Table I—Peroxide Number (PN) of Sorbitan Monooleate, Sorbitan Monostearate, and Polysorbate 60 Using the Spectrophotometric Method

| Surfactant | Peroxide Number Before Peroxide Removal | Peroxide Number After Peroxide Removal |
|---|---|---|
| Sorbitan Monooleate | 0.24[a] | <0.10 |
| Sorbitan Monostearate | 1.3 | <0.10 |
| Polysorbate 60 | 9.8[b] | <0.10 |

[a] By titrimetric assay the PN was determined to be 0.39. [b] By titrimetric assay the PN was determined to be 5.8.

The PN of the three surfactants in this study were determined by the spectrophotometric method before and after peroxide removal (Table I). For comparison, the PN of polysorbate 60 and sorbitan monooleate were determined before peroxide removal by the titrimetric assay.

The lower limit of <0.10 for the PN by the spectrophotometric method (Table I) was chosen because it corresponded to the lowest iodine concentration in the presence of purified surfactant used in establishing the linearity of the method. This lower limit was sensitive enough to assure that the peroxide level had been significantly reduced after extraction with sodium metabisulfite[7].

From the results shown in Table I, the titrimetric and the spectrophotometric method for polysorbate 60 and sorbitan monooleate agreed fairly well. However, the color transition at the titrimetric end point for sorbitan monooleate, from green to aqua, was difficult to observe. No such problems were encountered using the spectrophotometric method; hence, this method may provide a more accurate measure of the peroxide content of sorbitan monooleate than the titrimetric assay.

While the titrimetric assay worked well for polysorbate 60 and fairly well for sorbitan monooleate, it did not work at all for sorbitan monostearate. It was not possible to keep the sorbitan monostearate solubilized during the titration with aqueous thiosulfate using the titrimetric method. Therefore, the PN of sorbitan monostearate could only be determined using the spectrophotometric method detailed in this report.

In summary, a sensitive spectrophotometric method has been developed to quantitate the peroxides present in sorbitan monostearate and monooleate, and polysorbate 60. This method should be easily extended to include other poorly water soluble as well as water soluble surfactants.

[7] These authors feel that the lower limit of peroxide quantitation by this spectrophotometric method can be extended by 10-fold, to PN values at levels <0.01. This is based on our findings that Beer's law is valid at a 50-fold lower iodine concentration in the absence of surfactant.

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# Gas Chromatographic Method for Solvent Residues in Drug Raw Materials


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**Abstract** □ A gas chromatographic (GC) method for screening drug raw materials, soluble in aqueous media, for volatile solvent residues has been developed. After dissolution, separate portions of the drug are each separately extracted with *n*-octane, toluene, and ether and injected into a chromatograph equipped with a porous polymer column and a flame ionization detector. The range of extractant polarities provides chromatograms which, taken together, are free of interfering peaks from 0 to ~20 min. Peaks due to solvent residues in the drug are identified by retention time with confirmation of identity by GC-MS.



**Keyphrases** □ GC—solvent residues in drug raw materials, comparison with MS □ Solvent residues—drug raw materials, GC, comparison with MS


Drug raw materials are manufactured in an increasing number of countries. Whether, for a given drug, the same synthetic route is used universally or whether different routes are used, the necessarily diverse sources of raw materials, technical experience, and manufacturing conditions can lead to differences in the amount and kind of drug-related impurities (1-4). Solvent residues may also be present (1). These may be revealed by modern techniques such as liquid chromatography but, due to their volatility, not by thin-layer chromatography (a method often used to assess drug impurities). Besides being undesirable contaminants, solvent residues may interfere with the determination of drug-related impurities. The problem of solvent residues is recognized by the USP (5) which includes monographs involving, for example, tests for chloroform and ethyl acetate in colchicine, pyridine in diethylstilbestrol diphosphate, and isopropyl alcohol in dihydroxyaluminum aminoacetate. Work in this laboratory, reported herein, has shown for example, that some sulfinpyrazone and flurazepam hydrochloride raw materials are contaminated with toluene and acetone, respectively. To maintain surveillance over this situation, a method for the detection and quantitation of solvent residues in drug raw materials has been developed.

Each of three portions of an aqueous solution of the drug to be examined is individually extracted with ether, toluene, and *n*-octane, and the extracts are tested for volatile organic solvents by gas chromatography (GC). The three solvents were chosen to provide a range of polarities. This enhances the probability that any solvent residue in the drug will be substantially extracted into at least one of them. In addition, each of the three provides a different retention time range free of




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**Table I—Relative Retention Times of Organic Solvents**

| Solvent | Relative Rentention Time[a] |
|---|---|
| Methanol | 0.07 |
| Ethanol | 0.12 |
| Acetonitrile | 0.14 |
| Acetone | 0.18 |
| Dichloromethane | 0.18 |
| 2-Propanol | 0.19 |
| Ether | 0.21 |
| *n*-Pentane | 0.22 |
| 1-Propanol | 0.25 |
| Methyl ethyl ketone | 0.35 |
| Chloroform | 0.35 |
| Ethyl acetate | 0.36 |
| 1,2-Dichloroethane | 0.40 |
| 1-Butanol | 0.46 |
| Benzene | 0.48 |
| Carbon tetrachloride | 0.50 |
| Cyclohexane | 0.53 |
| 1,1,1-Trichloroethane | 0.64 |
| Pyridine | 0.79 |
| Toluene | 1.00 |
| Dimethylformamide | 1.11 |
| Isooctane (2,2,4-trimethylpentane) | 1.12 |
| *n*-Butyl acetate | 1.50 |
| *n*-Octane | 1.66 |
| Dimethyl sulfoxide | 2.29 |
| Cyclohexanone | 2.29 |

[a] Relative to toluene at ~9 min when these data were obtained.

main peak or impurity interference so that impurities extracted from the drug can be easily detected. Any such peaks are tentatively identified by comparison of their retention times with the known retention times of common solvents, with confirmation of identity by MS comparison with known standards.

## EXPERIMENTAL SECTION

**Materials and Apparatus**—Ether[1] (USP) and glass-distilled toluene[2] were used as received. *n*-Octane[3] (100 mL) was passed through three silica cartridges[4] prior to use. The drug raw materials were commercially available.

The gas chromatograph[5] was equipped with a flame ionization detector and a printer–plotter mechanism (attenuation 2↑5, corresponding to 32 pA/cm). The coiled glass column (0.91 m × 4 mm i.d.), packed with a porous polymer[6] (80/100 mesh), was adapted to the chromatograph with a short length of nickel tubing. The column, injector port, and detector temperatures were 210°C; gas flow rates were: nitrogen, 60 mL/min; hydrogen, 35 mL/min; air, 400 mL/min. Columns were conditioned for 72 h at 210°C with a nitrogen flow of 60 mL/min.

**Drug Dissolution**—Three solutions were prepared to contain ~200 mg of drug, accurately weighed in a minimum volume of aqueous solvent. The aqueous solvent, whether acidic, basic, or neutral, was chosen on the basis of a preliminary investigation to determine the conditions of maximum solubility. Thus, hydrochloric acid solution might be selected for a basic drug such as diazepam, whereas a sodium hydroxide solution would be selected for an acidic drug such as sulfinpyrazone.

Chromatographic profiles of the ether, toluene, and *n*-octane were obtained prior to use. Samples exhibiting significant impurity peaks were either purified or rejected. To each of the three drug solutions was added either toluene (1.0 mL), *n*-octane (1.0 mL), or ether (2.0 mL). Each tube was shaken vigorously for 2 min, centrifuged, and 2 μL of the organic phase was injected into the gas chromatograph.

Prior to beginning the actual examination of drug raw materials, the retention times of a number of possible volatile contaminants were determined (Table I). If an impurity peak was found in a drug extract, a tentative identification was made by reference to Table I and verified by injection of a solution of the suspected impurity in the appropriate solvent, either ether, toluene, or *n*-octane. Confirmation was by GC–MS[7] using GC conditions as described above with an electron ionization potential of 70 eV.

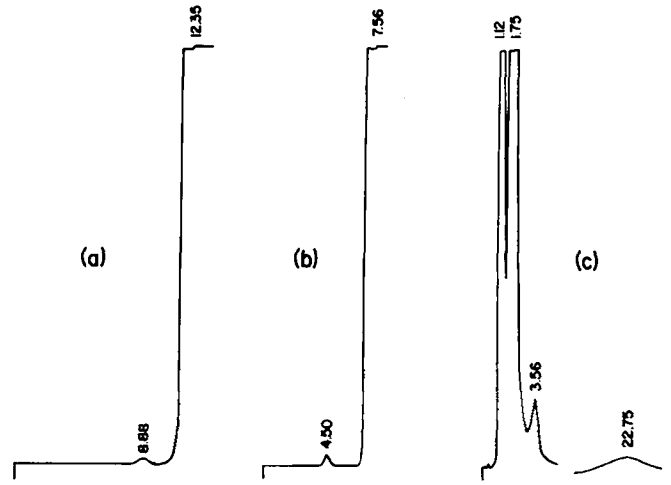


**Figure 1**—*Chromatograms of the extraction solvents. Key: (a) n-octane with an impurity at 8.88 min; (b) toluene with benzene at 4.5 min; (c) ether with several impurities.*

**Quantitation**—After identification, impurity levels were established by comparison to a three-point calibration curve. For example, for the quantitation of acetone, the calibration curve was prepared by shaking a 1-mL aliquot of each of three standard solutions of acetone in toluene (range, 1.58–0.0316 mg/mL) with the same volume of the aqueous solvent used for the dissolution of the drug raw material (Table II). Duplicate 2-μL aliquots of the organic phase representing an on-column range of 3.16–0.0632 μg acetone were chromatographed, and the response factor was calculated from the integrated area. For toluene, a three-point calibration curve was prepared in a similar manner using three standard solutions of toluene in *n*-octane (range, 0.866–0.0247 mg/mL) representing an on-column range of 1.732–0.0494 μg. Recovery of the impurity from the aqueous solution of the drug was determined by extracting a fresh sample of the drug with solvent containing a known amount of the impurity, usually one of the known solutions prepared for calibration purposes. This is equivalent to spiking the drug sample with a known amount of the impurity. Recovery, in percent, is given by: $(C_t - C_i/C_s) \times 100$, where $C_t$, $C_i$, and $C_s$ are the area counts obtained for the spiked sample, the sample itself, and the standard solution used to spike the sample, respectively.

## RESULTS AND DISCUSSION

The method was developed to screen drug raw materials for volatile organic solvent contaminants. Three portions of the material to be examined were

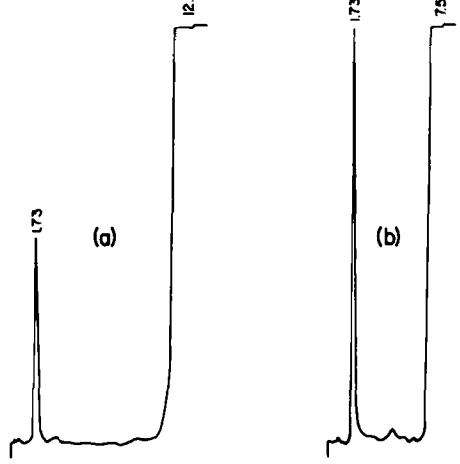


**Figure 2**—*Chromatograms of flurazepam extracts showing acetone at 1.73 min for the n-octane extract (a) and the toluene extract (b).*

[1] Mallinckrodt Chemical Works, St. Louis, Mo.
[2] Burdick and Jackson Inc., Muskegon, Mich.
[3] Gold Label grade; Aldrich Chemical Co., Montreal, Canada.
[4] Sep-Pak; Waters Scientific Ltd., Mississauga, Ontario, Canada.
[5] Model 5880A; Hewlett-Packard, Palo Alto, Calif.
[6] Chromosorb 106; Chromatographic Specialities, Brockville, Ontario, Canada.
[7] Model 5985; Hewlett-Packard.

**Table II—Solvent Residues in Drug Raw Materials**

| Drug[a] | Solvent, mL | *n*-Octane[b] Residue Found | *n*-Octane[b] Level, %[c] | Toluene[b] Residue Found | Toluene[b] Level, %[c] | Ether Residue Found |
|---|---|---|---|---|---|---|
| Chlordiazepoxide HCl (1) | $H_2O$(2) | —[d] | | Acetone | 0.015 (90) | — |
| Chlorpromazine HCl (1) | $H_2O$ (0.5) | Toluene | 0.04 (101) | — | | Toluene |
| Flurazepam HCl (8) | 2.5 M HCl (0.5) | Acetone | | Acetone | 0–0.51 (118) | — |
| Furosemide (5) | 2.5 M NaOH (1) | — | | Acetone | 0–0.05 | — |
| Naproxen (2) | 1 M NaOH (9) | Toluene | 0.02–0.05 (97) | — | | Toluene |
| Propranolol HCl (6) | $H_2O$ (2.5) | Toluene | 0–0.06 (99) | Acetone | 0–0.08 (85) | Toluene |
| Sulfinpyrazone (4) | 1 M NaOH (5) | Toluene | 0–0.33 (103) | — | | Toluene |

[a] Number of lots analyzed in parentheses. [b] Solvent residue levels are calculated on the basis of 400 μg of drug on-column. [c] Percent recovery in parentheses. [d] None detected.

extracted separately with *n*-octane, toluene, and ether. These extracts were chosen to provide a range of polarities to facilitate the extraction of impurities from aqueous drug solution and to leave open different retention time windows in the chromatograms (Fig. 1). Although good grades of these solvents were employed, they all contain minor impurities which are evident as peaks on the chromatograms.

The method described provides for minimum detectable levels of 0.002–0.005% (with respect to sampling technique equivalent to 400 μg of drug on column) volatile solvent in drug raw material, depending upon the solvent residue and its partition ratio between the organic and aqueous phases. If lower sensitivities can be tolerated, lesser amounts of drug raw material can be used.

Typical results are presented in Table II. Acetone was found in four of six lots of propranolol hydrochloride and in four of eight lots of flurazepam hydrochloride. For flurazepam, the acetone peak is clearly evident in the chromatograms of both the *n*-octane and toluene extracts (Fig. 2), but is, as expected, much larger in the latter. The acetone level, quantitated from the toluene extract, was ~0.5% in the sample illustrated; identity was confirmed by MS. The reproducibility of the acetone determination in these samples could not be established due to insufficient sample; however, the duplicate results for one of the flurazepam samples were 0.50 and 0.48%. Toluene was found in three of four samples of sulfinpyrazone. In this case, *n*-octane proved to be a better extract than ether and, of course, toluene could not be used. The level of toluene found in one of these samples was ~0.3% with reproducibility of 3% for five determinations; identity was confirmed by MS. In addition to the drugs listed in Table II, one or more lots of the following drug raw materials was examined, with the solvent given in parentheses: acetaminophen (1 mL 2.5 M NaOH), cimetidine (2 mL 1.0 M HCl), diazepam (0.5 mL 2.5 M HCl), phenytoin sodium (1 mL $H_2O$), metoprolol (0.5 mL 1 M HCl), pentobarbital sodium (0.5 mL $H_2O$), and triamterene (5 mL HCl). No solvent residues were detected in these lots.

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