International Journal of Pharmaceutics, 28 (1986) 211–218
Elsevier

IJP 00954

Studies on contamination of intravenous solutions from PVC-bags with dynamic headspace GC-MS and LC-diode array techniques

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(Received July 11th, 1985)
(Modified version received September 16th, 1985)
(Accepted October 5th, 1985)

Key words: intravenous solutions – polyvinylchloride (PVC) infusion bags – i.v. solutions-impurities/contamination – dynamic headspace gas chromatography mass spectrometry (DH-GC-MS) – gradient liquid chromatography (LC) with UV diode array detection (UV-DAD)

Summary

The contamination of intravenous solutions from PVC-bags was studied by: (1) dynamic headspace GC-MS of the PVC-material; and (2) screening and identification of the impurities in the intravenous solution by gradient liquid chromatography with a diode array UV-detector (LC-UV-DAD). In the study of the PVC-material, the plastic was heated to 120°C for 5–20 min in an oven, conditions similar to the heat sterilization process of the product. The volatile compounds were transferred into a GC-MS system. The intravenous solution in the PVC-bag was studied by injecting 1 ml of the solution into a gradient LC-UV-DAD system. Both studies show that a wide range of compounds including many unidentified are released from the PVC-material. The following compounds have been identified in a brand of Swedish intravenous solutions in 100 ml PVC-bags: di(2-ethylhexyl)phthalate, mono(2-ethylhexyl)phthalate, phthalic acid, 2-ethylhexanol, phthalide, butylhydroxyanisol, benzaldehyde, benzoic acid and phenol. In solutions from another manufacturer bisphenol-A and cyclohexanon were detected as well. The components were present at μg/l levels except for cyclohexanon which was in the mg/l level.

Introduction

Thermoplastics, like polyvinylchloride (PVC), have obtained wide acceptance as suitable packaging materials for pharmaceuticals. However, the introduction of polymeric materials has also increased the contamination risk due to release of chemicals from the plastics (Vincent and Lamy, 1971; Wood, 1980). Apart from the polymer itself, the plastics may contain other components including additives, monomers and oligomers, impurities, decomposition products and reaction products. Factors that may effect the level of these components are the molecular weight distribution of the polymer, the actual polymer used and the protection of the polymer from oxidation, the temperatures used during processing and the heat sterilization of the final product.

PVC, which is the dominating packaging material in the medical and pharmaceutical field, may contain up to 40% (w/w) of additives and it is well known that some of these additives con-

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stitute a contamination risk (Mori, 1979; Arbin and Östelius, 1980; Ulsaker and Teien, 1983).

In earlier investigations in our laboratory (Arbin et al., 1983) the migration of some target compounds from PVC-bags into intravenous (i.v.) solutions was investigated. Phthalates (mono- and di(2-ethylhexyl)phthalate and phthalic acid), acidic compounds (formic and acetic acid) and some metals (Ca, Zn, Cu, Pb, Cd) were quantified in the solutions.

The wide range of compounds with very different chemical properties that may be released from PVC necessitate, however, the use of screening methods in order to examine the total migration from the PVC-plastics and to obtain sufficient information about interactions between the package and the content.

In this study we have used dynamic headspace gas chromatography mass spectrometry (DH-GC-MS) (Jacobsson, 1984) and gradient liquid chromatography (LC) with ultraviolet diode array detection (UV-DAD).

The migration of chemicals from soft PVC bags into intravenous solutions have been studied with the following approach, DH-GC-MS on the plastic material followed by screening and identification of impurities in the solutions with LC-UV-DAD and GC-MS.

Materials and Methods

DH-GC-MS analysis of the PVC-material

Apparatus. Packard 428 gas chromatograph with a SE-54 fused silica capillary column (20 m, 0.22 mm i.d.) and a Jeol MS-300 mass spectrometer with an Incos 2400 data system. The column was held at 30°C for 2 min and then temperature programmed to 280°C with 10°C/min. The column was connected directly to the electron impact source of the mass spectrometer. The ionization energy of the mass spectrometer was 70 eV and a scan cycle time of 1.2 s (35–350 m/z) was used.

Method. The dry plastic sample (1–5 mg) from a 1-year-old PVC bag was heated at 120°C in an oven for 5–20 min in a flow of helium (20 ml/min). Volatile organic compounds desorbed from the solid matrix were collected in a glass trap cooled with liquid nitrogen. The enriched compounds were thereafter reinjected into the capillary column (Jacobsson, 1984).

LC-UV-DAD analysis of the i.v. solution

Apparatus. Valco loop injector 1 ml, Varian gradient pump LC 5000, Hewlett-Packard photodiode array detector 1040 A and a Nucleosil ODS (Macherey-Nagel) column 5 μm (200 mm, 4.6 mm i.d.). Mobile phase: acetonitrile/water pH 2.7 with a step gradient of 5% acetonitrile isocratic in 2 min, 5–50% in 28 min and 50–98% in 15 min.

Method. 1 ml of the i.v. solution was injected into the gradient LC system.

GC-MS screening of the i.v. solution

Apparatus. Carlo-Erba 4160 gas chromatograph equipped with a fused silica SE-54 capillary column (12 m, 0.21 mm i.d.) and a Jeol MS-300 mass spectrometer interfaced to an Incos 2400 data system. The column which was connected directly to the ion source, was programmed from 50°C to 280°C with 7°C/min.

Method. 100 ml of the i.v. solution was extracted with 10 ml methylene chloride. 1 μl of the methylene chloride extract was transferred into the capillary column by split injection.

Chemicals

Acetonitrile (Licrosorb, Merck), water (HPLC-grade, Fisons), phthalic acid, phenol, benzoic acid and dibutylphthalate (Merck), phthalide, di(2-ethylhexyl) phthalate (DEHP), bisphenol, butylhydroxyanisol (BHA) and benzaldehyde (Fluka), mono(2-ethylhexyl)phthalate (MEHP) (a gift from AB Hässle, Mölndal, Sweden), methylene chloride (analytical grade, Merck).

Samples

Sodium chloride 0.9 g/l i.v. solutions in 100 ml PVC-bags (about 1 year old) from: (i) ACO Läkemedel AB (F3M019); and (ii) Travenol (830617J31).

The plastic material in the ACO Läkemedel AB PVC bags came from Draka Plastics (Enkhuizen, Holland) and the bags were manufactured by DRG Flexible Packaging (Bristol, U.K.).

Identification

Tentative identification was carried out by DH-GC-MS. Identification of compounds in the solutions was based on comparison of LC-retention times and UV-spectra of reference compounds as well as by GC-MS analysis.

Results and Discussion

In this study we have used dynamic headspace GC-MS for screening of released volatile organic compounds from the dry PVC-plastics. The compounds have been tentatively identified, i.e. obtained mass spectral data were compared with library data.

Fig. 1 shows the reconstructed ion chromatograms obtained upon dynamic headspace analysis of PVC-materials from two different PVC-bags. Table 1 summarizes the tentatively identified compounds in the two chromatograms.

Many different compounds are present and can be released from the PVC materials (see Fig. 1). Whether these compounds are dissolved in the i.v. solutions or not, will depend on their chemical properties, i.e. the partition coefficient between PVC and water.

The very polar compounds, formic and acetic acid, are examples of compounds which are present in small amounts as decomposition products in the PVC-polymer. Due to the very high polarity of these compounds, the concentrations in the i.v. solutions were in mg/l amounts (Arbin et al., 1983). DEHP on the other hand, which is present in about 40% (w/w) of the PVC-material, has a very low partition to the water solution. The concentration of DEHP in the i.v. solution was only about 10 μg/l (Arbin et al., 1983).

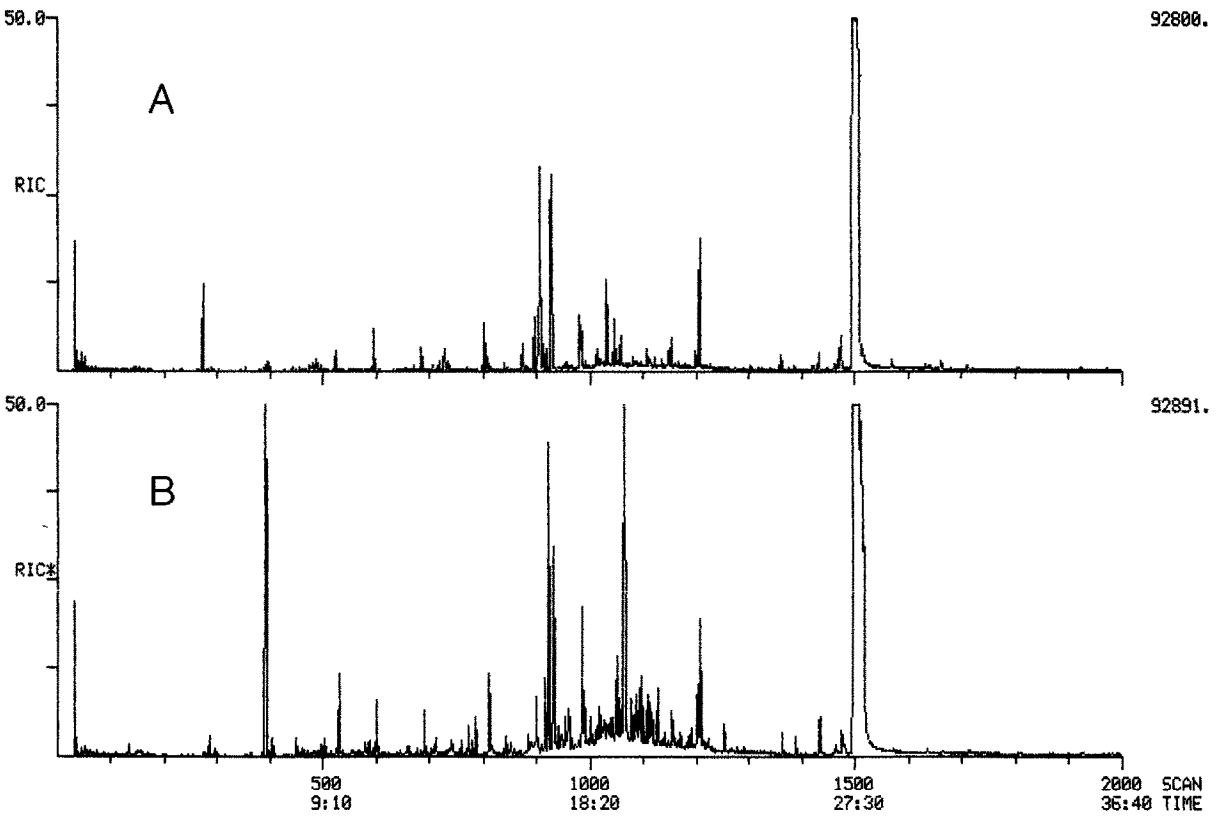

Fig. 1. Reconstructed ion chromatograms from two brands of PVC-plastics. For peak identification see Table 1. A: ACO 100 ml PVC-bag. B: Travenol 100 ml PVC-bag.

TABLE 1

TENTATIVELY IDENTIFIED COMPOUNDS IN THE PVC-MATERIAL BY DYNAMIC HEADSPACE GC-MS

Scan no.	ACO	Travenol
45	Ethanol	
47		Ethanol
51	Pentane	
52		Acrolein
110		Tetrahydrofuran
116	Acetic acid	
136		Acetic acid
154	Pentanal	
233	Toluene	
234		
248		Toluene
256		Aliphatic hydrocarbon
274	Cyclohexanol	
287		Cyclohexanol
292	2-Octene	
298		2-Octene
355	Xylene	
357		Xylene
365		Xylene
391	Heptanal	
393		Cyclohexanon
456	Aliphatic hydrocarbon C13	
488	2-Pentyl furan	
497		Trimethylbenzene
525	2-Ethyl-1-hexanol	
530		2-Ethyl-1-hexanol
555		Cresol
586		Methylstyrene
589		2-Methoxyphenol
596	Nonanal	
602		Nonanal
655	Fatty acid	
672	Naphthalene	
678		Naphtalene
686	Decanal	
691		Decanal
742		Nonanoic acid
760		1-Methyl-propenylbenzene
813		Isobensofuranone
907	1,1-Dimethylethyl-4-methoxyphenol (BHA)	(phthalide)
910		1,1-Dimethylethyl-4-methoxyphenol (BHA)
926	BHT	
932		BHT
981	Diethyl phthalate	
986		Hexadecane
1032	Hexadecanol	
1046	Heptadecane	
1058	Monopentyl phthalate	
1064		Monopentyl phthalate
1083	Tetradecanoic acid	
1089		Tetradecanoic acid
1123	Hexadecanoic acid	
1128		Hexadecanoic acid
1153	Dibutyl phthalate	
1155		Dibutyl phthalate
1205	Phthalate	
1209		Phthalate
1498	Di(-2-ethylhexyl) phthalate	
1500		Di(-2-ethylhexyl) phthalate

Purity profiles of the i.v. solutions were achieved by direct injection into a gradient LC-UV-DAD system which is a very powerful technique for screening of unknown compounds (Drenth et al., 1982; Ghijsen et al., 1982; Krstuiović and Colin, 1984).

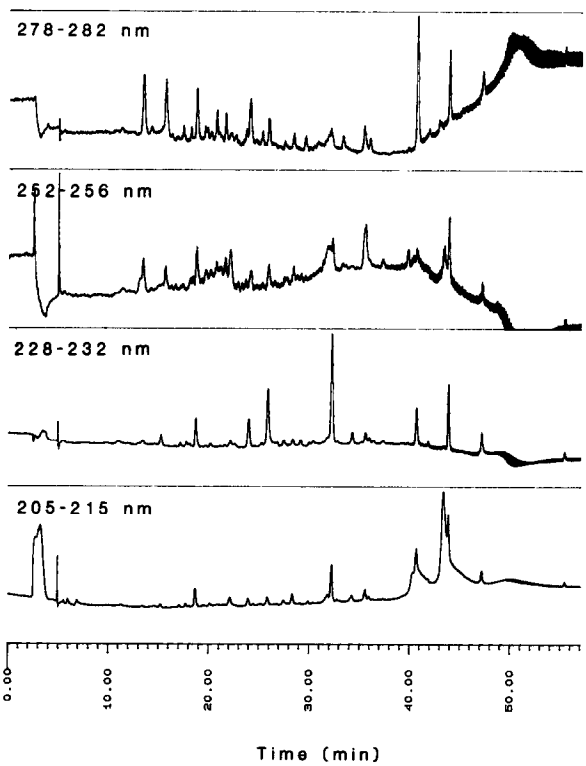

Fig. 2. LC-chromatograms of ACO Sodium chloride i.v. solution (F3M019) in 100 ml PVC-bag plotted at different wavelengths.

In comparison with conventional single wavelength detectors, LC-UV-DAD provides both multiwavelength and spectral information in a single chromatographic run and can be used as a universal detector for UV-absorbing compounds. In Fig. 2 chromatograms of an i.v. solution are plotted at different wavelengths.

In Fig. 3 UV-spectra of interesting peaks are plotted and compared with reference substances. A rapid general survey of spectral information can be obtained by presenting total absorbance chromatograms within a specified range (Figs. 4 and 5). Fig. 4 shows total absorbance chromatograms of two different i.v. solutions in the 100 ml PVC-bags investigated in Fig. 1. In Fig. 5 a blank chromatogram of HPLC grade water can be seen. In Table 2 concentrations of the identified compounds are listed. MEHP and phthalic acid are decomposition products and phthalide is an impurity from the plastiser DEHP. BHA and bisphenol-A are probably used as antioxidants. Cyclohexanone is known to be used as a solvent during the production of PVC bags and as an adhesive (Ulsaker and Korsnes, 1977). Phenol, benzoic acid and benzaldehyde in the solutions are, however, more difficult to derive, but they have been found in DH-GC-MS analysis of empty unused PVC-bags.

Although the gradient LC-UV-DAD method was intended to be a screening method and the quantitative aspects are not fully investigated, the relative standard deviation is below 10% for all the identified compounds and much lower for some of them, e.g. BHA 1.8% (n = 5).

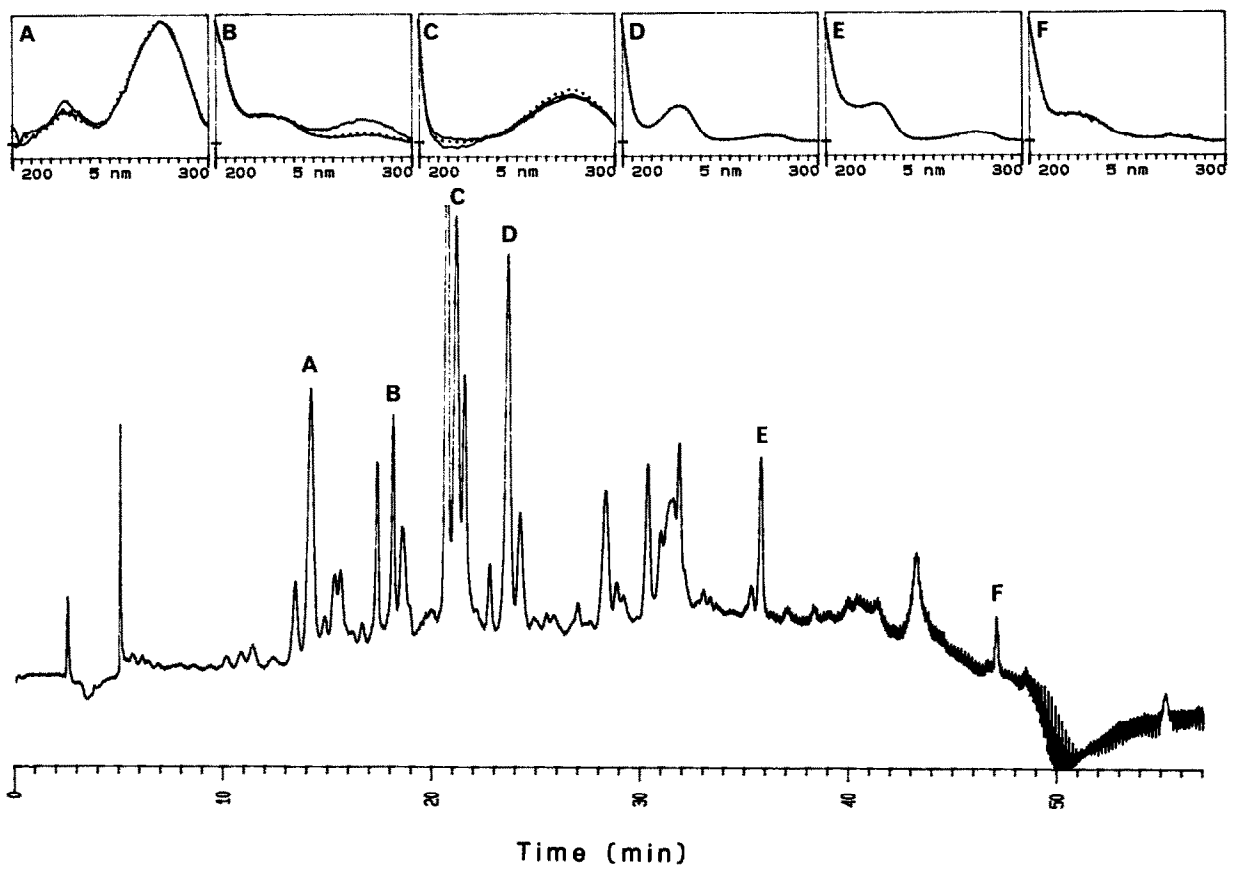

Fig. 3. LC-chromatogram of Travenol Sodium chloride i.v. solution (830617J31) in 100 ml PVC-bag at 254 nm with UV spectra of some interesting compounds plotted. A: not identified; B: phthalic acid; C: cyclohexanone; D: phthalide; E: Bisphenol-A; F: dibutyl phthalate.

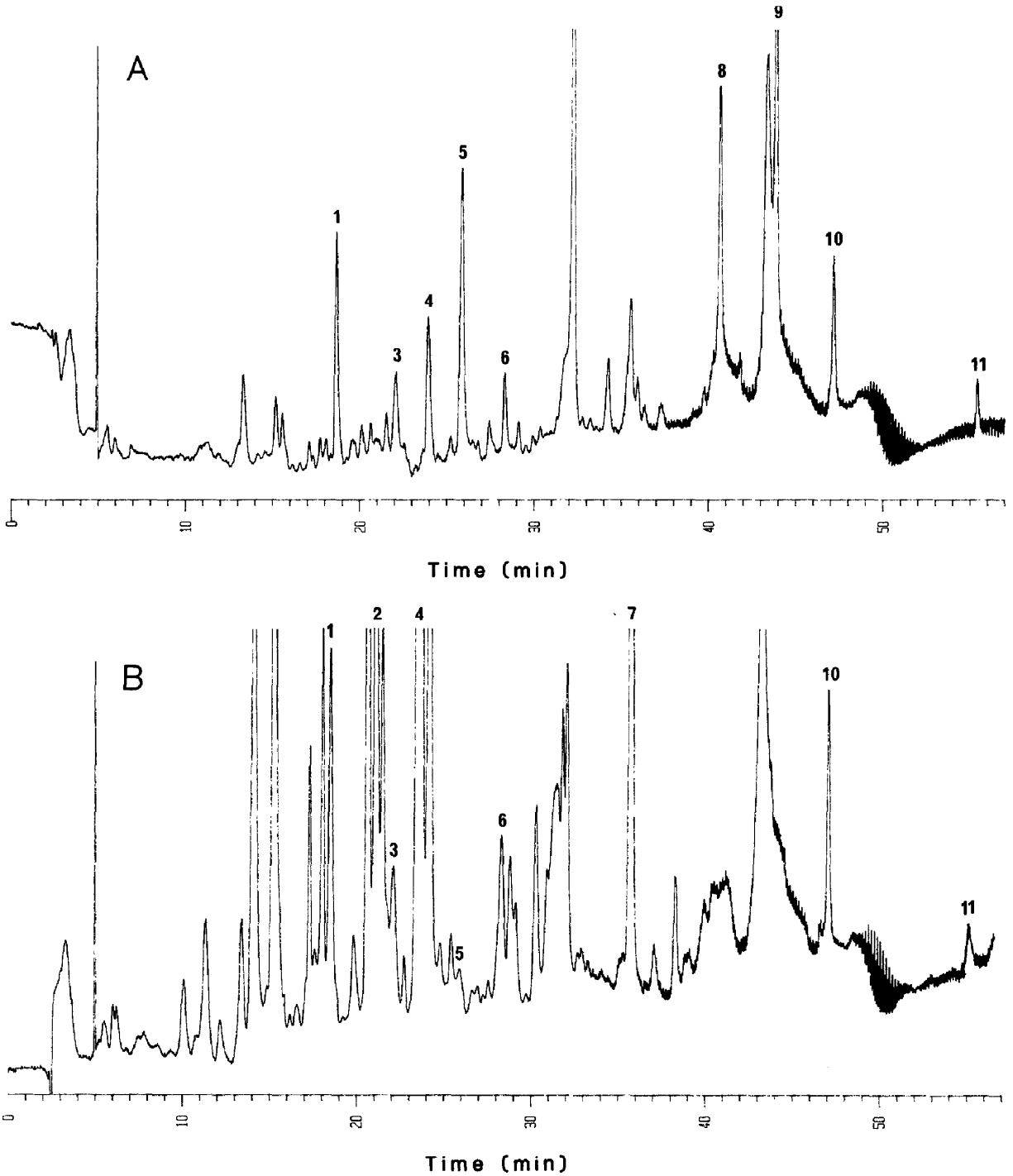

Fig. 4. Total absorbance LC-chromatograms of two different i.v. solutions in 100 ml PVC-bags. A: ACO Sodium chloride 9 g/l (F3M019). B: Travenol Sodium chloride 9 g/l (830617J31). 1: phthalic acid; 2: cyclohexanone; 3: phenol; 4: phthalide; 5: benzoic acid; 6: benzaldehyde; 7: Bisphenol-A; 8: butyl hydroxyanisol; 9: mono(2-ethylhexyl)phthalate; 10: dibutyl phthalate; 11: di(2-ethylhexyl)phthalate.

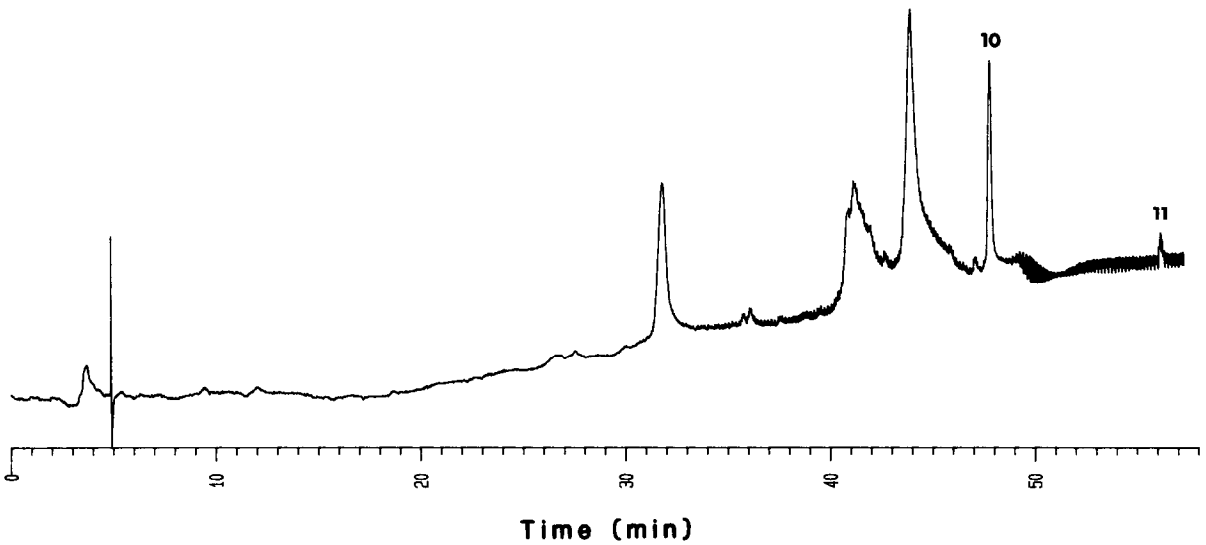

Fig. 5. Total absorbance LC-chromatogram of HPLC-grade water (Fisons). 10: dibutyl phthalate; 11: di(2-ethylhexyl)phthalate.

The LC results were confirmed by GC-MS analysis of a methylene chloride extract of the i.v. solutions. In this confirming study 2-ethyl hexanol could be identified in both solutions as well. This compound has very low UV-absorbance and could not be detected with the LC-system.

The impurity patterns differ between the two brands of PVC-bags. This is most obvious in the LC-chromatograms. Besides the use of different PVC-materials, the reason can be different water qualities which could, for example, account for some of the phthalates present and production processes, e.g. reprocessing of plastics, which may alter the properties of the plastic. Before autoclaving, the PVC-bag could be wrapped with a moisture-proof pack which itself could release compounds which may migrate through the PVC-wall into the solution, thus increasing the number of impurities in the solution. The ACO-bag is autoclaved without an outer wrapper, which is put on aseptically after the heat sterilization. At the time of analysis, the two i.v. solutions were of about the same age (about 1 year). Although some major impurities have been identified in the solutions, the study should be considered to be of a preliminary screening nature. The wealth of compounds which are released from the plastics, as indicated by the dynamic headspace studies and the liquid chromatograms with numerous unidentified peaks, call for further investigations.

TABLE 2

IDENTIFIED COMPOUNDS IN THE SODIUM CHLORIDE (9 g/l) i.v. SOLUTIONS IN 100 ml PVC BAGS

	Concentration (μg/ml)	
	ACO (F3M019)	Travenol (830617J31)
(1) Phthalic acid	0.026	0.027
(2) Cyclohexanone	–	35.00
(3) Phenol	0.024	0.029
(4) Phthalide	0.016	0.580
(5) Benzoic acid	0.029	–
(6) Benzaldehyde	0.005	0.013
(7) Bisphenol-A	–	0.320
(8) Butyl hydroxyanisol	0.058	–
(9) Mono (2-ethylhexyl)-phthalate	0.454	–
(10) Dibutyl phthalate	*	*
(11) Di(2-ethylhexyl)-phthalate	0.007	0.005

* Concentrations comparable to the blank gradient.

Conclusion

A wide range of compounds, including many unidentified, were released from the PVC material. Capillary GC-MS and gradient LC-UV-DAD are

excellent complementary screening techniques to study purity profiles of both the packaging material and the pharmaceutical preparation. Information from such studies makes it easier to investigate packaging materials for drugs and foodstuffs.

Acknowledgement

We thank Dr. Conny Bogentoft and Prof. Douglas Westerlund for valuable discussions on the manuscript.

References

Arbin, A. and Östelius, J., Determination by electron-capture gas chromatography of mono- and di(2-ethylhexyl)phthalate in intravenous solutions stored in poly(vinyl chloride) bags. J. Chromatogr., 193 (1980) 405–412.

Arbin, A., Östelius, J., Callmer, K., Sroka, J., Hänninen, K. and Axelsson, S., Migration of chemicals from soft PVC bags into intravenous solutions. Acta Pharm. Suec., Suppl., 3 (1983) 20–33.

Drenth, B.F.H., Ghijsen, R.T. and De Zeeuw, R.A., Universal multi-channel ultraviolet detection in the purity analysis of 2-ethyl-3-(4-hydroxybenzoyl)indolizine by high-performance liquid chromatography. J. Chromatogr., 238 (1982) 113–120.

Ghijsen, R.T., Drenth, B.H.F., Overzet, F. and De Zeeuw, R.A., Screening for unknown compounds by HPLC using a multichannel diode array UV-VIS spectrophotometer: application to drug metabolism. J. High Resolution Chromatogr. & Chromatogr. Commun., 5 (1982) 192–198.

Jacobsson, S., Analysis of volatile organic compounds in polymers by dynamic headspace and gas chromatography/mass spectrometry. J. High Resolution Chromatogr. & Chromatogr. Commun., 7 (1984) 185–190.

Krstulović, A.M. and Colin, H., Screening for unknown compounds in complex matrices analysed by liquid chromatography: an overview. Trends Anal. Chem., 3 (1984), 43–50.

Mori, S., Contamination of water and organic solvents stored in plastic bottles with phthalate ester plasticizers. Anal. Chim. Acta, 108 (1979) 325–332.

Ulsaker, G.A. and Korsnes, R.M., Determination of cyclohexanone in intravenous solutions stored in PVC-bags by gas chromatography. Analyst, 102 (1977) 882–883.

Ulsaker, G.A. and Teien, G., Gas chromatographic-mass spectrometric identification of 9,10-epoxysterate in human blood. Analyst, 108 (1983) 521–524.

Vincent, G.E. Jr. and Lamy, P.P., Plastics: a pharmacist's concern. Hosp. Pharm., 6 (1971) 19–25.

Wood, R.T., Validation of elastomeric closures for parenteral use: an overview. J. Parent. Drug Assoc., 34 (1980) 286–294.