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Received June 14, 1982.
Accepted for publication August 4, 1982.
This work has received financial support from the Officina del Desarrollo Científico (Universidad de Chile), Project Q1574-8212.

Comments on the USP XX Gas Chromatographic Analysis of Alcohol in Drugs and Drug Formulations

Keyphrases □ GC—USP XX GC analysis of alcohol in drugs and drug formulations □ Alcohol—USP XX GC analysis in drugs and drug formulations

To the Editor:

The analysis of the alcohol content in drug formulations is a part of not only elixir and tincture monographs but also is included as a limit test for residual alcohol from the synthesis of some drug substances.

The performance of a divinylbenzene polymer for the GC analysis of alcohol was described previously (1), and it was concluded that there were definite advantages with the use of porous polymer beads for the analysis of alcohol in pharmaceuticals. In 1975 the 12th edition of the "Official Methods of Analysis of the Association of Official Analytical Chemists" (2) adopted a GC method for the analysis of alcohol in drugs which was based on a collaborated method developed previously (3). This procedure utilized a flame ionization detector and a column packed with a 80–100 mesh copolymer of ethylvinylbenzene and divinylbenzene[1] (I) operated at 130° with a retention time of ~5 min for acetonitrile, the internal standard. The USP XX (4) changed the chromatographic procedure for alcohol to essentially that cited previously (3). The change of the column packing to I was an improvement in the USP method since it eliminated interferences caused by column bleed and the late elution of water experienced with the earlier polyethylene glycol column. Unfortunately, it now appears that a suitable grade of I is no longer commercially available.

Data to support this conclusion was developed during a recent evaluation of the alcohol analysis for dexamethasone elixir.[2] Six lots of I, including both the 80–100 and 100–120 mesh sizes, were evaluated to determine the extent of the problem. These lots represent commercially available materials between 1976 and 1981. Both coiled and U-shaped glass columns were packed and used with three different gas chromatographs[3]. Even though both the temperature and the nitrogen flow rate were adjusted, complete baseline separation of the alcohol and acetonitrile peaks was not achieved with any lot of Compound I. The alcohol peak also exhibited marked tailing, which was not present in the chromatograms published by Falcone (3) or those by Hollis (5) who did some of the first experimental work with porous polymer beads. The acetonitrile peak remained symmetrical regardless of packing pretreatment, column temperature, or whether injected alone or with alcohol. Tailing of the alcohol peak can be reduced by either the chloroform soxhlet extraction of I prior to packing the column or by raising the column temperature. The change in resolution can be attributed to the interaction of alcohol with residual polymerization compounds in I. Tailing and resolution factors calculated during this evaluation are listed in Table I.

During conditioning, current lots of I released vapors suggestive of the drying oils found in paints. This odor can also be detected in the bulk packing container, yet the remainder of a bulk lot which was received in 1968 is odorless. The difference in the odor itself indicates that there has been some change in the polymer synthesis which introduces different residual compounds. IR analysis of the oily residue extracted with chloroform showed that at least three compounds are vaporized during column conditioning. A brochure (6) distributed by the manufacturer of I states that "... any residual chemical in the bead can contribute to spreading of the peak, change in retention time, or loss of resolution." This brochure also recommends conditioning for at least 2 hr at 250°. All columns that were evaluated had been conditioned at 235° for 16 hr. One column that was conditioned for a second 16-hr period did not show any improvement in its performance. Only the 100–200 mesh lot, which was exhaustively extracted with chloroform, showed a reduction in the tailing of the alcohol peak. The observed experimental results substantiate the manufacturer's information about residual chemicals in the polymer beads, in that there has been a deterioration in peak resolution, and there is tailing for hydroxyl compounds which was not observed in the collaborative study (3). There is also great variation in column performance between different batches of I.

It is the opinion of this author that the data in Table I demonstrate that acetonitrile is no longer a suitable internal standard for the GC analysis of alcohol. Either the resolution factor or the alcohol tailing factor requirement of USP XX can be met but not both with the same set of chromatographic conditions and the 100–200 mesh size specified in the Alcohol Determination monograph. Of the lots tested, only one lot of 80–100 mesh met all the requirements, except for mesh size, of the system suitability test. A series of five replicate injections of the alcohol standard preparation onto this column had a relative standard deviation (*RSD*) of 2.98% for the peak height ratios, which is less than the 4.0% required by this system suitability test. The *RSD* for the peak area ratios from these same injections was 0.28%. The average result cal-

[1] Poropak Q, Waters Associates, Milford, Mass.
[2] Analyses were part of a study for the Food and Drug Administration's Compendial Monograph Evaluation and Development Program for Dexamethasone monographs in the USP XX.
[3] Hewlett-Packard, model 5830A; Schimadzu, model GC-MINI2; Nuclear-Chicago, model 4740.

0022-3549/82/1200-1424$01.00/0
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Table I—Ranges of Flow, Temperature, Retention Times, Tailing (T), and Resolution (R) for Alcohol and Acetonitrile Chromatographed on a Copolymer of Ethylvinylbenzene and Divinylbenzene [a]

Lot/Year	Temperature	Flow rate, ml/min	R	Alcohol		Acetonitrile	
				T	t_R [b]	T	t_R [b]
			80–100 Mesh				
Pre-1976	125°	61	1.2	1.2	4.78	1.0	6.32
N.D./1976	125°	65	1.6	1.6	3.96	N.D. [c]	5.26
1971/1979	115–130°	39–65	1.2–1.5	1.3	3.19–8.38	N.D.	4.13–10.82
010/1981	110–120°	50–64	2.0–2.4	1.1–1.5	5.76–8.74	1.0–1.1	7.84–12.06
			100–120 Mesh				
1850/1980	110–120°	54–62	1.3–1.4	N.D.	5.55–7.27	N.D.	712–9.33
1850/1980 [d]	160°	60	1.43	6.5	4.71	0.87	6.10
009/1981	115–120°	59	2.6–3.0	3.7–3.8	6.73–7.73	1.0–1.1	9.10–10.47
009/1981 [e]	120–165°	58–61	2.0–2.6	1.6–2.0	2.32–6.61	1.0–1.2	3.01–8.99

[a] USP XX system suitability test for the gas chromatographic analysis of alcohol specifies $R \geq 2$, T for alcohol ≤ 1.5, and a retention time between 5 and 10 min for acetonitrile. [b] Retention time in minutes. [c] Not determined. [d] Column had a 2.6-mm i.d. The difference in the alcohol tailing is attributed to interaction with the column walls. [e] The copolymer was extracted with chloroform for 3 hr and air dried prior to packing the column.

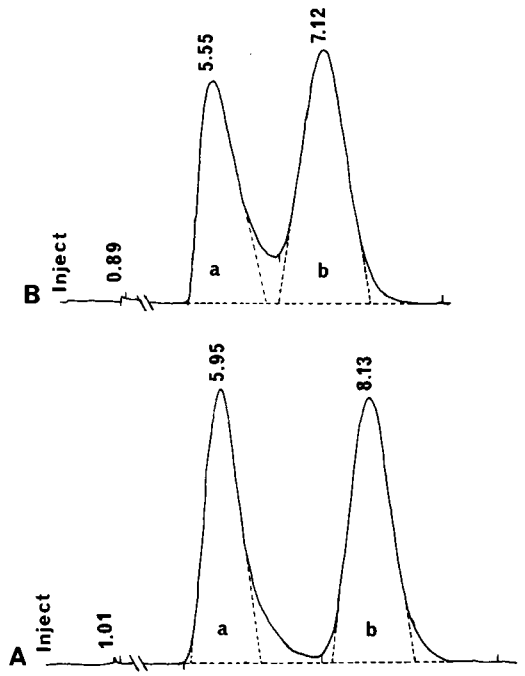

Figure 1—*Typical chromatograms on 80–100 mesh I, 120°, and attenuation of 2^{10} on lot 010 (59 ml/min) (A) and lot 1971 (54 ml/min) (B) for alcohol (a) and acetonitrile (b). Retention times are in minutes.*

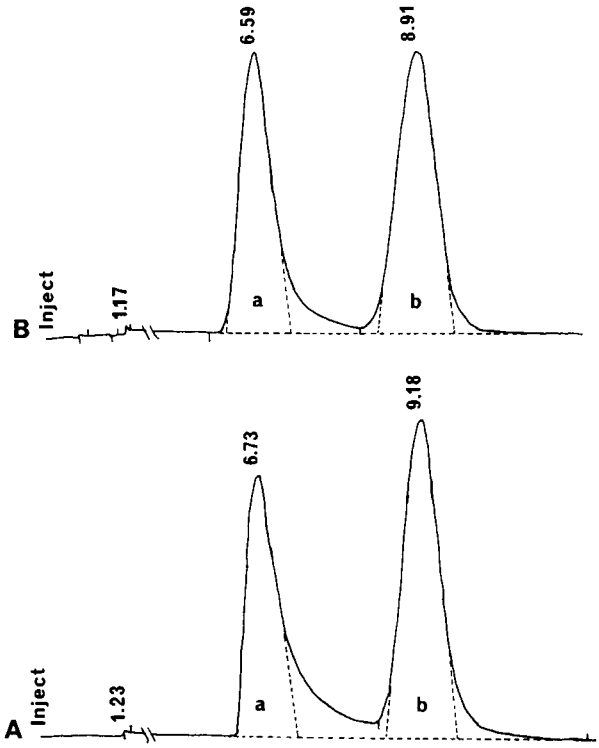

Figure 2—*Typical chromatograms on 100–200 mesh I, 120°, 58 ml/min, and attenuation of 2^{10} on log 009 (A) and lot 009 packed after chloroform extraction (B) for alcohol (a) and acetonitrile (b). Retention times are in minutes.*

culated from the peak height ratios had a 4.5% negative bias compared with a 99.5% recovery for area ratios. A series of 10 standard injections onto the chloroform pretreated 100–200 mesh packing had an *RSD* of 4.32 and 1.66% for the peak height and area ratios, respectively. The negative bias for the average result calculated from peak height ratios was 3.5% compared with a 99.3% recovery for peak areas. Reproducibility studies for the evaluation of each of the three possible internal standards (acetonitrile, methanol, 2-propanol) consistently produced data demonstrating that peak height ratios have larger relative standard deviations than peak area ratios. It was not uncommon to find a factor of 10 difference in the results. Greatest precision and accuracy can be achieved with peak area measurements.

Representative chromatograms for the 80–100 and the 100–120 mesh sizes of I are shown in Figs. 1 and 2, respectively. Inspection of the chromatograms in these figures shows that even when a resolution factor >2 is achieved, there is no baseline separation between the alcohol and the acetonitrile peaks. Clearly, a new internal standard is needed. A suitable internal standard should at least achieve baseline resolution from the sample peak, particularly when the sample peak is the only peak in the chromatogram. Either a new internal standard and a higher column temperature or a different column packing should replace those in the USP XX, in addition to a change to peak area ratios in the calculation formula. An alternative column packing might be the copolymer of styrene–divinylbenzene[4] (II). At 140° and 40 ml/min helium, 80–100 mesh II had retention times of 2.2 and 3.6 min for alcohol and acetonitrile, respectively. Resolution was 2.72. The tailing factor for alcohol was 1.8; that for acetonitrile, 1.3. Reproducibility was not evaluated for this

[4] Chromosorb 101, Johns-Manville, Denver, Colo.

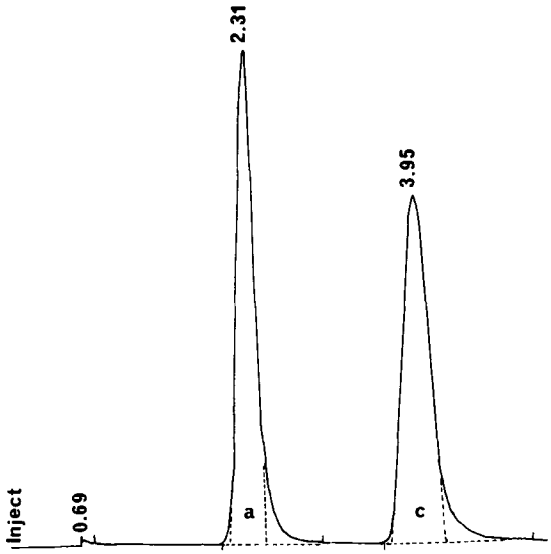

Figure 3—*Typical chromatogram for alcohol (a) and 2-propanol (c) on 100–120 mesh, I, 165°, 59 ml/min, and attenuation of 2^{11} on lot 009 packed after chloroform extraction. Retention times are in minutes.*

packing material. Before any recommendation to change to this polymer could be made, additional investigations would have to be performed to determine if the USP tailing factor for the alcohol peak could be met.

Work in this laboratory has identified 2-propanol as a suitable, readily available internal standard for the analysis of alcohol in drugs and drug formulations. At 165° and 59 ml/min nitrogen, alcohol and 2-propanol had retention times of 2.3 and 4.0 min, respectively, on a column packed with 100–120 mesh I which had been extracted with chloroform. Resolution was 4 with a tailing factor of 1.2 for alcohol and 1.5 for 2-propanol. Two sets of 10 replicate injections of 0.2% solutions of alcohol and 2-propanol had *RSD* values of 0.62 and 0.58% for peak area ratios. Peak height ratios were 4.70 and 7.62%, respectively. A second lot of 100–120 mesh I was tested using the same chromatographic conditions. The RSD for the peak area ratios of 13 standard injections that were interspersed throughout 22 sample injections was 1.42%. A representative chromatogram with a 2-propanol internal standard can be found in Fig. 3.

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Received July 1, 1982.
Accepted for publication September 13, 1982.
The author thanks Ruth Johnson and Dr. Kurt Steinbrecher of this laboratory for supplying gas chromatograms on one lot of I and on II, respectively.