography A, 811 (1998) 145–150

JOURNAL OF CHROMATOGRAPHY A

Analysis of residual solvents by fast gas chromatography

Ted K. Chen[a,*], Joseph G. Phillips[a], William Durr[b]

[a]*Department of Analytical Sciences, SmithKline Beecham Pharmaceuticals, P.O. Box 1539 (UW2960), King of Prussia, PA 19406-0939, USA*

[b]*Department of Chemistry, Jackson State University, Jackson, MS 39217, USA*

Received 28 November 1997; received in revised form 19 February 1998; accepted 20 February 1998

Abstract

Using a 10 m×0.1 mm I.D. DB-624 capillary column, fast separation of 40 commonly used solvents can be achieved in a single analysis in less than 4.9 min. For typical determination of trace solvents in drug substance, the analysis time can further be shortened to less than 1.5 min using combined temperature and pressure programming. The technique was illustrated for sample introduction by both direct injection and via headspace.

Keywords: Solvents, residual; Pharmaceutical analysis

1. Introduction

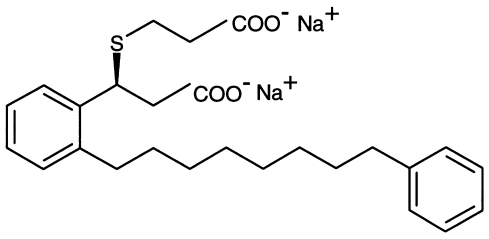
Drug products should contain no higher levels of residual solvents than can be supported by safety data [1,2]. Reliable methods that are also fast are required to monitor these levels. There have been considerable discussions in the development of compendial methods for the analysis of residual solvents in drug substance, excepients and drug products [3–10].

There is also increasing focus in the pharmaceutical industry to reduce cycle time and increase productivity and throughput. Fast elution in residual solvent analysis can be achieved by appropriate individual matching of analyte solvent(s) with stationary phases, column dimension and chromatographic conditions. Recent developments in fast gas chromatography (GC) also include the introduction of short 1-m Multi-Cap multicapillary column [11]. In early pharmaceutical development however, many different solvents are used in many different synthetic routes to prepare many different drug substances that are destined for many different dosage forms in clinical trials. In this diverse environment, a fast, general screening procedure for identification and measurement that is applicable to the largest number of commonly used solvents would be advantageous.

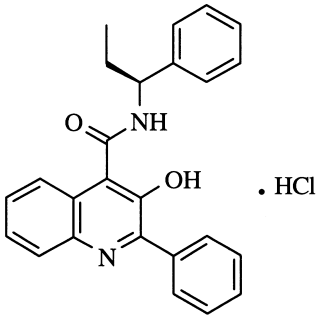
We report here, a fast, general screening method for the separation of commonly used International Committee on Harmonization (ICH) class 2 and class 3 [1] organic solvents in less than 5 min in a single analysis using a 0.1-mm internal diameter (I.D.) DB-624 capillary column. This would require over 45 min using current methods employing either a megabore or a 30 m×0.32 mm I.D. column [5–7]. For typical determination of trace solvents in a drug substance, the analysis time can further be shortened to less than 1.5 min using combined temperature and pressure programming. The appropriate chromato-

*Corresponding author.

0021-9673/98/$19.00
PII: S0021-9673(98)00155-1



SK&F 106203-Z_2



SB 223412-A

Fig. 1. Structures of SK&F 106203-Z_2 and SB 223412-A.

graphic conditions can easily be derived from the screening method. This is demonstrated with two drug substances, SK&F 106203-Z_2, an acid, and SB 223412-A, a base (see Fig. 1 for structures). The procedure for standard and sample preparation remain the same as that used in the current methods. Detailed comparison of chromatographic results with that obtained using either a megabore or a 30 m×0.32 mm I.D. column is not the purpose of this communication.

2. Experimental

2.1. Apparatus

The type of equipment used for the method development is described, but any equipment that is equivalent can be used.

Analysis was performed using a Hewlett-Packard (HP) 6890 GC system equipped with electronic pressure control (EPC), a split/splitless injector, a flame ionization detector and a nano-liter adapter for the autoinjector. A 4-mm straight quartz liner (Restek, Bellefonte, PA, USA) with quartz wool plug was used. For headspace analysis, a Perkin-Elmer HS 40XL valveless headspace analyser was connected to the HP6890 GC system through the straight liner without quartz wool plug. Data were acquired and processed using a Waters 860 networked computer system. A data acquisition rate of 50 data points per second was used.

2.2. Chemicals

Drug substance, SK&F 106203-Z_2 and SB 223412-A (Fig. 1) were synthesized in the laboratory. All solvents were either of HPLC grade obtained from J.T. Baker (Phillipsburg, NJ, USA), or of high-purity grade from Aldrich (Milwaukee, WI, USA). High-purity dimethyl sulfoxide (DMSO) was obtained from Burdick and Jackson (Muskegon, MI, USA). Water was filtered through a Milli-Q purification system.

2.3. Chromatographic conditions

The chromatographic conditions for separation on a 30 m×0.32 mm I.D., 1.8-μm film thickness column have been published previously [5,7]. Hewlett-Packard GC Method Translation software [12] was used extensively for this method development.

2.3.1. System 1: fast screening procedure

Separation was performed on a 10 m×0.1 mm I.D., 0.4-μm film thickness DB-624 (bonded 6% cyanopropylphenyl–94% dimethylpolysiloxane) capillary GC column which was custom-prepared by J&W Scientific (Folsom, CA, USA). The injection size was 0.2 μl. Helium was used as the carrier gas, and was maintained at 38.1 p.s.i. constant pressure. The split ratio was 1:120. The oven temperature program was: 35°C for 0.69 min, then 20°C/min to 90°C, then 50°C/min to 180°C and held for 1 min. The sample concentration was 1:10 000 (v/v) each analyte solvent in DMSO. The injection port temperature was held at 140°C. (Pressure unit in p.s.i. can be converted to SI unit, kPa using the conversion factor: 1 p.s.i.=6.8948 kPa).

2.3.2. System 2: typical analysis of residual solvent in drug substance

In addition to the oven program described in System 1, a pressure program was also used. The initial headpressure was 76.2 p.s.i. for 0.9 min, then increased by 35 p.s.i./min to 100 p.s.i. The split ratio was 1:60. The injection port temperature was held at 140°C.

2.3.3. Headspace analysis

Chromatographic condition described in System 1 was used. The headpressure for the autosampler was set at 40 p.s.i. The sample was equilibrated at 90°C for 20 min, and then injected for analysis. The injection time was 0.06 min.

2.4. Sample preparation

Solvents for analysis by System 1 were prepared in DMSO and serially diluted in DMSO.

Accurate standards for analysis by System 2 of isopropanol, *n*-propanol, *tert*.-butanol and *n*-butanol in water were prepared and serially diluted with water. Concentration of each solvent in the range 0.00025 mg/ml to 0.35 mg/ml were prepared. About 50 mg of SK&F 106203-Z_2 drug substance were accurately weighed into separate autosampler vials and dissolved in 1 ml of the appropriate standard. *n*-Butanol was used as the internal standard.

For headspace analysis, 2.5 mg of SB 223412-A drug substance was weighed into a 3.3-ml headspace sample vial, dissolved in 0.1 ml dimethylformamide (DMF) and mixed.

3. Results and discussion

The separation of 38 commonly used ICH class 2 and class 3 solvents is shown in Fig. 2. An expanded chromatogram is shown in Fig. 3. The retention time of each solvent in Fig. 2 is listed in Table 1 according to its elution order. Four ICH Class 1 solvents are also included for reference. We chose a narrow bore DB-624 column because this column, in the 30 m×0.32 mm I.D. configuration, has provided baseline separation of most commonly used solvents in a single analysis [5,6]. This 6% cyanopropylphenyl–94% dimethylpolysiloxane stationary

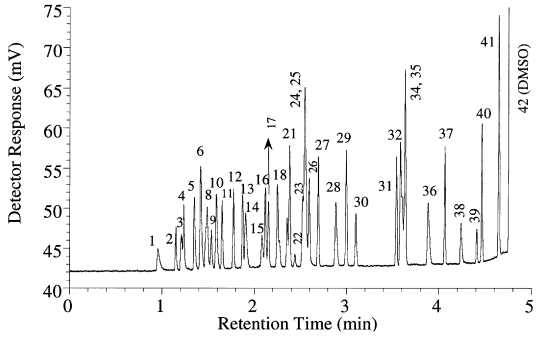


Fig. 2. Separation of commonly used organic solvents.

phase has also been adopted in USP [13] and EP [14] compendial methods for residual solvent analysis. Except for benzene and 1,2-dichloroethane which coeluted with 2-methoxyethanol, and for methyl acetate which elutes very close to acetonitrile (Fig. 2 Table 1), unique retention time could be obtained within 5 min for all solvents tested. This separation using conventional method with 30 m×0.32 mm I.D., 1.8-μm thickness DB-624 capillary column, would require over 45 min [5–7,15].

The tailing factor for *n*-butanol in the fast screening procedure is 1.3 (Fig. 2). The 0.4-μm film thickness provided good compromise between resolution and short analysis time. The fast elution, good peak shape and narrow peak width resulted in excellent column efficiency. The number of theoretical plates for eight randomly chosen solvents covering the retention time range 0–4 min was separately obtained for both columns, and is shown in Table 2. The precision of this general screening procedure for 26 randomly chosen solvent standards (see Table 1)

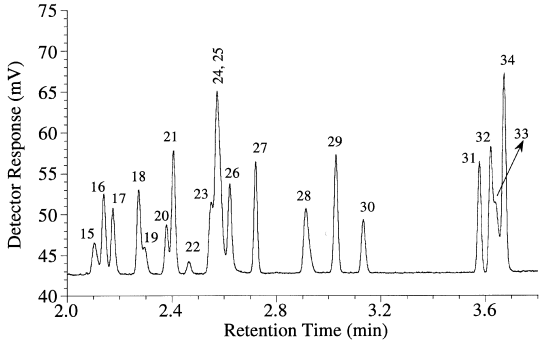


Fig. 3. Expanded chromatogram.

Table 1
Separation of commonly used ICH class 2 and class 3 organic solvents

Peak No.	Solvent	ICH solvent class	Retention time (min)
1	Methanol[a]	2	0.96
2	Pentane	3	1.16
3	Ethanol[a]	3	1.22
4	Diethyl ether[a]	3	1.25
5	Acetone[a]	3	1.36
6	2-Propanol[a]	3	1.43
7	Methyl acetate	3	1.49
8	Acetonitrile[a]	2	1.50
9	Methylene chloride[a]	2	1.55
10	*tert*.-Butanol[a]	[b]	1.60
11	Methyl *tert*.-butyl ether (MTBE)	3	1.67
12	*n*-Hexane[a]	2	1.79
13	Isopropyl ether[a]	[b]	1.89
14	1-Propanol[a]	3	1.92
15	Nitromethane	2	2.10
16	Methyl ethyl ketone (MEK)[a]	3	2.14
17	Ethyl acetate[a]	3	2.18
18	Tetrahydrofuran (THF)[a]	3	2.27
19	Chloroform[a]	2	2.30
20	1,1,1-Trichloroethane	1	2.38
21	Cyclohexane	2	2.41
22	Carbon tetrachloride	1	2.47
23	2-Methyl-1-propanol	3	2.55
24	Benzene	1	2.57
25	1,2-Dichloroethane	1	2.57
26	2-Methoxyethanol	2	2.57
27	Isopropyl acetate	3	2.62
28	*n*-Heptane[a]	3	2.72
29	*n*-Butanol[a]	3	2.91
30	Methylcyclohexane	2	3.03
31	1,4-Dioxane[a]	2	3.13
32	Methyl isobutyl ketone[a]	3	3.58
33	Pyridine	2	3.62
34	3-Methyl-1-butanol[a]	3	3.64
35	Toluene[a]	2	3.67
36	1-Pentanol (*n*-amyl alcohol)	3	3.92
37	*n*-Butyl acetate[a]	3	4.11
38	Dimethylformamide (DMF)[a]	2	4.28
39	*m*-Xylene[a]	2	4.45
40	*p*-Xylene[a]	2	4.51
41	*o*-Xylene[a]	2	4.70
42	Dimethyl sulfoxide (DMSO)	3	4.91

[a] Analyte solvents included in the mixture used in precision study.
[b] No classification from ICH (International Committee on Harmonization).

is excellent (<2.0% R.S.D. by peak area for 10 replicate analyses).

For typical determination of residual solvents in a drug substance when only a solvent, or a single small set of solvents needs to be analysed, the analysis time can further be reduced to less than 1.5 min. The appropriate choice of the internal standard and chromatographic condition can easily be derived from the screening procedure. This is demonstrated in Fig. 4 for the determination of residual isopropanol, *n*-propanol and *tert*.-butanol spiked into 50 mg SK&F 106203-Z_2 drug substance with *n*-butanol as

Table 2
Column efficiency for the fast screening procedure

Analyte	No. of theoretical plates	
	Column: 30 m×0.32 mm I.D., 1.8-μm film thickness DB-624	Column: 10 m×0.1 mm I.D., 0.4-μm film thickness DB-624
Methanol	16 827	11 513
Acetone	31 765	47 269
Isopropanol	25 086	42 159
tert.-Butanol	24 463	58 069
n-Propanol	28 494	62 380
Tetrahydrofuran	44 341	121 535
n-Butanol	35 999	134 928
Toluene	260 587	306 104

the internal standard. The limit of detection (LOD) for each analyte solvent is 0.0005% (w/w) each analyte in drug substance, or 0.00025 mg/ml each solvent. The linearity range of each analyte solvent (R^2=0.9999), from LOD to 0.7% (w/w), or 0.00025 mg/ml to 0.35 mg/ml is comparable to current methods which uses a 0.32 mm I.D. column. The precision for 10 replicate injections of the analyte solvents at the 0.3% (w/w), or 0.15 mg/ml level is <2.0%. The recovery of each solvent is in the range 99.7–100.2%.

We have observed the artifactual formation of dimethyl sulfide (DMS) when hydrohalide salts of drug substances are dissolved in DMSO and analysed via direct injection [16]. As with any direct injection, judicious care of injection port liner, as well as timely replacement of injection port liner is necessary to minimize analyte solvent–drug matrix interaction in the injection port liner which may lead to poor peak shape, column deterioration and irreproducible results. For samples with difficult matrices, headspace analysis may be preferable. A chromatogram of residual toluene in SB 223412-A dissolved in DMF and analysed by headspace analysis is shown in Fig. 5.

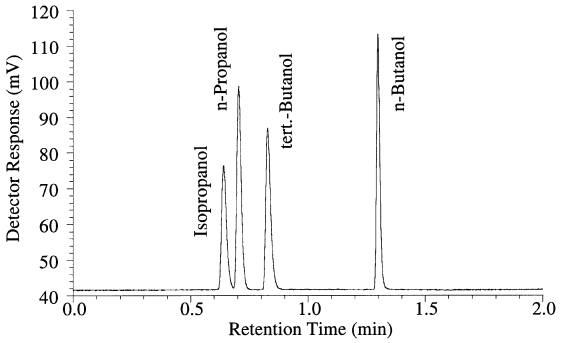


Fig. 4. Typical analysis of residual solvents in SK&F 106203-Z_2.

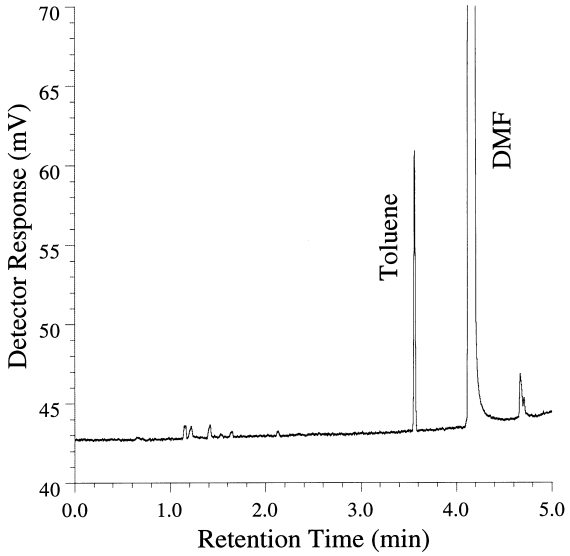


Fig. 5. Headspace analysis of residual toluene from 2.5 mg of SB 223412-A.

4. Conclusion

Using a 10 m×0.1 mm I.D. DB-624 capillary column, fast separation of 38 commonly used ICH I, ICH class 2 and class 3 solvents can be achieved in a single analysis in less than 4.9 min. For typical determination of residual solvents in a drug substance or drug product, the analysis time can further be shortened to less than 1.5 min using combined temperature and pressure programming. The procedure for standard and sample preparation is the same as in the current methods. We have used water and DMSO as the dissolution solvent; other solvents can also be substituted. With appropriate sample introduction such as headspace [7–10] and solid-phase microextraction [17], the present method can also be applied to drug products with difficult matrices. The migration of methods employing the megabore, or the 30 m×0.32 mm I.D. columns to the fast GC configuration can be greatly facilitated by the recent advent of software for method translation and retention time locking.

Acknowledgements

We thank Enno Moeckel and Dave Thornton for technical assistance, and Ron Neu and Lee Marotta (Perkin-Elmer, Norwalk, CT, USA) for a loan of the Perkin-Elmer headspace analyser. Sponsorship by SmithKline Beecham Pharmaceuticals of a Graduate Degrees for Minorities in Engineering and Science (GEM) summer internship (to W.D.) is gratefully acknowledged.

References

[1] International Committee on Harmonization (ICH) Q3C Guideline for Residual Solvents, Step 4 Draft, July, 1997.
[2] In-Process Revision Pharm Forum 14 (1988) 3601.
[3] M.S. Bergren, D.W. Foust, J. Chromatogr. 469 (1989) 161.
[4] T.D. Cyr, R.C. Lawrence, E.G. Lovering, Pharm Forum 18 (1992) 2964.
[5] T.K. Chen, W. Moeckel, H.L. Suprenant, M.Y.K. Ho, Pharm Forum 17 (1991) 1475.
[6] T.K. Chen, W. Moeckel, H.L. Suprenant, M.Y.K. Ho, Pharmeuropa 4 (1992) 196.
[7] K.J. Dennis, P.A. Joseph, Pharm Forum 18 (1992) 2964.
[8] W.C. Kidd, Pharm Forum 19 (1993) 5063.
[9] V.J. Nauhgton, Pharm Forum 20 (1994) 7223.
[10] R.B. George, P.D. Wright, Anal. Chem. 69 (1997) 2221.
[11] Alltech Multi-Cap Capillary Columns, Alltech Associates Bulletin, No. 356.
[12] Hewlett-Packard GC Method Translation, Hewlett-Packard, Little Falls, Wilmington, DE.
[13] United States Pharmacopoeia, Organic Volatile Impurities <467>, Methods I, IV and V.
[14] European Pharmacopoeia, Section V.3.3.9.-2 Residual Solvents, System A.
[15] T.K. Chen, SmithKline Beecham Pharmaceuticals internal results, data not included in this communication.
[16] T.K. Chen, D.W. Thornton, M.Y.K. Ho, Int. J. Pharm. 59 (1990) 211.
[17] R.J. Bartelt, Anal. Chem. 69 (1997) 364.