Survey of Chlorinated Hydrocarbons and Other Organic Volatile Impurities in Captopril Raw Materials and Tablets

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INTRODUCTION

The United States Pharmacopeia (1) has recently placed limits of 50 ppm on chloroform and 100 ppm on benzene, 1,4-dioxane, dichloromethane, and trichloroethylene in several hundred drug raw materials. These limits apply mainly to drugs used chronically, defined as being for periods of more than 30 days. In addition, there is a USP limit of 500 μg per day of dichloromethane in film-coated tablets. The European Pharmacopeia proposes limits of 50 ppm for acetonitrile and chloroform, 100 ppm for benzene and 1,4-dioxane, 500 ppm for *n*-butanol, 2-methylpropanol and dichloromethane, and 1000 ppm for dimethylformamide, 2-methoxyethanol, methanol, toluene, and formamide (2).

USP Methods I, II, and IV for organic volatile impurities (1), to be used as specified in individual monographs, base impurity identification solely on gas chromatographic retention time. It has been shown that these methods carry a considerable likelihood of false positives (3). False positives are unlikely to be a problem with Method III, which uses a mass spectrometric detector but which is burdened with high cost and complexity, or with proposed Method V (4), which is based on a column (DB-624, 6% cyanopropylphenyl 94% dimethylpolysiloxane) giving better resolution of all impurities. EP proposals are based on a two-column procedure, a screening step to provide preliminary evidence of a controlled volatile impurity above the limit and a second column to confirm the identity and amount of any compounds so identified.

The results of a survey of organic volatile impurities in captopril raw material and tablet samples are reported in this Note. The results fully support the need for limits on volatile impurities and demonstrate the potential for false positives in procedures which base identification on a single retention time.

MATERIALS AND METHODS

Chemicals

Captopril raw materials from five manufacturers and tablets from three manufacturers, received between June and November of 1990, were available for analysis. Local tap water is sufficiently free of volatile organic compounds to be used without treatment for direct injection analysis. Before use in the purge and trap apparatus, at a concentration ratio of 5000:1, the water was purged with nitrogen for 1 hr. Other chemicals were reagent grade or better.

Equipment

A Hewlett Packard Model 5890 gas chromatograph equipped with an FID detector, a 7673A autosampler, a Model 3393A integrator with a HP 9114B disk drive, and a 5% phenyl methylsilicone capillary column (DB-5, 1.5-μm film, 30 m × 0.53 mm; J & W Scientific) was used. Samples for Fourier transform infrared (FTIR) analysis were prepared with a Tekmar LSC-2000 automatic concentrator equipped with a Tenax trap, coupled by a capillary interface to a Hewlett–Packard 5890 gas chromatograph containing the same type of column as above. The chromatograph was connected to a Digilab Model FTS-40 FTIR by a light pipe maintained at 225°C.

Solutions

Test Solution. Approximately 17 mg of captopril was weighed into a 1.7-ml vial, which was crimp capped. Using a syringe, 1.7 ml of water was added to the vial.

Standard Solution. Ten milligrams of each of dichloromethane, benzene, trichloroethylene, and 1,4-dioxane and 5.0 mg of chloroform were transferred by syringe to a 1-liter volumetric flask containing solvent-free water at room temperature. One milliliter of this solution was diluted to 10 ml in a volumetric flask to give final concentrations of 0.5 μg/ml chloroform and 1.0 μg/ml of the other compounds.

Tablet Test Solution. Two or three tablets were placed in a tube and water was added to give a final concentration of 10 mg/ml, based on the label claim of captopril. The tube was capped with a Teflon-lined stopper, shaken for 5 min, and centrifuged. A 1.7-ml vial was filled with supernatant and crimp sealed.

Chromatography

The injector was operated in the splitless mode with a purge flow of about 82 ml/min activated at 0.5 min. Gas flow rates were as follows: helium carrier gas, 6.5 ml/min; nitrogen makeup gas, 28 ml/min; air, 385 ml/min; and hydrogen, 34 ml/min. The oven temperature program was 35°C for 4 min, 5°C/min to 50°C, 20°C/min to 150°C, and hold for 15 min. The injector temperature was 140°C and the detector temperature was 250°C.

Procedure

Aliquots (1.0 μl) of the standard and test solutions and of the water used to prepare them were injected and the chromatograms recorded. Peaks present were tentatively identified by comparison to a table of retention times of common organic volatile impurities, prepared using the procedure described herein. The identity of compounds judged to

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Table I. GLC Retention Times of Organic Volatile Impurities

Code	Compound	Retention time (min)
1	Methanol	1.40
2	Ethanol	1.65
3	Acetone	1.85
4	t-Butanol	2.12
5	Dichloromethane	2.20
6	2-Butanone	3.10
7	Ethyl acetate	3.50
8	Chloroform	3.55
9	Benzene	4.75
10	Trichloroethylene	6.01
11	t-Butyl acetate	6.12
12	1,4-Dioxane	6.32

be present in excess of 100 ppm was confirmed by FTIR using the procedure below. These compounds were quantitated by peak area comparison to an external standard of the compound.

Identification by FTIR

A solution of 100 mg captopril in 5.0 ml nitrogen-purged water was placed in the 5-ml fritted disk sparger of the purge and trap apparatus. It was purged at ambient temperature for 4 min with helium (40 ml/min), heated to 80°C over an interval of 2 min, and purged for a further 11 min. The trap was dry purged with helium for 4 min and, with the capillary interface at −150°C, heated to 180°C over a 4-min interval. The temperature of the capillary interface was raised to 220°C over a 0.75-min interval, thus transferring the purged solvents to the gas chromatograph. The latter was operated under the conditions described above. FTIR data were stored at a rate of one full scan/sec, with each scan set containing the average of four interferograms. The Sadtler V8 vapor phase library was searched (Search 32) for matching infrared spectra.

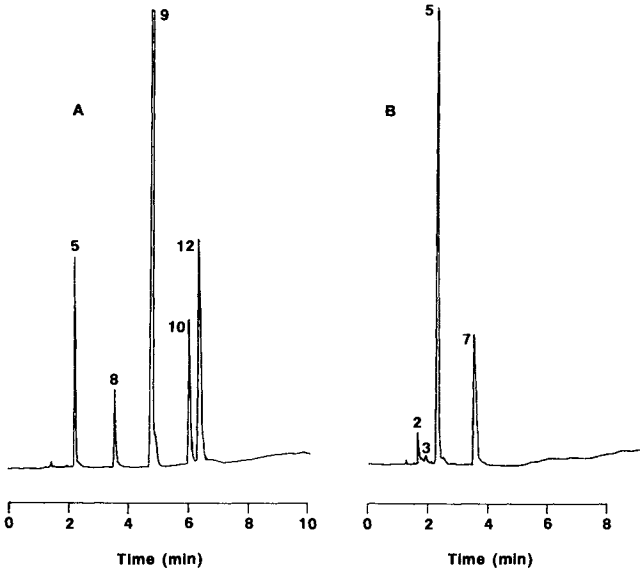

Fig. 1. (A) Chromatogram of a solution containing 10 μg/ml each of chloroform, benzene, 1,4-dioxane, dichloromethane, and trichloroethylene (about 10 times the USP limit). (B) Chromatogram of drug raw material sample A2. The main peaks are dichloromethane and ethyl acetate.

RESULTS AND DISCUSSION

Retention times of five organic volatile impurities controlled by the USP, and several other volatile compounds,

Table II. Volatile Impurities in Captopril Raw Materials (ppm)[a]

Mfr.[b]	1	2	3	4	5	6	7	8	11
A1	50	50	20*		970*	40	600*		
A2		60	15		3550		200		
A3		65		6	1040*		350*		
A4		120	60		2800		130		
A7		230*	770*		2400*				
A8		60	15		600		200		
A9	10	140	40*		3700*	30*	160*		
B1	15		20	90	400*				345*
B2	100			30	500*				250*
B3	40			50*	650*				300*
B4	40		35		1650				270
B5	50				1800				440
C[c]			20		100	30		3150*	140
D1	10	100			1660*		720*		
D2			2200*			70	100*		
E	No organic volatile impurities were detected								

[a] The identity of compounds marked with a superscript asterisk was confirmed by GC/FTIR. Blank spaces indicate that the compound was not detected. Minimum detectable levels were between 3 and 15 ppm, depending on the compound.

[b] Letters refer to manufacturers, and numbers to individual lots.

[c] This sample also contained 45 ppm *n*-propanol.

are listed in Table I, with the codes by which they are designated in subsequent tables. A chromatogram showing the resolution of five USP limited compounds and another of a captopril raw material sample are presented in Fig. 1. Relative standard deviations of the peak responses for each compound were less than 10%.

Sixteen captopril raw material samples were examined for organic volatile impurities. The results in Table II show that 13 of 16 samples examined contain dichloromethane at levels far above the proposed USP limit of 100 ppm (5). One sample contained chloroform, also well above the proposed USP limit, and another contained 2200 ppm acetone. Eleven of the samples do not meet the proposed EP limit of 500 ppm dichloromethane and one does not meet the USP chloroform limit of 50 ppm, as proposed for captopril. Seven samples contain methanol, but none above the proposed EP limit of 1000 ppm.

Table III. Volatile Impurities in Captopril Tablets (ppm)[a]

Mfr.[b]	1	2	3	4	5	6	7	8
TE1	20*							1600*
TE2	20	70			550*		40*	
TE3	40	240	20*		1500*		150*	
TE4	20							1900
TE5	20	100	30	40	800		440	
TE6	20	100	10		1600		510	
TE7	10	110	30		1300		600	
TE8	200	40	10		570		130	
TE9	30	80	10	40	1400		580	
TE11	10	30	30		510		120	
TF1	20	460	30*		1800*	40*	70*	
TF2	10	2600*	40*		1400*	30*	60*	
TF3	30	400	70		1700	20	220	
TF4	20	440			1800	20	240	
TF6	20	780		70	1400	20	230	
TF7	20	930		50	1700	20	230	
TF8	20	680			1260		230	
TG1	20							

[a] As parts per million relative to the labeled amount of drug. The identity of compounds marked with a superscript asterisk was confirmed by GC/FTIR. Blank spaces indicate that the compound was not detected.

[b] Letters refer to manufacturers, and numbers to individual lots.

In the system described in this paper, ethyl acetate and chloroform have similar retention times, 3.50 and 3.55 min, respectively, as do trichloroethylene, t-butyl acetate, and 1,4-dioxane, at 6.01, 6.12, and 6.32 min, respectively. Single column identification procedures are likely to carry a heavy burden of false positives.

Organic volatile impurity levels in 18 tablet products are given in Table III. There are no current or proposed limits for organic volatile impurities in tablets, although there is a USP requirement for methylene chloride in coated tablets (6). Of the tablet products examined, none of which were coated, only one does not contain either dichloromethane or chloroform in excess of the corresponding limits proposed by the USP and the EP for raw materials.

The results presented in this paper support the actions of the USP and the EP in setting limits for organic volatile impurities in drug raw materials. Specifically, they indicate the widespread, but not universal, use of chlorinated hydrocarbons in the manufacture and/or recrystallization of captopril.

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