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ARTICLES

High-Performance Liquid Chromatographic Determination of Simvastatin in Medical Drugs[1]

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Abstract—A simple and rapid HPLC method for the determination of simvastatin using a C18-Hypersil column and acetonitril–phosphate buffer–methanol (5 : 3 : 1, v/v/v) as a mobile phase with detection at 230 nm was proposed. Commercial pharmaceutical tablets were analyzed with a linear range for simvastatin up to 1.884 mg % and a regression coefficient of 0.9995. The method is found to be precise, accurate, reliable, and selective.

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INTRODUCTION

Simvastatin belongs to the statin drug family, the members of which are used as cholesterol-lowering agents for patients with hypercholesterolemia [1]. This semisynthetic drug (Fig. 1) exhibits a very important hepatic first-pass metabolism by inhibiting 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMG-CoA) and reduces low-density lipoproteins [2, 3]. Synthesis of statin compounds is associated with the presence of some impurities that are carried over either from the fermentation process or from the isolation procedure [4]. Therefore, it is required to monitor the quality of these drugs throughout the production process.

Several methods can be employed in separation, purification, and determination of these compounds [5–8]. Traditional analytical methods are time consuming and expensive, as they require large amounts of reagents. Alternatively, chromatographic techniques have potential for economical large-scale purification, as they combine shorter analysis time with high sensitivity and less frequent use of impurity standards [9]. This work aims at the determination of simvastatin using HPLC.

EXPERIMENTAL

Chemicals and reagents. Simvastatin was supplied by Middle East Pharmaceutical Industries Co. Potassium dihydrogen phosphate, HPLC grade, was obtained from Fisher Scientific Co. All solvents used were HPLC grade.

Phosphate buffer (pH 4.5) was prepared by dissolving 3.45 g of potassium dihydrogen phosphate in 900 mL of distilled water and adjusting the pH with potassium hydroxide then completed to 1000 mL by the addition of distilled water. The solvent solution contains buffer and *n*-propanol at a ratio of 2 : 1.

Apparatus. The HPLC system consisted of the following components: a Shimadzu LC-6A liquid chromatograph; a CTO-10A column oven equipped with a Rheody valve 20 μL sample injection loop; a SPD-6AV UV-visible detector; a C-R3A chromatopac integrator; and a C18-Hypersil 250 × 4.6 mm, 5 μm column.

Chromatographic conditions. The isocratic separation was achieved using a C18-Hypersil column (250 × 4.6 mm, i.d. 5 μm packing) supplied by Shimadzu (Japan). A precolumn dry packed with silica gel (Hypersil, city, state, country) was inserted in front of the injector to protect the analytical column. A mobile phase consisting of an aqueous acetonitrile, buffer, and methanol (5 : 3 : 1, v/v/v) was maintained at a flow rate

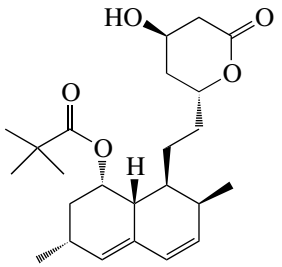

Fig. 1. Structure of simvastatin.

[1] The text was submitted by the authors in English.

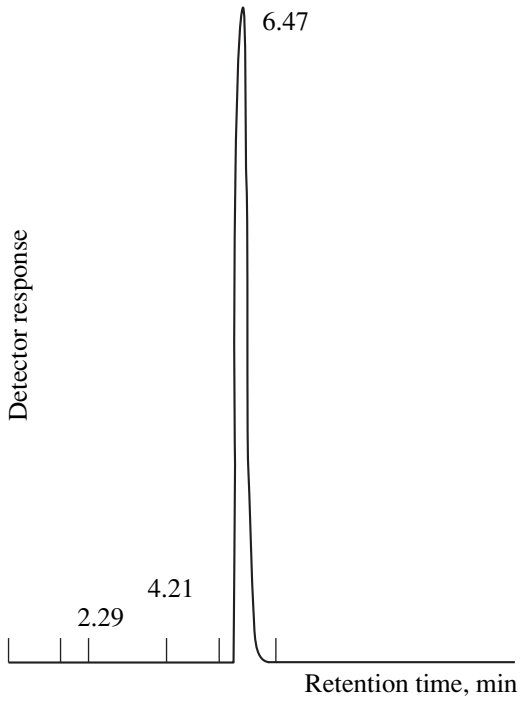

Fig. 2. HPLC chromatogram of simvastatin.

of 2.5 mL/min. The analytes were detected at 230 nm (Fig. 2).

Sample preparation. Tablets containing 10 mg of simvastatin were placed in six mixing vessels, and 900 mL of solvent solution were placed in each vessel at 37 ± 0.5°C. After 60 min of mixing, samples of 10 mL simvastatin solution were taken from each vessel, filtered through a 0.45 μm membrane, and degassed in a sonication water bath (Sharp UT-105) before injection into the chromatograph.

Measurement. Three samples (20 μL) of each standard were injected separately, and the average peak of each sample was recorded as a function of the response areas of simvastatin of the test solution, A_t, and of the standard solution, A_s. The percentage of dissolved simvastatin with respect to labeled amount was calculated as

$$\% \text{ Simvastatin} = 100\left(\frac{A_t}{A_s}\right)\left(\frac{1}{1.1}\right)c_s,$$

where c_s is the concentration of the standard solution (mg/100 g).

RESULTS AND DISCUSSION

Determination of simvastatin in its tablet dosage form using HPLC at 238 nm was tested (Fig. 1). The method was validated taking into account linearity, precision, accuracy, specificity, and sensitivity. Figure 3 shows the calibration curve for a standard solution ranging from 0.6 to 1.8 mg %. The data were correlated

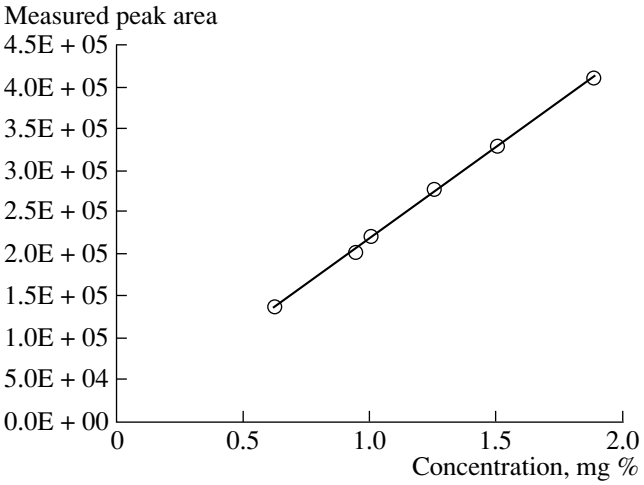

Fig. 3. Calibration curve for simvastatin.

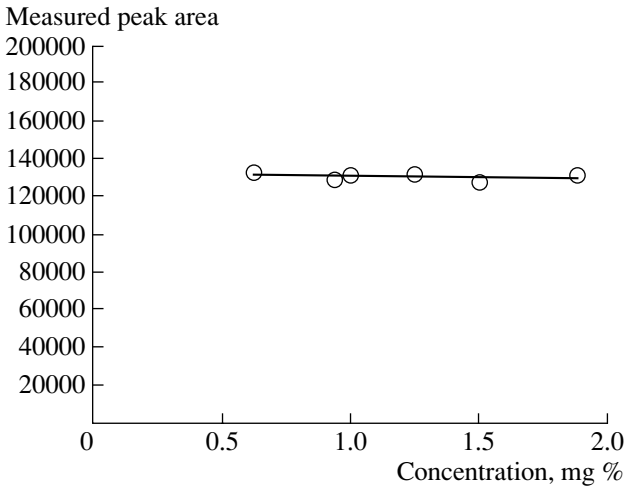

Fig. 4. Repeatability study of simvastatin determination in the standard solution.

using the least squares method with a linearity regression equation of $Y = 270.01x + 218\,936$ and a correlation coefficient of 0.9995.

An assay of precision and accuracy was carried out by analysis of six standard solutions of 0.6 mg % in triplicate. The operating conditions were kept constant over short intervals of time. The standard deviation (SD) and the relative standard deviation (RSD) for these samples were calculated to be 1783.58 and 1.37%, respectively. Intermediate precision was taken into account where interlaboratory variations, such as analysis at different period of times using different instruments by different analysts, were considered (Fig. 4). Table 1 shows the peak areas for six different samples accompanied with their SD and RSD obtained for such variations. It is shown that the RSD was less that 2% for all samples obtained by different persons using different instruments at different periods of time.

Table 1. The effect of variation of measuring times, instruments, and analysts on precision study of simvastatin determination

Sample number	Variation of analysis times ($\times 10^3$)	Variation of instruments ($\times 10^3$)	Variation of analysts ($\times 10^3$)
1	204.9	390.5	204.1
2	205.1	380.7	208.5
3	201.5	380.5	213.6
4	197.8	384.9	211.8
5	200.8	388.7	208.6
6	195.7	381.4	212.9
SD	3.7	4.3	3.6
RSD	1.87%	1.10%	1.71%

Table 2. Accuracy study for simvastatin determination in tablet preparation

% of labeled content	Added content of simvastatin to mixture (mg)	Found content of simvastatin in mixture (mg)	Average	Mean of average recovery (RSD, %)	RSD, %
50	25.0	0.5851	0.5742	96	1.39
		0.5743			
		0.5683			
		0.5723			
		0.5815			
		0.5637			
100	50	1.2560	1.2279	102.33	1.72
		1.2347			
		1.2363			
		1.2331			
		1.2123			
		1.1954			
150	75	1.7865	1.7833	99.1	0.45
		1.7582			
		1.7779			
		1.7835			
		1.7804			
		1.8133			

These results indicate that the method is reliable. The accuracy of the recommended procedure was checked by preparing three mixtures of each excipient and simvastatin containing 50, 100, and 150% of simvastatin. Six replicates were prepared for each mixture, and the results obtained were statistically treated as described in Table 2. It is shown that the RSD ranges from 0.45 to 1.72%. The effects of various compounds on the determination of simvastatin were studied. The specificity of simvastatin was obtained by refluxing with 0.1 N NaOH solution and 10% hydrogen peroxide and was exposed to UV light overnight. It was shown that the peak representing the simvastatin was pure, this purity being verified by a diode array detector.

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