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Note

High-performance liquid chromatographic determination of terfenadine in commercial tablets

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Terfenadine, α-(4-*tert.*-butylphenyl-4-(α-hydroxyl-α-phenylbenzyl)-1-piperidine butanol, is a new H_1-histamine receptor antasgonist with little or no sedative properties[1,2]. At present, tablets are the only dosage form available in the U.S.A. (Seldane®, 60 mg).

This paper describes the quantitative determination of terfenadine in commercial tablets by a simple and rapid high-performance liquid chromatographic (HPLC) procedure. The only other analytical procedure published in the literature is that involving radioimmunoassay (RIA)[3]. For routine analysis as in quality control, RIA is expensive and time consuming compared to the HPLC assay.

EXPERIMENTAL

Materials

Terfenadine was provided by Merrell-Dow (Cincinnati, OH, U.S.A.) and thiothixene by Mylan Pharmaceuticals (Morgantown, WV, U.S.A.). HPLC grade acetonitrile and methanol, sodium acetate anhydrous and glacial acetic acid were obtained from Fisher Scientific (Pittsburgh, PA, U.S.A.).

Apparatus and HPLC conditions

The HPLC system consisted of a dual-piston, positive-displacement pump (Model M6000A, Waters Assoc., Milford, MA, U.S.A.), an automatic injection module (WISP-710B, Waters Assoc.), a variable-wavelength absorbance detector (Schoeffel 770, Schoeffel Instrument Corp., NJ, U.S.A.) and an electronic integrator (Model 3390 A, Hewlett-Packard).

Chromatographic separations were made on a Waters μBondapak C_{18} reversed-phase column (30 cm × 3.9 mm I.D.).

The mobile phase was 0.05 *M* sodium acetate buffer (pH 5.0)–acetonitrile (1:1), filtered through a nylon 0.45-μm membrane (Schleicher and Schüll). The chromatograph was operated at ambient temperature using a flow-rate of 1 ml/min (3000 p.s.i.). Effluents were monitored at 225 nm. The injection volume was 20 μl.

In order to determine the amount of terfenadine in commercially available tablets, standard curves were constructed from relative peak areas obtained from the integrator.

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Standard solutions

Standard terfenadine solutions were prepared by dissolving accurately weighed amounts of the pure substance in methanol to produce final concentrations of 10–80 μg/ml. All standard solutions contained 10 μg of thiothixene per ml as internal standard. Calibration curves were constructed by plotting ratios of terfenadine to internal standard peak areas against known concentrations of terfenadine.

Terfenadine extraction from tablets

A representative sample, consisting of 20 tablets, was weighed to determine the average tablet weight. One tablet was crushed in a glass mortar to a fine powder. An accurately weighed portion of the powder, equivalent to 50 mg of terfenadine, plus 10 mg of thiothixene were transferred to a 50-ml volumetric flask. Methanol (40 ml) was added to the flask. The sample was stirred for 45 min using a small stir bar and a magnetic stirrer. The stir bar was then removed and the sample flask was brought to volume with methanol. After thorough mixing, an aliquot of the sample solution was transferred to a glass scintillation vial and was centrifuged at 500 *g* for 30 min.

A 500-μl portion of the supernatant was diluted to 10 ml with methanol prior to injection of 20-μl into the chromatograph.

RESULTS AND DISCUSSION

Fig. 1 shows a typical chromatogram of terfenadine and internal standard (thiothixene). For each compound, sharp, symmetrical peaks were obtained with

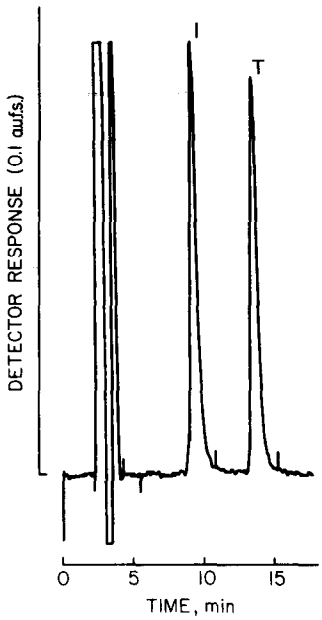

Fig. 1. Chromatogram showing terfenadine (peak T, retention time = 14.50 min) and internal standard, thiothixene (peak I, retention time = 9.84 min).

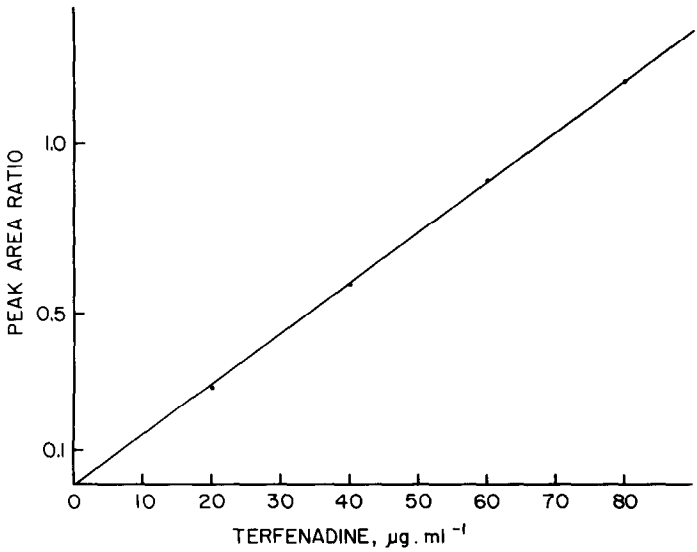

Fig. 2. Typical standard curve for terfenadine.

baseline resolution and minimal tailing. The retention times were 14.68 ± 0.03 min (mean ± S.D.) for terfenadine and 9.93 ± 0.03 min (mean ± S.D.) for internal standard.

A typical standard curve is shown in Fig. 2. Linearity was demonstrated by injecting various amounts of terfenadine over the concentration range 10–80 μg/ml with a constant amount of internal standard (10 μg/ml).

Reproducibility of the standard curve determined for four days is indicated in Table I. Excellent day-to-day reproducibility of the slope of the curve was obtained (C.V. = 2.79%).

Analysis of commercial tablets

The retention times of the suspected terfenadine from the tablet and pure ter-

TABLE I

DAY-TO-DAY REPRODUCIBILITY OF THE SLOPE

Day	*Slope*	*Coefficient of determination*
1	0.0139	0.9993
2	0.0148	0.9999
3	0.0140	0.9995
4	0.0146	0.9998
Mean	0.01433	
S.D.	0.0004	
C.V. (%)	2.79	

TABLE II

ANALYSIS OF COMMERCIAL TABLETS

Tablet number	*Claimed amount (mg/tablet)*	*Obtained amount (mg/tablet)*	*Percent recovery*
1	60	61.04	101.73
2	60	59.66	99.43
3	60	60.89	101.48
4	60	60.54	100.90
5	60	59.90	99.83
Mean			100.67
S.D.			1.01
C.V. (%)			1.00

fenadine were identical. The terfenadine extraction procedure from commercial tablets was excellent with no unidentified peaks in the chromatograms after 20 μl injection of samples. Five commercial tablets were analyzed and the average percent recovery was 100.67 with S.D. 1.01 and C.V. 1.00% (Table II).

In conclusion, the present HPLC assay has been found successful and will be useful for routine analysis as in quality assurance of terfenadine tablets. In addition, this novel assay provides the basis for a rapid, specific and precise quantitative method for the simultaneous determination of terfenadine and its major metabolites in biological samples (work in progress).

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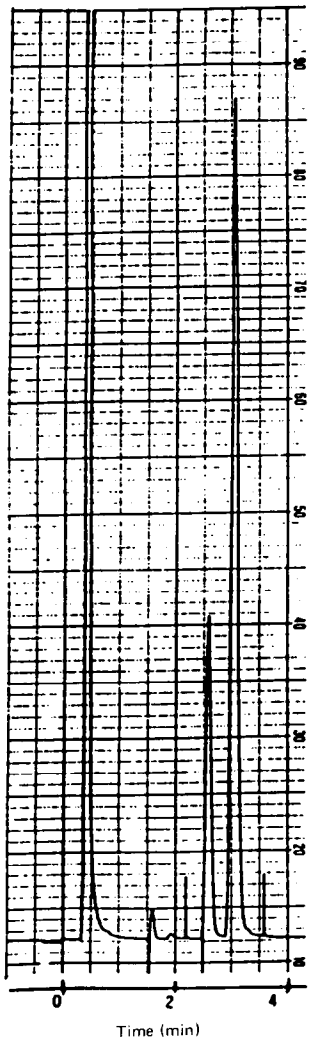

Fig. 2. Gas chromatogram of 5-norbornene-2-carboxaldehyde, a synthetic precursor of cyclothiazide. Column: 6 ft. × 2 mm I.D. glass column containing 10% Carbowax 20M on 80–100 mesh Supelcoport. Column temperature 140°C, injector at 190°C, flame ionization detector at 250°C. Nitrogen carrier gas at 20 ml/min. A 2-μl aliquot of a 0.5 mg/ml solution was injected.

minima and the spectra were superimposable with only minor deviations, supporting the conclusion that these components were stereoisomers[3].

Therefore an attempt was made to separate completely the cyclothiazide components. It was found that cyclothiazide USP could be separated into four components using a Waters Nova-Pak C_{18} (150 × 5 mm I.D.) (steel) column eluted at 1 ml/min with a mobile phase of acetonitrile–tetrahydrofuran–water–acetic acid (18:10:71.7:0.3) and with UV detection at 271 nm. Peak areas of the four components were 34.7, 36.8, 15.2 and 13.1%. The chromatogram is shown in Fig. 1.

The synthesis of cyclothiazide involves the reaction of 4-chloro-6-chloroben-