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The development and stability assessment of extemporaneous pediatric formulations of Accupril

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Abstract

Quinapril, the active ingredient in Accupril® tablets, is an ACE inhibitor used to treat hypertension. Quinapril is unstable in aqueous solution and therefore the development of a liquid formulation is a significant challenge. Previous studies show the rate of degradation of quinapril into its two major degradants to be pH dependent, indicating the parent compound to be most stable in the narrow pH range of 5.5–6.5. Accupril (20 mg) and readily available pharmaceutical components were combined to generate three formulations that are stable for at least 28 days, possess acceptable appearance, and are palatable to pediatric patients. To combat the presence of magnesium carbonate in the Accupril tablets, which increase the pH of the solution above 6.5, several pharmaceutically available buffers were incorporated. Nine prototypes were developed and their characteristics evaluated after 1 week under stressed conditions. The three that most closely matched the stability criteria were chosen for a definitive stability study. A stability-indicating method was developed and validated for these studies. All three formulations met the following specifications when stored at 5 °C for 6 weeks; Quinapril remained ≥90% intact and the two known degradants did not reach values ≥3.0% individually or ≥5.0% combined.

Keywords: Accupril; Excipients; Quinapril hydrochloride; Pediatric; Stability; Extemporaneous formulation

1. Introduction

Recently, attention has been drawn to the need for pediatric formulations of marketed drugs (Farrar et al., 1996; Wells, 1996; CDER, 2000; Nahata, 1999). Clinical studies adequate for pediatric labeling of drugs are often more costly, pose patient recruitment challenges, encompass unique ethical and practical issues and involve greater potential liability than comparable studies carried out in adult populations (Farrar et al., 1996; Wells, 1996; Nahata et al., 1998). As a

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result the 'off-label' use of pharmaceutics in children is widespread because few alternatives exist. The problem not only exists in the labeling of marketed drugs for the pediatric population, but also in the lack of suitable formulations. It is difficult or impossible for children and infants to swallow the solid dosage forms of most marketed compounds. Furthermore, dosing is an issue, as most commercially available medications are available in doses that are significantly too large for the pediatric population and cannot easily and reproducibly be divided into smaller doses (e.g. enteric-coated tablets). Moreover, these dosages make it difficult or impossible to dose based on body weight. One solution is an extemporaneously prepared solution which is a solution prepared by a pharmacist made from solid dosage forms and dissolved or suspended to create palatable syrups.

Medications to treat hypertension are an example of a potential need for pediatric extemporaneous solutions. ACE inhibitors are widely used in treatment of pediatric hypertension and have been found as particularly effective treatments for hypertension in infants (Sinaiko, 1994). Most antihypertensives are administered orally and are only available in solid oral dosage forms. Typically, pharmacists are asked to prepare these medications as an extemporaneous solution. Several vehicles have been used by pharmacists for these preparations, such as water, citrate buffers, and commercially available vehicles (e.g. OraSweet, and simple syrup). However, only limited chemical stability, microbial sterility, appearance, and storage conditions are known for many of these medications after they are prepared extemporaneously. Despite several publications that address this in part (Stewart et al., 1985; Ahmed et al., 1988; Boulton et al., 1994; Allen and Erickson, 1996, 1998; Schlatter and Saulnier, 1997), only limited information on a handful of active ingredients is available. Currently, the marketed form of enalapril, Vasotec® (Merck & Co., Inc.), contains labeling directions to prepare 200 mL of a 1.0 mg/mL suspension. The suspension contains Bicitra and OraSweet SF, is refrigerated and is stable for up to 30 days. Like quinapril, the degradation of enalapril is pH dependent. However, unlike quinapril, enalapril has only one degradant. In solutions above pH 5, enalapril forms the poorly absorbable enalaprilat (Boulton et al., 1994). In addition to that on the label, other solutions/suspensions of enalapril have been studied with varying success (Boulton et al., 1994; Schlatter and Saulnier, 1997; Nahata et al., 1998). Prior to this study, there has been no known stability data for quinapril (the active ingredient of Accupril® (Pfizer Inc.) tablets) in commercially available vehicles. Stabilization of quinapril is more complex than enalapril since two degradation products are formed, one catalyzed in acidic pH and one catalyzed in basic pH.

The purpose of the present study was to develop an extemporaneous pediatric formulation for Accupril that is palatable, possesses acceptable appearance, and is stable for at least 28 days. Like other ACE inhibitors (Gu and Strickley, 1987, 1988; McEvoy, 1992), quinapril is unstable in solution; quinapril degrades 9% after 24 h in aqueous solution at room temperature (Pfizer Inc., 1981). The rate of formation of the two major degradants is pH dependent, with quinaprilat forming under basic conditions and the cyclic product forming under acidic conditions (Pfizer Inc., 1982) (Fig. 1). Past studies of quinapril in aqueous solutions indicate it to be stable only in a narrow pH range of 5.5–6.5 (Pfizer Inc., 1982; Freed et al., 2003). The large amount of magnesium carbonate present in the Accupril tablet formulation contributes to the challenge, by raising the pH well above 6.5 of the solution/suspension.

Several readily available pharmaceutical components were mixed to form nine different prototypes, and their characteristics evaluated upon mixing and after 1 week under stressed conditions. To combat the pH effects of magnesium carbonate in the tablet formulation, buffers were incorporated into the prototype formulations. The three prototypes that most closely matched the stability criteria were then chosen for the formal stability study. A stability-indicating HPLC-UV method was developed to resolve the peaks of interest (quinapril and its two known degradants) from those resulting from the excipients in the Accupril enteric-coated tablets and the extemporaneous formulations. This method was atypical in that temperature was adjusted during suitability to maintain resolution.

2. Materials and methods

2.1. Materials

Accupril® tablets (20 mg; Lot 24751 V) and standards of Quinapril, Quinaprilat and the cyclic prod-

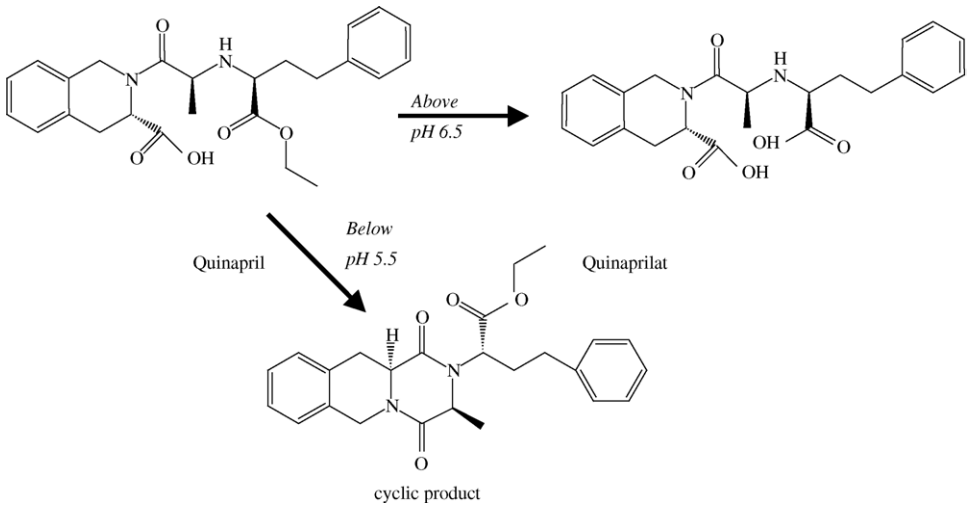

Fig. 1. Chemical structure of Quinapril, Quinaprilat; and the cyclic product.

uct were obtained from Pfizer Inc. The placebo tablet powder blend was prepared by blending magnesium carbonate, lactose monohydrate, gelatin NF, crospovidone, magnesium stearate, opadry brown Y-5-9020, purified water, and wax candellila FCC in ratios consistent with Accupril tablets. Acetonitrile (Chrom AR) and water (HPLC grade) were purchased from Mallinckrodt. Potassium phosphate, dibasic, phosphoric acid and sodium hydroxide (1N) were obtained from J.T. Baker, while the methane sulfonic acid was from Lancaster.

Kphos® neutral tablets (Lot 1B16) were obtained from Beach Pharmaceuticals. Each tablet contains 852 mg dibasic sodium phosphate anhydrous, 155 mg monobasic potassium phosphate, and 130 mg monobasic sodium phosphate monohydrate, to yield approximately 250 mg phosphate, 298 mg sodium (13.0 mEq) and 45 mg of potassium (1.1 mEq) per tablet. Bicitra® (Lot 1A003) is a product of Draxis Pharma and contains sodium citrate dihydrate (500 mg/5 mL) and citric acid monohydrate (334 mg/5 mL). Both OraSweet™ (Lot 182963) and OraSweet SF™ (Lot 132736) are products of Paddock Laboratories. The former consists of purified water, sucrose, glycerin, sorbitol, and flavoring agents. It is buffered with citric acid and sodium phosphate and preserved with methylparaben and potassium sorbate. OraSweet SF contains purified water, glycerin, sorbitol, sodium saccharin, xanthan gum and flavoring agents. It is buffered with citric acid and sodium citrate and preserved with methylparaben, propylparaben and potassium sorbate. Simple syrup (Lot 333318) consists of sucrose, purified water, and 0.1% sodium benzoate as a preservative and is a product of Humco.

2.2. Instrumentation

All HPLC analyses were conducted on an Agilent 1100 series instrument (Agilent Technologies), equipped with a thermostatted column compartment, a variable wavelength detector, and a quaternary pump. An Agilent diode array detector (also an 1100 series HPLC) and Chemstation software were used for the forced degradation and peak purity determination. The HPLC method employed Zorbax Reliance cartridge columns (3 μm particle size, 6.0 mm i.d. × 40 mm length). A Fisher Scientific, Model AR 25 pH meter was used for pH determination. Both a Jouan, Model C412, centrifuge and Acrodisc CR syringe filters (25 mm, 0.45 μm pore size, PTFE membrane; Pall Gelman) were used in sample preparation. The 5 °C stability chamber employed was from Forma Scientific (Model 3660), while the 25 °C/60% RH stability chamber was a Model LHL-112.

2.3. Stability-indicating method

The method employed an 8-min linear gradient, beginning at 10:90:0.2 (i.e. 9.98%, 89.82% and 0.20%)

and ending at 70:30:0.2 (i.e. 69.86%, 29.94%, 0.20%) acetonitrile:water:methane sulfonic acid monitored at 214 nm, with a flow rate of 1.2 mL/min, and an injection volume of 20 μL. All peaks of interest elute in less than 10 min.

The method was validated for selectivity, linearity and range, recovery, limit of quantitation (LOQ), and method precision. Unfortunately, resolution of the method was not found to be overly rugged, varying with both the age and lot of the column. Adjusting the column temperature for each run based upon the system suitability (16–25 °C) was found to be a valuable parameter to maintain a resolution of 1.5 or better throughout the life of the column and to combat lot-to-lot variability. Adding a resolution standard both as part of the system suitability and the bracketing standards ensured resolution from sample to sample. A bracketing standard was run every six samples, and system suitability every 24 h.

2.4. Standard preparation

A standard stock solution of quinapril was prepared at approximately 100 μg/mL in a solution of 35% (v/v) acetonitrile and 65% potassium phosphate, dibasic (0.05 M, pH adjusted to 6.5 with phosphoric acid). A standard stock solution of the cyclic product was prepared in 35% acetonitrile/aqueous buffer, while quinaprilat was dissolved in 0.01N NaOH, then further diluted in 35% acetonitrile/aqueous buffer. Solutions of a 'related compounds' standard were prepared by combining the quinaprilat and the cyclic product standards to yield a concentration of approximately 0.5 μg/mL each. The related compounds and quinapril standards were injected to show system suitability and used as bracketing standards for quantitation. In addition, the formulation samples were bracketed with one injection of their respective formulations to serve as a resolution standard.

2.5. Prototype stability preparation

Initially, nine extemporaneous prototypes were developed and assessed for their stability under accelerated (ambient) conditions for 1 week. They consisted of one crushed Accupril tablet and one of the following formulations: Seventy percent (v/v) of OraSweet, OraSweet SF or simple syrup combined with either Kphos alone (30% (v/v)), Kphos and Bicitra (15% (v/v) each), or water alone (30% (v/v)). The above excipients were chosen for their taste masking and buffering capabilities.

2.6. Formal stability preparation

Specifications for stability were set to conform with those from the marketed tablets, i.e. quinapril remained ≥90% intact and the two known degradants did not reach values ≥3.0% individually or ≥5.0% combined. The three prototypes that most closely matched the above-mentioned goals were further studied to determine if the stability of quinapril was acceptable when stored at 5 °C for 6 weeks. These formulations were prepared from Accupril (20 mg) tablets dissolved in 15% (v/v) Kphos, 15% (v/v) Bicitra, and 70% (v/v) of either OraSweet (Formulation 1), OraSweet SF (Formulation 2), or simple syrup (Formulation 3).

The three formulations and their respective placebos were assayed and the percent concentration determined initially and then after $t = 24$ h under 25 °C/65% RH storage conditions, and $t = 24$ h, 1, 2, 3, 4, and 6 weeks of storage in 5 °C stability chambers.

One hundred Accupril tablets (20 mg) were added to each of three 2-L volumetric flasks. Five tablets of Kphos were crushed with a mortar and pestle and placed in each of three 500-mL volumetric flasks. The powder was dissolved in and filled to volume with HPLC grade water. Three hundred milliliters of this Kphos solution was then added to each flask containing the Accupril tablets. The 2-L flasks were vigorously shaken for 2 min, then allowed to sit on the bench top for an additional 15 min. A volume of 300 mL of Bicitra was added to each 2-L flask. The flasks were once again shaken vigorously for 2 min. Each flask was then filled to volume with one of three syrups—OraSweet (Formulation 1); OraSweet SF (Formulation 2); or simple syrup (Formulation 3). The flasks were shaken to ensure thorough mixing and aliquoted (approximately 200 mL) into 200-mL PET amber bottles. Seven bottles of each formulation were placed in a 5 °C stability chamber, while two bottles of each were added to a 25 °C/60% RH stability chamber.

A placebo of each formulation was prepared to serve as controls. Approximately 2.06 g of a placebo

tablet blend (equivalent to the excipients present in 10 Accupril tablets) was added to a solution of Kphos (30 mL), prepared as above into a 200-mL volumetric flask. The flask was vigorously shaken for 2 min, and then allowed to sit for 15 min. Bicitra (30 mL) and the respective syrups were added to each flask as above. The suspensions were thoroughly shaken and aliquoted into two bottles each. One bottle of each formulation was placed in a 5 °C and 25 °C/60% RH stability chamber.

2.7. Sample preparation for analysis

At the predetermined time interval, one bottle of each formulation and one of each placebo were removed from the stability chamber(s). The bottles were allowed to warm to room temperature. Each formulation and corresponding placebo was then aliquoted into a small scintillation vial for observation of appearance and pH determination. Additional aliquots (approximately 13–14 mL) were removed from each bottle and placed in 15 mL polystyrene centrifuge tubes. The samples were centrifuged at 3000 rpm for approximately 5 min. Ten milliliters of supernatant was removed using a volumetric pipette and added to a 100-mL volumetric flask. The flask was then filled to volume with 35% (v/v) acetonitrile and 65% potassium phosphate, dibasic (0.05 M, pH adjusted to 6.5 with phosphoric acid). The flask was shaken, and the solution was filtered into HPLC vials using Acrodisc CR syringe filter.

2.8. Example labeling instructions for the preparation of Accupril extemporaneous suspension (200 mL of 1.0 mg/mL)

Prepare Kphos® (Beach Pharmaceuticals) buffer by crushing one Kphos® neutral tablet and dissolving it in100 mL sterile water for irrigation. Add 30 mL of the Kphos® buffer to a 200-mL polyethylene terephthalate (PET) bottle with a screw cap containing ten 20 mg tablets of Accupril (Pfizer Inc.). Shake for at least 2 min, then remove the cap and let the concentrate stand for 15 min. Following the 15-min hold time, shake the concentrate for an additional minute. Add 30 mL of Bicitra® (Johnson & Johnson) and shake for 2 min. Add 140 mL Ora-Sweet SF™ (Paddock Laboratories, Inc) and shake the suspension to disperse the ingredients. The suspension is ready to be used. It can be stored for up to 28 days under refrigerated conditions at 2–8 °C (36–46 °F). Shake the suspension before each use.

3. Results and discussion

3.1. Stability-indicating method

Initially, the assay/purity method for the Accupril tablets was assessed for suitability with a variety of syrups and buffers. This method employed a Zorbax Reliance cartridge and an isocratic mobile phase consisting of 35% acetonitrile, 65% water and 0.2% methane sulfonic acid at 1.2 mL/min. An injection volume of 20 μL was used and the system was monitored at 214 nm. With the addition of the extemporaneous excipients, the assay/purity method for the Accupril tablets was no longer selective. For example, Fig. 2 shows the three compounds of interest, quinapril, quinaprilat and the cyclic product, spiked into OraSweet. Quinaprilat is buried amongst several matrix peaks, while quinapril also lacks baseline resolution. These data prompted the development of a new method in order to ensure selectivity against formula-

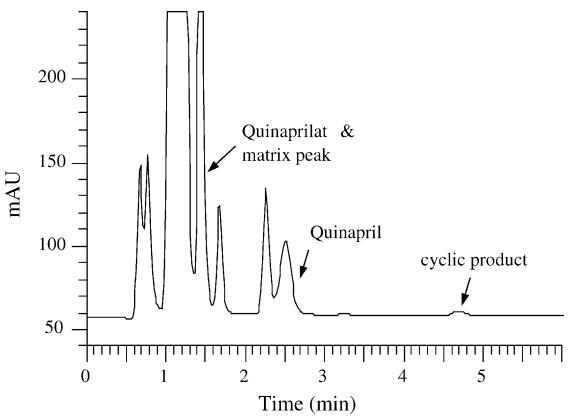

Fig. 2. OraSweet SF spiked with standard of quinapril, quinaprilat and the cyclic product. Mobile phase: 65/35 (v/v) water/ACN + 0.2% methane sulfonic acid; 1.2 mL/min, ambient temperature, column: Zorbax Cyano Reliance cartridge (3 μm × 6.0 mm); 214 nm. This was the analytical release and stability method for marketed Accupril tablets, and indicated significant interference from potential pediatric excipients.

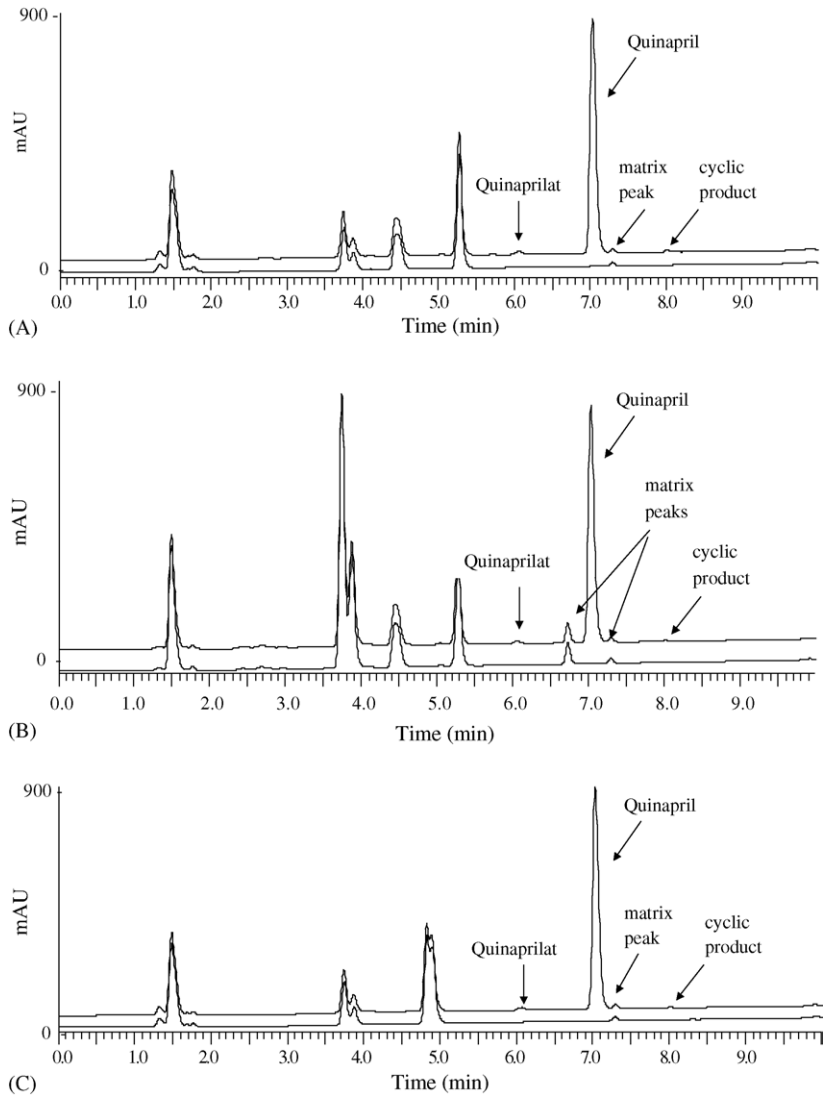

Fig. 3. Overlay of (A) Formulation 1; (B) Formulation 2; and (C) Formulation 3 and their respective placebo formulation (bottom) after storage at 5 °C for 6 weeks.

tion components. The UV spectra of the pharmaceutical solutions and the components of interest revealed that simple wavelength adjustments to increase selectivity would be insufficient. Slight changes in the isocratic mobile phase did not achieve adequate selectivity gains.

Numerous mobile phases and columns were screened to achieve retention of both the quinaprilat a dicarboxylic acid, and the less polar cyclic impurity. The original mobile phase/Zorbax CN column used for the marketed product, still had the best characteristics. The implementation of gradient methods increased separation and resolution of the three compounds from one another and most of the excipient peaks. However, despite the evaluation of numerous step and linear gradients, Quinapril could not be suffi-

ciently resolved from two flanking matrix peaks in the OraSweet SF-containing samples (only one such peak existed for the other two formulations). Employing Dry Lab (Dry Lab 2000, version 3.0.09; LC resources, Walnut Creek, CA) showed that a much higher theoretical plate count was needed to achieve the desired resolution. Since a slightly longer Zorbax Reliance Cyano column was not commercially available, two columns were coupled together in series to increase plate count. This gave the required selectivity for all the peaks of interest (Fig. 3). Although resolution was maintained throughout a several hour analysis, the columns did not always show run-to-run reproducibility. It was discovered that the resolution, could be altered to the designated minimum value of 1.5 by simply adjusting the column temperature a few degrees cooler. As the columns aged and were replaced throughout the 6-week stability study, the column temperature ranged from 16 to 25 °C. System suitability was maintained by adding a resolution standard to the both the system suitability and as a bracketing standard. Although, the temperature was adjusted for inter-run resolution, once achieved, the resolution was constant within a single run.

The method was then validated. The detector response was found to be linear ($r^2 = 0.9997$, relative response factors (RRF) within ±3.0% of that for the targeted standard concentration of 100 μg/mL) between 50 and 110% of the analytical concentration of quinapril. Low-level linearity was determined for quinaprilat and the cyclic impurity from 0.05 to 5% of the targeted assay concentration of quinapril and found to be acceptable ($r^2 = 1.000$ for both; RF within 10% of that for the single point calibration level of 0.5 μg/mL). The limit of quantitation of quinaprilat and the cyclic product was determined to be ≤0.05% (w/w) relative to quinapril, with a signal-to-noise of ≥10:1, %R.S.D. ≤ 20.0%, RF within 10% of that for the single point calibration concentration of 0.5 μg/mL for six replicate injections. Accuracy, recovery and method precision of quinapril were determined to be acceptable in each of the formulations, as the experimental values were within ±3.0% absolute of the target value of the API and the %R.S.D. (percent relative standard deviation) was ≤2.0% for six preparations. These parameters were also acceptable for the two degradation products in each of the formulations, with the experimental values being within ±10% of the specification level (1.5%) of the degradation products and a %R.S.D. ≤ 10% for six preparations. Sample and standard solutions were determined to be stable for 1 week at 5 °C and for a 24-h HPLC run.

In order to establish the selectivity and stability-indicating nature of the method, the extemporaneous prototype formulations were placed under accelerated conditions of 37 °C for 1 week, and peak purity of the active component and method selectivity was determined.

3.2. Prototype stability

Table 1 shows the stability of nine prototypes. The prototypes containing both Kphos and Bicitra were buffered to a pH near 5.5, and were determined to be the most stable, with less than 2.2% quinaprilat and less than 1.4% cyclic impurity forming at room temperature after 1 week. The solutions containing only water yielded a pH of 8.8 (simple syrup), 8.4 (OraSweet SF) and 6.8 (OraSweet). While only a very small amount

Table 1
Stability results for extemporaneous pediatric prototype formulations

One week stability	5 °C		RT (accelerated conditions)		pH
Components	% Quinaprilat	% Cyclic product	% Quinaprilat	% Cyclic product	
OraSweet/water	0.76	0.22	4.22	0.48	6.8
OraSweet/Kphos	0.72	0.28	4.00	0.42	6.8
OraSweet/Kphos/Bicitra	0.36	0.37	1.88	1.31	5.4
OraSweetSF/water	0.85	0.25	4.81	0.29	8.4
OraSweet SF/Kphos	0.71	0.22	4.15	0.26	8.1
OraSweet SF/Kphos/Bicitra	0.44	0.29	2.13	0.76	5.5
Simple syrup/water	–	–	9.24	0.25	8.8
Simple syrup/Kphos	1.14	0.25	–	–	8.1
Simple syrup/Kphos/Bicitra	0.64	0.30	2.12	0.77	5.4

Table 2
Stability results for extemporaneous pediatric formulations prepared with Accupril tablets and readily available pharmaceutical components

Sample component	Initial	24 h, 5 °C	24 h, 25 °C/65 RH	1 week, 5 °C	2 week, 5 °C	3 week, 5 °C	4 week, 5 °C	5 week, 5 °C
Formulation 1								
CI-906	99.0	99.5	98.4	96.2	99.1	100.0	97.4	97.9
CI-928	0.25	0.31	0.55	0.56	0.68	0.92	1.02	1.35
PD 109488	0.31	0.26	0.45	0.42	0.50	0.60	0.61	0.76
Formulation 2								
CI-906	99.2	99.1	98.4	96.5	99.0	97.8	97.4	98.2
CI-928	0.21	0.28	0.50	0.46	0.62	0.75	0.89	1.41
PD 109488	0.18	0.19	0.29	0.24	0.33	0.35	0.33	0.42
Formulation 3								
CI-906	99.2	100.0	98.7	96.0	99.0	99.9	98.3	97.5
CI-928	0.23	0.30	0.59	0.56	0.71	0.96	1.10	1.42
PD 109488	0.19	0.21	0.30	0.29	0.33	0.40	0.32	0.39

Each reported value is the average percent initial concentration remaining for $n = 3$ replicates. Formulation 1: 15% (v/v) Kphos, 15% Bicitra, and 70% OraSweet. Formulation 2: 15% (v/v) Kphos, 15% Bicitra, and 70% OraSweet SF. Formulation 3: 15% (v/v) Kphos, 15% Bicitra, and 70% simple syrup. Specifications: Quinapril was deemed stable if it remained ≥90% intact and the two known degradants did not reach values ≥3.0% individually or ≥5.0% combined.

of the cyclic product formed in these solutions after 1 week at RT, a fairly large amount of quinaprilat was observed (9.2, 4.8, and 4.2%, respectively). The solutions containing only Kphos resulted in a pH of 8.1 for the simple syrup and OraSweet SF and a pH of 6.8 for OraSweet. As with the water-containing solutions, higher amounts of quinaprilat were observed. This was somewhat expected due to the lack of buffering capability of the simple syrup, and the inherent buffering capability of the OraSweet.

3.3. Formal stability study

The three formulations that contained both Kphos and Bicitra with each of the three syrups studied were then prepared and a formal stability study lasting 6 weeks was conducted. The data in Table 2 shows that quinapril is stable in all three extemporaneous formulations for 6 weeks when stored at 5 °C. These samples resulted in a mean concentration of quinapril greater than 97% of the initial concentration in all three extemporaneous formulations. The degradation products increased as a function of time, however, the amount formed remained <3.0% each and <5.0% total (Table 2), the target specifications for the impurities based on the tablet specifications. The average value of quinaprilat formation remained below 1.5%, while that of the cyclic product was less than 1.0% in all formulations studied. The listed values were calculated by comparing the peak area of quinapril, quinaprilat, and the cyclic product to that of the respective standards that bracket them. The listed results were an average of the three separate sample preparations.

Table 3
Appearance data for the extemporaneous pediatric formulations prepared with Accupril tablets and readily available pharmaceutical components under stability study

Time period	Observations
Formulation 1	
Initial	•Color: pinkish red •Small white particles suspended, some settling after a few minutes
$t > 0$	No change in appearance observed at any of the time points
Formulation 2	
Initial	•Color: pinkish red •Small white particles suspended •Better suspension than Formulation 1 or 3
$t > 0$	No change in appearance observed at any of the time points
Formulation 3	
Initial	•Color: pinkish red, with more of a yellowish tint than others •Small white particles suspended, some settling after 15 min
$t > 0$	No change in appearance observed at any of the time points

Table 4
The pH of the extemporaneous pediatric formulations prepared with Accupril tablets and readily available pharmaceutical components under stability study

Sample component	Initial	24 h, 25 °C/65% RH	24 h, 5 °C	1 week, 5 °C	2 week, 5 °C	3 week, 5 °C	4 week, 5 °C	6 week, 5 °C
Formulation 1	5.4	5.3	5.4	5.5	5.4	5.4	5.5	5.5
Formulation 2	5.5	5.4	5.4	5.5	5.5	5.4	5.5	5.5
Formulation 3	5.7	5.6	5.6	5.7	5.7	5.6	5.8	5.8

The results of the accelerated storage, 24 h at 25 °C/60% RH, were also found to be acceptable, with quinapril remaining above 98.0% of the initial concentration. The two degradants remained less than 0.6%, with quinaprilat once again forming to a greater extent than the cyclic product (0.55% mean versus 0.35% mean). No new degradants (≥0.5%) were observed at either storage condition.

The reddish color of the enteric-coating on the Accupril tablets coupled with the slight yellowish tint of the liquids gave the suspension a pinkish red color. Although the quinapril was completely dissolved, not all of the tablet excipients were soluble in the liquid media, which resulted in a suspension of white particles. The suspensions settled during storage but could be re-suspended by agitation. The OraSweet SF-containing formulation was observed to possess better suspension of the particles, as the majority of the particles remained uniformly suspended for at least 15 min. The physical appearance of all three formulations remained unchanged throughout the time period of the study (Table 3).

The importance of pH was demonstrated in the prototype results. Past solution studies (Pfizer Inc., 1982) have shown quinapril to be most stable between the pH 5.5 and 6.5. The data in this study support this previous observation, as the pH of the extemporaneous prototype formulations that were found to be most stable were in this range. Unlike other ACE inhibitors, such as enalapril, it is necessary to adhere to a narrow pH range in order to ensure the stability of quinapril. This is in contrast to enalapril which forms one degradant at pH ≥5 (Schlatter and Saulnier, 1997). Furthermore, a large buffering capacity was needed in the solution/suspension formulations to combat the pH effects of the tablet excipient magnesium carbonate. The three formulations studied maintained a constant pH throughout the stability study (Table 4).

4. Conclusions

A stability-indicating method was developed and validated to test quinapril and its known degradation products in complex solutions. Although, there was extensive interference from excipients, a long shallow gradient and temperature control were able to maintain selectivity and the necessary resolution.

A stable liquid extemporaneous formulation of quinapril, compounded from Accupril tablets was achieved by dissolving tablets in commercially available buffers and sweetened syrups (refer to Section 2.8 for example labeling instructions). The stabilization of this formulation was difficult due to the inherent instability of the active ingredient in Accupril tablets, which readily decompose to two degradation products. The necessity to maintain a narrow range of pH in solution was established. The presence of a significant quantity of basic excipients in the tablet formulation increased the complexity and necessity of buffering capacity of the pediatric formulation.

Quinapril is stable in all three extemporaneous formulations evaluated—Accupril Tablets dissolved in (Formulation 1) 15% Kphos/15% Bicitra/70% OraSweet; (Formulation 2) 15% Kphos/15% Bicitra/70% OraSweet SF; and (Formulation 3) 15% Kphos/15% Bicitra/70% simple syrup when stored at 5 °C for 6 weeks. Furthermore, the pH and appearance of the formulations remained constant throughout the 6-week time interval. Although all three proposed formulations met the stability requirements set forth, the improved suspension obtained from the one containing OraSweet SF made this the formulation of choice.

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