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Development and validation of a stability indicating HPLC method for determination of lisinopril, lisinopril degradation product and parabens in the lisinopril extemporaneous formulation

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Abstract

The purpose of the research described herein was to develop and validate a stability-indicating HPLC method for lisinopril, lisinopril degradation product (DKP), methyl paraben and propyl paraben in a lisinopril extemporaneous formulation. The method developed in this report is selective for the components listed above, in the presence of the complex and chromatographically rich matrix presented by the Bicitra® and Ora-Sweet SF™ formulation diluents. The method was also shown to have adequate sensitivity with a detection limit of 0.0075 μg/mL (0.03% of lisinopril method concentration). The validation elements investigated showed that the method has acceptable specificity, recovery, linearity, solution stability, and method precision. Acceptable robustness indicates that the assay method remains unaffected by small but deliberate variations, which are described in ICH Q2A and Q2B guidelines.

Keywords: HPLC; Lisinopril; Methyl paraben; Propyl paraben; Degradation product quantitation; Method development; Method validation; Extemporaneous

1. Introduction

Lisinopril ((*S*)-1-[N^2-(1-carboxy-3-phenylpropyl)-L-lysyl]-L-proline dihydrate, molecular formula: $C_{21}H_{31}N_3O_5{\cdot}2H_2O$) is an orally active angiotensin-converting enzyme (ACE) inhibitor used for the treatment of hypertension, heart failure, and acute myocardial infarction [1]. It is currently supplied as 2.5, 5, 10 and 20 mg tablets designated as PRINIVIL® (a product of Merck & Co. Inc.) and ZESTRIL® (a product of AstraZeneca UK Limited). Recent studies have been completed in pediatric patients using an extemporaneous formulation of lisinopril prepared from 20 mg ZESTRIL® or PRINIVIL® tablets [2]. The development of this extemporaneous formulation allows physicians to adjust the dose for pediatric patients and provides for a more convenient dosage vehicle for those patients with difficulty swallowing tablets. The extemporaneous formulation was prepared from 20 mg PRINIVIL® or ZESTRIL® tablets in the presence of two syrups (formulation diluents): Bicitra® (NDC 17314-9330-1) and Ora-Sweet SF™ (NDC 0574-0302-16) [3].

There are numerous methods to quantify lisinopril in single component or multicomponent tablets, including spectrophotometry [4–6], high performance liquid chromatography (HPLC) [7,8], capillary electrophoresis [9], gas–liquid chromatography (GLC) [10], and polarographic [11]. The polarographic method can additionally be used for the determination of lisinopril in biological fluids along with radioimmuno-assay [12] and a method utilizing optical density measurements [13]. Spectroscopic and spectrofluorometric methods can provide low levels of detection on the order of 0.1%, however, they are not selective for lisinopril degradation products. One of the advantages of HPLC/UV is that methods can be selective and sensitive [14,15].

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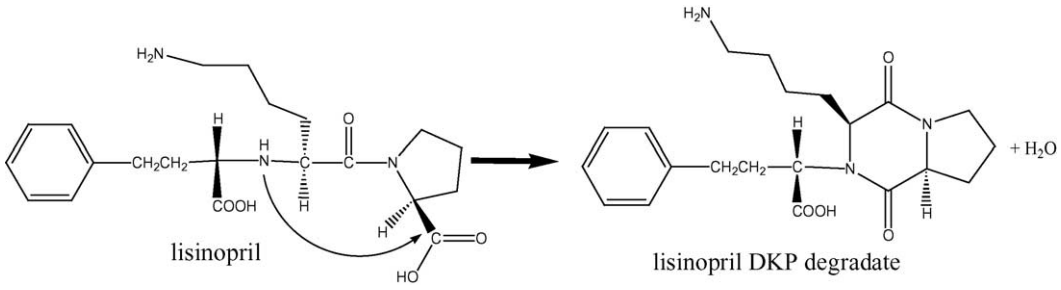

Fig. 1. Structures of lisinopril and lisinopril DKP degradation product.

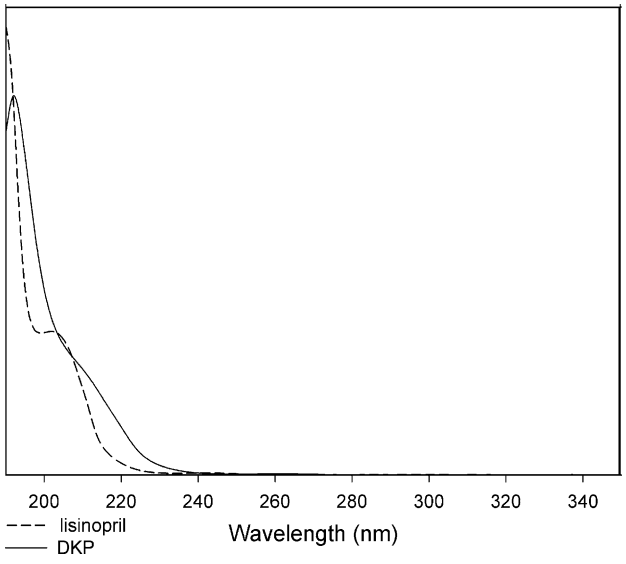

Fig. 2. On-line UV spectra for lisinopril (30 μg/mL) and DKP (73 μg/mL) in 91:9 30 mM KH_2PO_4 (pH 2.2):acetonitrile, 10 mm cell pathlength. *Note*: no UV features for either lisinopril or DKP were observed past 260 nm.

It is well known that, the primary degradation product for lisinopril is lisinopril DKP (DKP), which occurs through an intramolecular condensation (Fig. 1) [16]. The UV–vis spectrum of the lisinopril DKP degradation product exhibits a slight red shift relative to the lisinopril parent molecule (Fig. 2). The observed red shift is attributed to the formation of a second amide bond in lisinopril DKP.

2. Experimental

2.1. Chemicals and reagents

PRINIVIL® and ZESTRIL® tablets were manufactured by Merck & Co. Inc. (Whitehouse Station, NJ, USA) and AstraZeneca UK Limited (London, UK), respectively. Lisinopril standard (Merck & Co. Inc.), methyl paraben (Aldrich) and propyl paraben (Aldrich) were used as received. Ora-Sweet SF™ was manufactured by Paddocks Labs (St. Paul, MN, USA). Bicitra® was manufactured by Alza Pharmaceuticals (Mountain View, CA, USA). Water was obtained from an in-house USP-quality water purification system. USP water is defined as purified water obtained by distillation, ion-exchange treatment, reverse osmosis, or other suitable process and complies with regulations of the U.S. Environmental Protection Agency with respect to drinking water [1]. Reagents and solvents used were HPLC grade or USP-NF grade and were used without further purification.

2.2. Equipment

2.2.1. Instruments

The HPLC system consisted of an Agilent (Wilmington, DE, USA) 1100 series HPLC quaternary pump G1311A, Agilent 1100 series diode array detector (DAD) G1315A with a 10 mm pathlength cell, Agilent G1316A column heater and Agilent Degasser G1322A.

2.2.2. Analytical columns

Analytical columns investigated were the Alltech (Deerfield, IL, USA) Platinum EPS C8 (250 mm × 4.6 mm i.d., 5 μm), Mac-Mod Hydrobond AQ C8 (150 mm × 4.6 mm i.d., 5 μm) and a Hewlett-Packard RP-8 Licrosorb (200 mm × 4.6 mm i.d., 10 μm).

2.2.3. Chromatographic conditions

Mobile phase flow rate was 1.0 mL/min. Detection wavelength was 215 nm to maximize sensitivity for DKP relative to lisinopril, since DKP amounts are several orders of magnitude lower. Mobile phases contained varying compositions of potassium phosphate dibasic monohydrate and acetonitrile.

2.3. Preparation of solutions

All samples and standards were diluted using potassium phosphate buffer (pH 2.2, 30 mM):acetonitrile (91:9, v/v).

2.3.1. Preparation of standards

Lisinopril DKP stock standard solution was prepared by accurately weighing ∼9 mg into a 100 mL volumetric flask and then diluting to the mark with potassium phosphate buffer (30 mM, pH 2.2):acetonitrile (91:9, v/v). Methyl paraben and propyl paraben stock standard solutions were prepared by accurately weighing ∼15 and ∼10 mg separately into 25 mL volumetric flasks, respectively. Each paraben was initially dissolved in 5 mL of acetonitrile then diluted to volume with

water. Lisinopril working standard solutions were prepared by accurately weighing approximately 17 mg of standard into a 500 mL volumetric flask, then dissolving in approximately 300 mL of potassium phosphate buffer (30 mM, pH 2.2):acetonitrile (91:9, v/v). An amount of 2.0 mL lisinopril DKP, 10 mL of methyl paraben, and 4 mL of propyl paraben stock standard solutions were then transferred to the 500 mL volumetric flask, followed by dilution to volume with potassium phosphate buffer (30 mM, pH 2.2):acetonitrile (91:9, v/v).

2.3.2. Preparation of placebo and sample solutions

Placebo sample solutions were prepared by placing 10 lisinopril placebo tablets in a 200 mL poly(ethylene terephthalate) bottle. Next, 10 mL of USP H_2O was added followed by shaking for one minute to disperse the tablets. Finally, 30 mL of Bicitra® and 160 mL of Ora-Sweet SF™ were added to the bottle followed by gentle shaking for 30 s.

Pediatric sample solutions were prepared by substituting Zestril® or Prinivil® tablets in place of placebo tablets.

2.3.3. Preparation of system suitability solution

System suitability solution was prepared by diluting 1.0 mL of the placebo solution to 50 mL using a solution containing lisinopril (30 μg/mL) and lisinopril degradation product (DKP) (0.36 μg/mL).

3. Results and discussion

3.1. Methods development and optimization

The method developed herein was used for the simultaneous determination of lisinopril at 25 μg/mL and DKP at the 0.025 μg/mL. The initial method investigated is that developed for lisinopril tablets to quantify lisinopril and lisinopril DKP [1]. A mixture of lisinopril and DKP standard chromatographed according to this method illustrates two primary peaks (Fig. 3), namely lisinopril (∼8 min) and DKP (∼18 min).

Table 1
Compositions of Ora-Sweet SF™ and Bicitra®

Ora-Sweet SF™	Bicitra®
USP H_2O	Sodium citrate
Glycerin	Citric acid
Sorbitol	USP H_2O
Sodium saccharin	
Xanthan gum	
Methyl paraben	
Propyl paraben	
Potassium sorbate	
Citric acid	
Sodium citrate	
Flavoring	

The lisinopril extemporaneous formulation involves dispersing lisinopril tablets in Ora-Sweet SF™ and Bicitra® to form 1.0 mg/mL lisinopril suspensions. The compositions of Bicitra® and Ora-Sweet SF™ are shown in Table 1.

As expected, many peaks attributable to the suspension diluent are present in the first 40 min window of the lisinopril tablet method. This chromatogram exhibited eight peaks over 0.05% (Fig. 4), four of that are readily identified as sodium citrate (∼2.5 min), citric acid (∼4 min), methyl paraben (∼18 min) and propyl paraben (∼35 min) by spiking in authentic samples of each component. Overlaying these two chromatograms (Fig. 5) shows that a Bicitra®/Ora-Sweet SF™ component co-elutes with lisinopril and that DKP co-elutes with methyl paraben.

Therefore, it was necessary to develop a new method in order to achieve the desired selectivity for lisinopril and DKP. Selectivity for methyl parben and propyl paraben was also desired to gauge the chemical stability of these two preservatives.

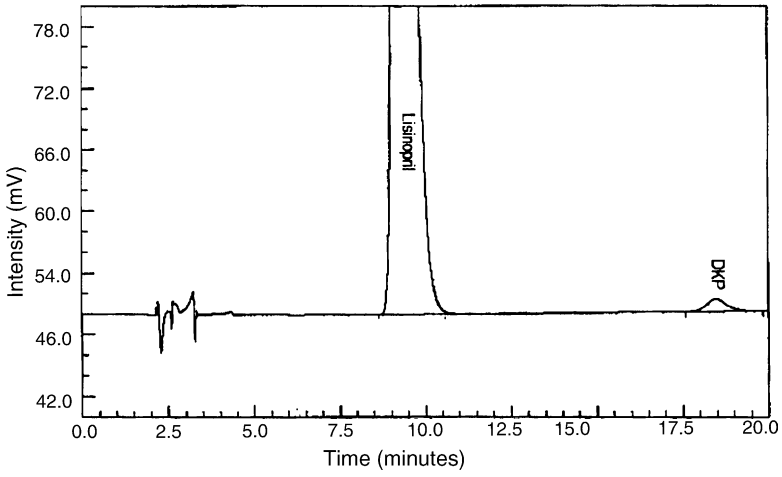

Fig. 3. Chromatogram of lisinopril (30 μg/mL) and DKP (0.03 μg/mL) standard run by the method in [1]: Hewlett-Packard RP-8 Lichrosorb (200 mm × 4.6 mm i.d., 10 μm). Potassium phosphate buffer (pH 2.2, 30 mM):acetonitrile (82:18, v/v), 1.0 mL/min, 20 μL injection volume, 40 °C column temperature, 215 nm detection wavelength.

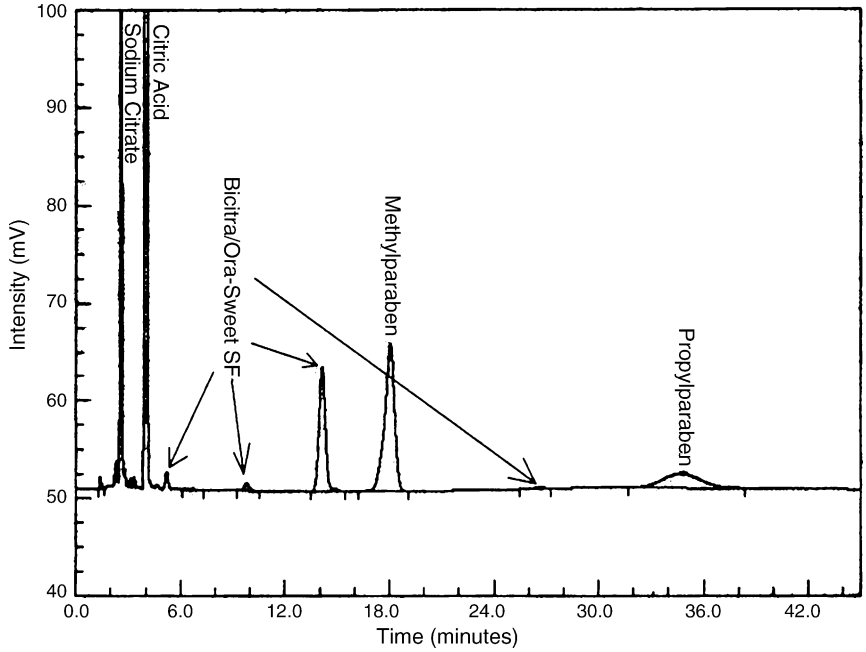

Fig. 4. Chromatogram of Bicitra® and Ora-Sweet SF™ (method concentration) run by method in [1]: Hewlett-Packard RP-8 Lichrosorb (200 mm × 4.6 mm i.d., 10 μm), potassium phosphate buffer (pH 2.2, 30 mM):acetonitrile (82:18, v/v), 1.0 mL/min, 20 μL injection volume, 40 °C column temperature, 215 nm detection wavelength.

The initial changes to the method focused on resolving lisinopril and DKP from an unknown component of the Ora-Sweet SF™/Bicitra® mixture and methyl paraben, respectively. As expected, the early eluting components were found to be very sensitive to changing acetonitrile composition. The retention of Ora-Sweet SF™/Bicitra® components increased significantly with decreasing acetonitrile concentration. The retention of lisinopril was relatively unaffected by decreasing acetonitrile concentration, thus before resolution between the co-eluting component and lisinopril was achieved, many of

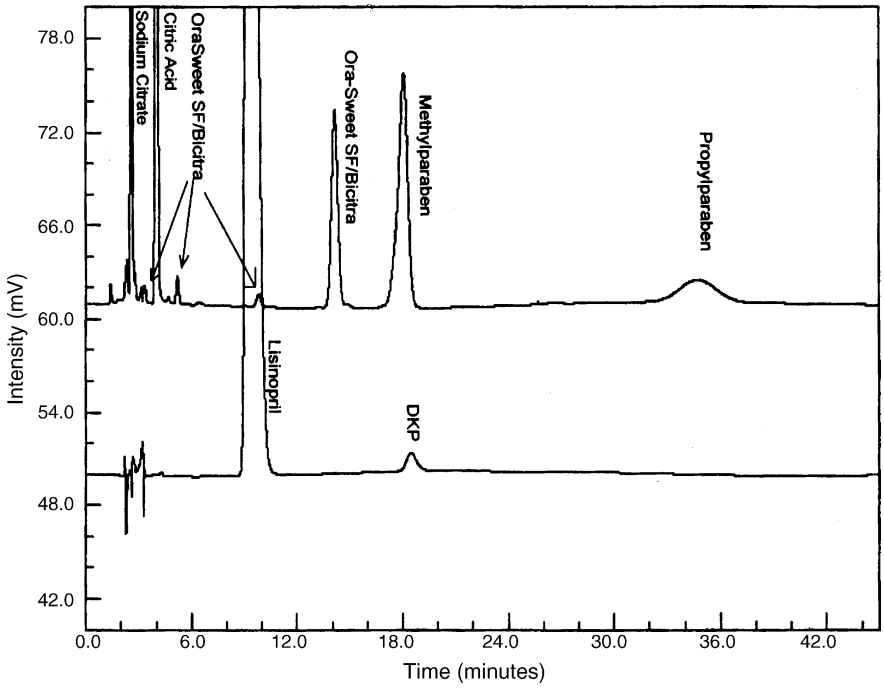

Fig. 5. Overlay of Bicitra/Ora-Sweet SF and lisinopril/DKP standard by the method in [1]: Hewlett-Packard RP-8 Lichrosorb (200 mm × 4.6 mm i.d., 10 μm), potassium phosphate buffer (pH 2.2, 30 mM):acetonitrile (82:18, v/v), 1.0 mL/min, 20 μL injection volume, 40 °C column temperature, 215 nm detection wavelength.

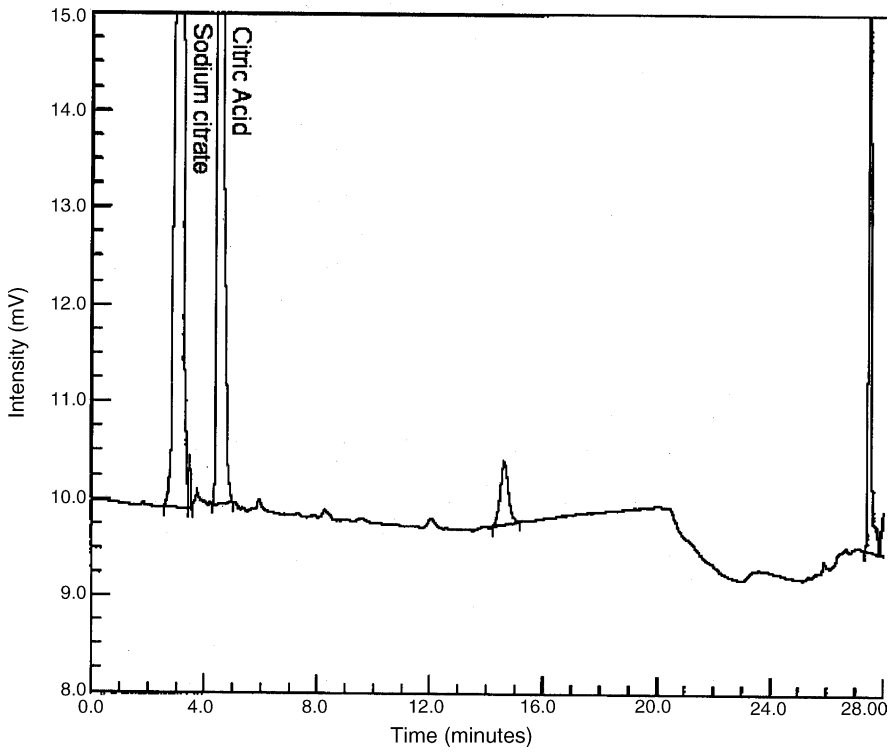

Fig. 6. Chromatogram of Bicitra®: Alltech Platinum EPS C8 (150 mm × 4.6 mm i.d., 5 μm) mobile phase A: potassium phosphate buffer (pH 2.2, 30 mM):actonitrile (91:9, v/v); mobile phase B: acetonitrile, at 16 min ramp B 5%/min for 9 min, then hold for 10 min, 1.0 mL/min, column temperature 40 °C, injection volume 20 μL, 215 nm detection wavelength.

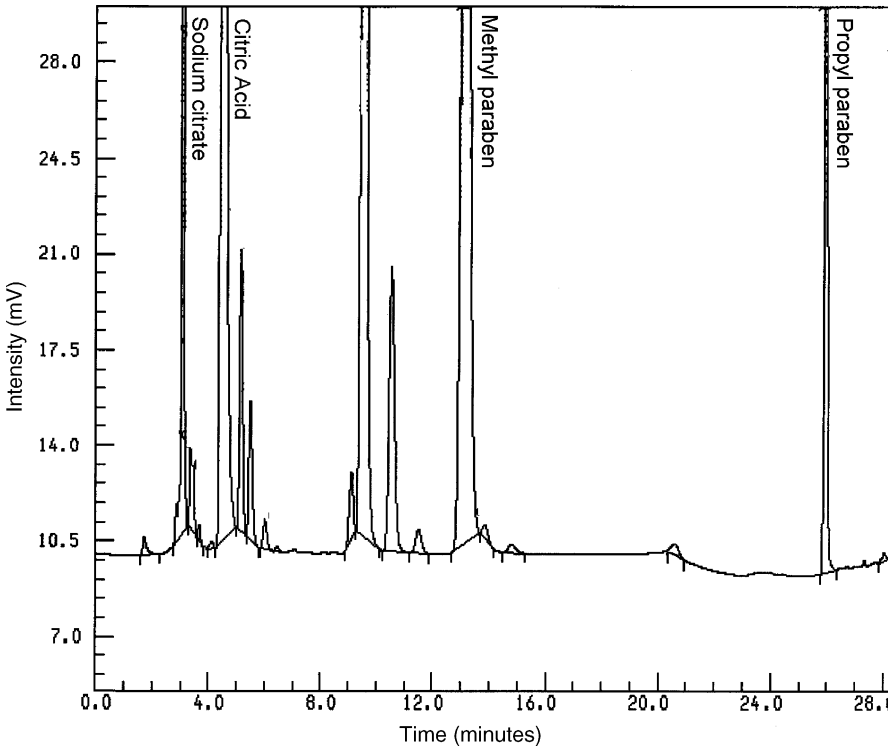

Fig. 7. Chromatogram of Ora-Sweet SF™: Alltech Platinum EPS C8 (150 × 4.6mm i.d., 5 μm) mobile phase A: potassium phosphate buffer (pH 2.2, 30 mM):acetonitrile (91:9, v/v); mobile phase B: acetonitrile, at 16 min ramp B 5%/min for 9 min then hold for 10 min, 1.0 mL/min, column temperature 40 °C, injection volume 20 μL, 215 nm detection wavelength.

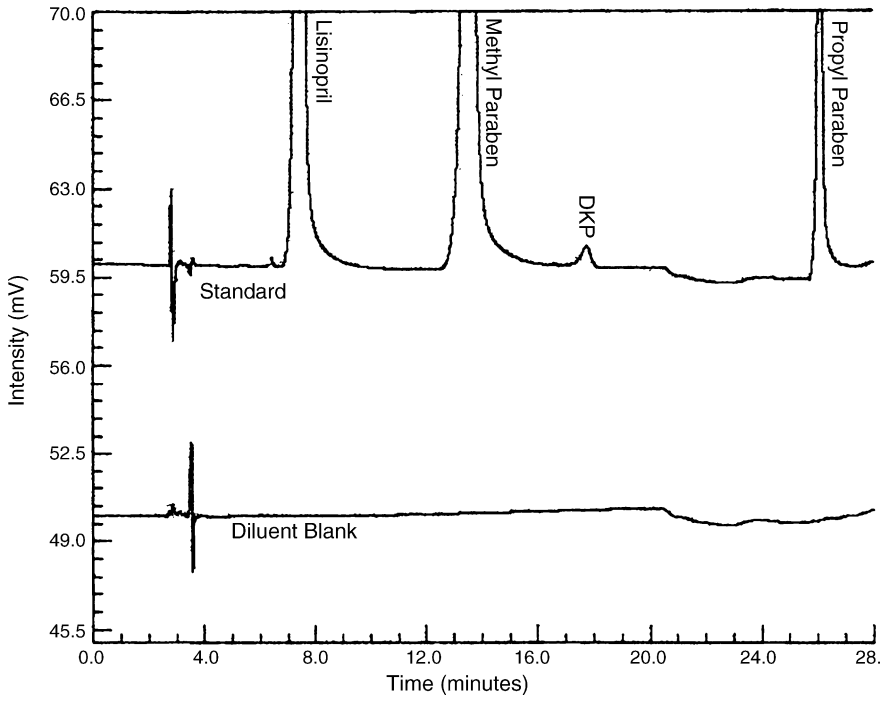

Fig. 8. Chromatogram of standard (top) and diluent blank (potassium phosphate buffer (pH 2.2, 30 mM):acetonitrile (91:9, v/v), bottom): Alltech Platinum EPS C8 (150 mm × 4.6 mm i.d., 5 μm) mobile phase A: potassium phosphate buffer (pH 2.2, 30 mM):acetonitrile (91:9, v/v), at 16 min ramp B 5%/min for 9 min then, hold for 10 min, 1.0 mL/min, column temperature 40 °C, injection volume 20 μL, 215 nm detection wavelength.

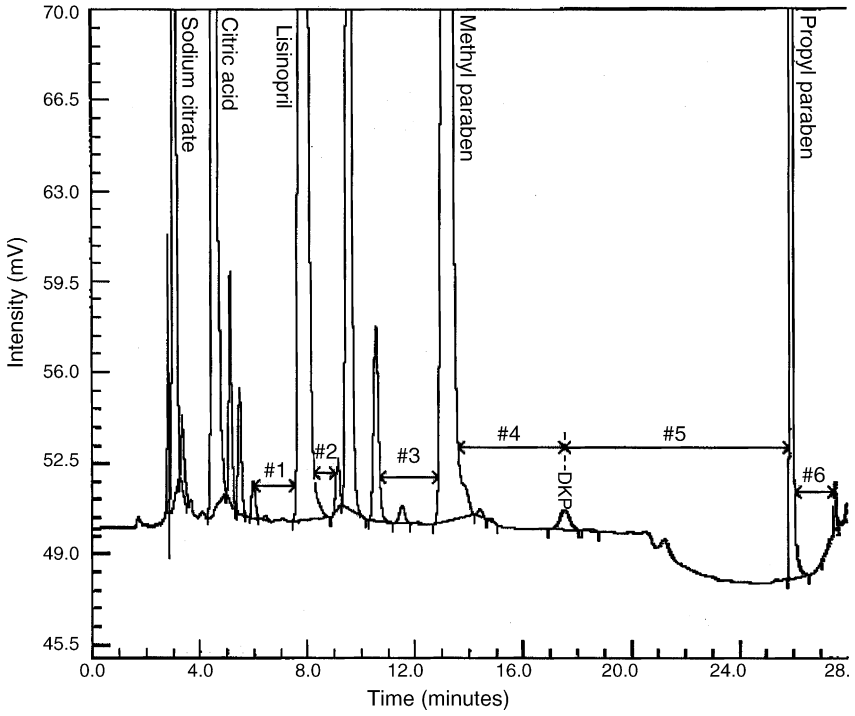

Fig. 9. Component mixture: Alltech Platinum EPS C8 (150 mm × 4.6 mm i.d., 5 μm) mobile phase A: potassium phosphate buffer (pH 2.2, 0.030 M):acetonitrile (91:9, v/v); mobile phase B: acetonitrile, at 16 min ramp B 5%/min for 9 min then hold for 10 min, 1.0 mL/min, column temperature 40 °C, injection volume 20 μL, 215 nm detection wavelength.

the early eluting components started co-eluting with lisinopril.

The inability to resolve the components of interest on the Licrosorb RP-8 column suggested the need to look at the other stationary phases with increased polarity. Two different columns, a Mac-Mod Hydrobond AQ C8 (150 mm × 4.6 mm i.d., 5 μm) and Alltech Platinum EPS C8 (150 mm × 4.6 mm i.d., 5 μm) were first screened to examine retention of lisinopril, DKP, methyl paraben and propyl paraben. Both columns showed adequate retention of DKP, methyl paraben and propyl paraben but the Hydrobond AQ showed poor retention of lisinopril. Consequently, development on this column was stopped while development on the Platinum EPS C8 continued. The desired selectivity for lisinopril, methyl paraben and DKP was accomplished using isocratic conditions and lowering the acetonitrile content in the mobile phase from 18 to 9%. Subsequently, the elution of propyl paraben from the column was expedited using a gradient (linear, 9–54% over 9 min) to shorten the method run time.

Injecting Bicitra® according to the modified method showed five peaks, two of which are attributable to sodium citrate (∼3 min) and citric acid (∼5 min) (Fig. 6). Injecting Ora-Sweet SF shows an additional 16 peaks (Fig. 7), four of which are attributable to sodium citrate (∼3 min), citric acid (∼5 min), methyl paraben (∼14 min) and propyl paraben (∼26 min). Injecting a solution mixture of the components of interest (Fig. 8) also identifies lisinopril (∼7 min) and DKP (∼18 min). Finally, an injection of a mixture of OraSweet SF™, Bicitra®, lisinopril, and DKP (Fig. 9) shows the adequate selectivity achieved for lisinopril, methyl paraben, DKP, and propyl paraben from the extemporaneous solution components.

Thompson et al. reported on the stability of an extemporaneous preparation of lisinopril using the method discussed herein [17]. Several stability studies were carried out on the formulation preparations. The first study involved placing extemporaneous preparations at 25 °C/35% RH for a period of 6 weeks. Samples were taken at 0, 1, 2, 4, and 6 weeks. The second study was a photostability study, carried out by exposing the extemporaneous preparation to full International Conference on Harmonization stressing conditions (a minimum of 1.2 million lux-hours of visible light, followed by a minimum of 200 Wh/m^2 of ultraviolet light). The final study carried out on the extemporaneous preparation was an in-use stability study, were samples are repeatedly taken from the same preparation, stored at 25 °C/60% RH, over a period of 4 weeks. This final study simulated actual usage by patients. All three studies concluded that for lisinopril, methyl paraben, and propyl paraben there were no significant differences over the lifetime of the studies. A 0.1% increase in DKP was observed for the extemporaneous preparations after 6 weeks at 25 °C/35% RH and also for the in-use study. These data confirm that, the method developed can adequately assess the chemical stability of the lisinopril extemporaneous formulation.

Table 2
Summary of accuracy, recovery and linearity data for lisinopril and DKP

Lisinopril		DKP	
Approximate level	Mean	Approximate level	Mean
50	99.2	0.1	104.1
75	99.2	0.5	103.7
100	99.0	0.7	108.5
125	99.0	1.0	105.5
150	99.3	1.5	106.1
Correlation coefficient (R)	Slope	Correlation coefficient (R)	Slope
1.00	0.992	1.00	1.06

3.2. Method validation

3.2.1. Selectivity

The diluent blank (potassium phosphate buffer (pH 2.2, 30 mM):acetonitrile (91:9, v/v)) chromatogram (Fig. 8, bottom), Bicitra® chromatogram (Fig. 6), and Ora-Sweet SF™ chromatogram (Fig. 7) show that there are no placebo peaks co-eluting with either lisinopril or DKP. Two small peaks elute on the tail of methyl paraben, however, these peaks contribute to less than 0.3% of the total area for methyl paraben and are therefore considered to be neglibible for the purpose of this method. This method is selective for lisinopril, DKP, methyl paraben and propyl paraben in the Bictra® and OraSweet SF™ matrix.

3.2.2. Accuracy

Method accuracy was determined by spiking placebo-based solutions with lisinopril and determining recovery. Five levels with concentrations ranging from approximately 50 to 150% of method concentration for lisinopril (25 μg/mL) were prepared in duplicate. Recoveries for lisinopril ranged from 98.6 to 99.8% with a mean of 99.1% and an R.S.D. of 0.3%. Table 2 lists these recovery values. Accuracy for DKP was also performed in a similar manner with concentrations ranging from approximately 0.1 to 1.5% of method concentration for lisinopril. Recoveries for DKP ranged from 102.9 to 105.5% with a mean of 104.1% and a R.S.D. of 0.8%. Table 2 also lists these recovery values.

3.2.3. Linearity and sensitivity

Response for the detector was determined to be linear over the range of 12.5–37.5 μg/mL (50–150% of method concentration for lisinopril) and 0.025–0.375 μg/mL (0.1–1.5% of method concentration for lisinopril) for DKP. Correlation coefficients, and slopes were obtained by plotting theoretical concentration versus actual concentration for both lisinopril and DKP (Table 2). Signal-to-noise ratios for a 0.1% solution typically ranged from 13 to 20.

Response for the detector was also determined to be linear for both parabens across the range of 50–150% of method concentration. Correlation coefficients, and slopes were obtained by plotting percent of method concentration versus

Table 3
Recovery and linearity data for methyl paraben and propyl paraben

Methyl paraben		Propyl paraben	
Approximate level	Mean	Approximate level	Mean
50	95.5	50	91.2
75	95.7	75	93.0
100	95.5	100	91.9
125	95.5	125	92.6
150	95.1	150	91.5
Correlation coefficient (R)	Slope	Correlation coefficient (R)	Slope
1.00	0.949	1.00	0.917

percent measured for both components. Correlation coefficients for both methyl paraben and propyl paraben were greater than 0.999. Slopes for methyl paraben and propyl paraben were 0.9494 and 0.9172, respectively. Table 3 summarizes these data.

3.2.4. Ruggedness

Method ruggedness was demonstrated by having two analysts perform assay testing on three separate lots of Zestril® tablets and three separate lots of Prinivil® tablets. Each analyst prepared samples in duplicate and used separate instruments, reagents, diluent, and mobile phase solutions. R.S.D.s ($n = 4$) for all of the samples for each lot were less than 2.0% indicating acceptable robustness. Table 4 summarizes these data.

Table 4
Summary of ruggedness data

Tablet lot	Label claim lisinopril (%)		R.S.D. ($n = 4$) (%)
	Analyst 1	Analyst 2	
Prinivil® J8227	103.8	101.6	1.9
	104.5	100.3	
Prinivil® K5612	99.6	100.8	0.6
	100.6	100.7	
Prinivil® K6156	101.6	100.0	0.8
	101.5	100.5	
Zestril® CSH871	101.6	103.1	0.7
	102.0	101.4	
Zestril® CSJ281	101.8	102.8	0.4
	102.0	102.2	
Zestril® CSJ151	101.3	102.2	0.8
	100.7	100.5	

3.2.5. Robustness

Method robustness was performed by making small incremental changes to buffer ionic strength, pH, column temperature and acetonitrile concentration. Column to column variability was also investigated using two new columns each from a different lot and one old column (>1 year old). System suitability solution and placebo solutions were then run after these changes were made.

Six critical resolution pairs were identified and numbered for this method (numbered 1–6 in Fig. 9). Resolution

Table 5
Summary of minimum resolution values for method robustness testing

Method parameter	Lisinopril (critical separation)[a]	Methyl paraben[a]	DKP (critical separation)[a]	Propyl paraben[a]
Column				
35 °C	4.96	4.43	7.73	10.44
Temperature (°C)				
40	3.56	4.21	4.54	9.08
45	3.70	3.94	8.72	11.48
pH				
2.0	4.02	4.29	4.77	9.46
2.2	3.56	4.21	4.54	9.08
2.4	3.42	4.04	5.40	9.54
Ionic strength (mM)				
20	2.83	4.25	10.02	10.89
30	3.56	4.21	4.54	9.08
40	4.78	4.14	7.72	10.89
CAN (%)				
7	2.72	4.07	16.59	9.81
9	6.05	4.21	4.54	9.08
11	4.76	4.35	5.60	11.85
Column batch				
#1	3.79	4.07	8.06	10.80
#2	3.56	4.21	4.54	9.08
#3	3.16	4.35	8.24	11.99

[a] Resolution was defined as, $R_s = \frac{2[(t_R)_B - (t_R)_A]}{W_A + W_B}$, where $(t_R)_B$ is the retention time of peak B, $(t_R)_A$ the retention time of peak A, W_A and W_B are the widths for peaks A and B, respectively [1].

of methyl paraben with the component eluting at approximately 11.4 min and also those peaks eluting on the tail of methyl paraben not considered critical to the intended use of this method. Bias introduced by these peaks co-eluting with methyl paraben was less than 0.3%. Likewise, the resolution between DKP and the component eluting at approximately 18.5 min was also not considered critical since the response of Ora-Sweet SF 14 was insignificant relative to DKP.

A summary of the method alterations is provided in Table 5. All critical separations were achieved with the indicated minimum baseline resolution.

4. Conclusion

An HPLC method has been developed and validated and found to be acceptable for the quantitation of lisinopril, DKP, methyl paraben and propyl paraben in lisinopril pediatric samples prepared with Bicitra® and Ora-Sweet SF™ diluents. The method is able to monitor down to 0.025 μg/mL (0.10% relative to lisinopril) levels of the key degradate (DKP) and thus is suitable for assessing the extemporaneous formulation stability as evidenced by the stability studies discussed by Thompson et al.

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