PEER REVIEWED

The Stability of Lisinopril as an Extemporaneous Syrup

Abstract

The stability of lisinopril as an extemporaneous syrup compounded from powder was studied. The lisinopril syrup (2 mg/mL) was prepared by incorporating lisinopril powder dissolved in water into simple syrup. Samples of the syrup were stored in amber-colored plastic bottles at 5 and 23°C. At various times during the 30-day study period, the concentration of lisinopril was determined by a stability-indicating high performance liquid chromatography assay procedure. Samples were also visually inspected for color and clarity. Over the 30-day study period, the percentage of the initial concentration remained between 97.46% and 100.54% for the 23°C samples and 98.15% and 100.74% for the 5°C samples.

Introduction

The angiotensin-converting enzyme (ACE) inhibitors appear to act primarily through the suppression of the renin-angiotensin-aldosterone system. Inhibition of ACE leads to a reduction of peripheral arterial resistance in hypertensive patients, along with an increase in sodium and fluid loss. Additionally, a number of these agents are used in adjunctive therapy in the management of congestive heart failure in patients not responding adequately to diuretics and digitalis. The ACE inhibitor lisinopril is currently only available as a tablet. An alternative dosage form is not an option for patients unable to swallow tablets (ie, infants and patients with carcinoma of the throat or cachexia).[1] The purpose of this study was to investigate the stability of lisinopril in an oral-liquid dosage form at a concentration useful in clinical practice.

Materials

All chemicals used were of reagent grade or better and used without further purification. All water used was distilled and further purified by filtration (Norganic® Filtration Cartridges, Millipore Corporation, Bedford, MA). All solvents were of high-performance liquid chromatography (HPLC) grade. Lisinopril was purchased from Sigma Chemical Co., St. Louis, MO (Lot 73H0893). Syrup was prepared according to a method described elsewhere.[2]

Methods

Preparation and Storage of Solutions

Lisinopril (1 g) was dissolved in distilled water (30 mL). The resultant solution was incorporated into syrup using geometric dilution to a final volume of 500 mL (2 mg/mL). The syrup was divided between six amber plastic prescription bottles. Three sample bottles were stored at 5°C and three at 23°C. Aliquots of each sample bottle were diluted to appropriate concentrations and analyzed in duplicate at time zero, and at 1,2,4,8,12 and 24 hours and on days 2,3,7,14, 21 and 30. Additionally, aliquots of each sample bottle were visually assessed for color and clarity at each sampling time.

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High-Performance Liquid Chromatograph

A fully automated, computer-controlled, HPLC system consisting of the following, from Waters Corporation, Milford, MA: solvent-delivery pump (model 510), refrigerated autosampler (model 712 WISP™), programmable multiple-wavelength detector (model 490E Programmable Multiwavelength Detector) set at 215 nm; and C_8 analytical column (Supelcosil® LC-8 HPLC Column 25 cm x 4.6 mm, 5 mm, Supelco, Inc., Supelco Park, Bellefonte, PA) heated to 40°C was used for the analyses.

Lisinopril concentrations were determined by a modification of a previously published method.[2] The mobile phase consisted of potassium phosphate monobasic (0.03 M) adjusted to pH 4.1 with phosphoric acid and acetonitrile (80:20) with 1-octanesulfonic acid sodium salt (0.004 M). The flow rate was set at 1.5 mL per minute. The bottles were shaken well prior to sampling. Each sample was

Table 1. Stability of Lisinopril 2 mg/mL[a] in Syrup at 23 and 5°C.

	23°C	5°C
Initial Concentration	2.09 ± 0.44	2.09 ± 0.44
1 hour	99.1 ± 1.09[b,c]	99.15 ± .60
2 hours	98.67 ± .75	99.19 ± 1.23
4 hours	98.54 ± .84	98.48 ± .83
8 hours	98.27 ± .82	98.19 ± .45
12 hours	97.88 ± .45	98.15 ± .28
24 hours	99.18 ± 2.5	98.73 ± .76
2 days	99.32 ± .55	98.58 ± .53
3 days	98.41 ± .81	100.12 ± 1.32
7 days	99.82 ± .45	99.92 ± .33
14 days	97.46 ± .41	98.44 ± .46
21 days	100.2 ± .65	98.15 ± .68
30 days	100.54 ± .22	100.74 ± .71

a. Nominal concentration
b. Triplicate samples were prepared and analyzed with duplicate determinations for each (n=6).
c. Percent initial concentration

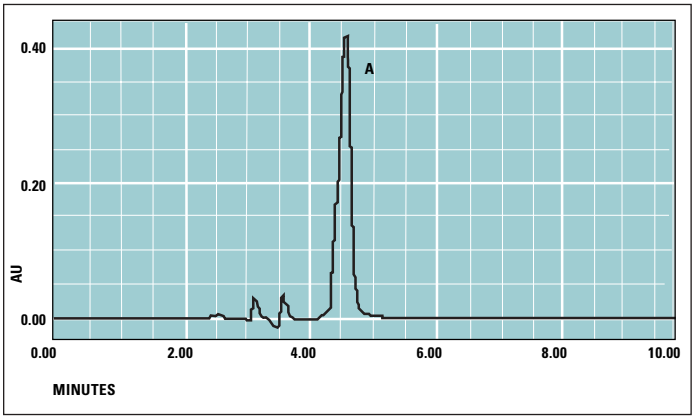

Fig. 1. Representative chromatogram of time-zero injection of lisinopril (A).

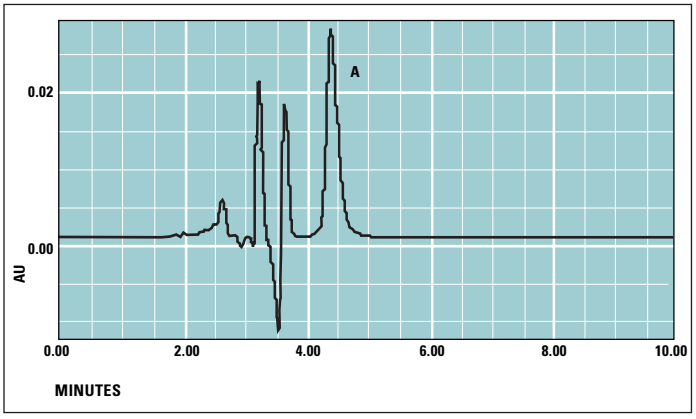

Fig. 2. Representative chromatogram of lisinopril (A) after one hour reflux with concentrated acid.

diluted with water:methanol (4:1) to 0.2 mg/mL, a concentration for which the detector signal was established to respond linearly (Fig. 1). A five-point standard curve was constructed daily using drug concentrations of 0.05 to 0.4 mg/mL, which demonstrated linearity (r^2 = 0.998). Sample concentrations were determined by inserting the computer-integrated peak areas for the samples into the regression equation generated by the standard curve. The standard error of the mean for replicate injections of the same sample or standard solution was less than 4%.

Evidence of noninterference by degradation products with the sample peaks was obtained. Aqueous solutions of lisinopril (2 mg/mL) and lisinopril in syrup (2 mg/mL) were prepared. One milliliter of each solution was diluted 1:5 with 0.1 M sodium hydroxide solution, and a second milliliter of each was diluted 1:5 with 0.05 M sulfuric acid. Each of the resultant solutions was heated under reflux conditions for one hour, and 20-mL samples of each were then assayed. In all cases there appeared to be no interfering peaks from degradation products (Fig. 2).

Data Analysis

Individual determinations for each drug after time zero were reported as percentages of the initial mean concentration. Stability was defined as the retention of >95% of the initial concentration of the drug.

Results

None of the samples formed a visible precipitate or changed in color or clarity. Over the 30-day study period, the percentage of the initial concentration remained between 97.46% and 100.54% for the room temperature samples and 98.15% and 100.74% for the refrigerated samples (Table 1).

Conclusions

Lisinopril when incorporated into syrup (2 mg/mL) is stable at both 23 and 5°C for 30 days. It is the recommendation of the authors that, even though no microbial growth was observed, the product should be stored at 5°C to inhibit microbial growth.

References

1. Kaplan S. New drug approaches to the treatment of heart failure in infants and children, *Drugs* 1990; 39:388-393.
2. *United States Pharmacopeia XXIII/National Formulary 18*. United States Pharmacopeial Convention, Inc., Rockville, MD, 1995 pp 895-896, 2314.