Stability Study of Pediatric Oral Suspensions Indicated in the Treatment of Cardiovascular Disease

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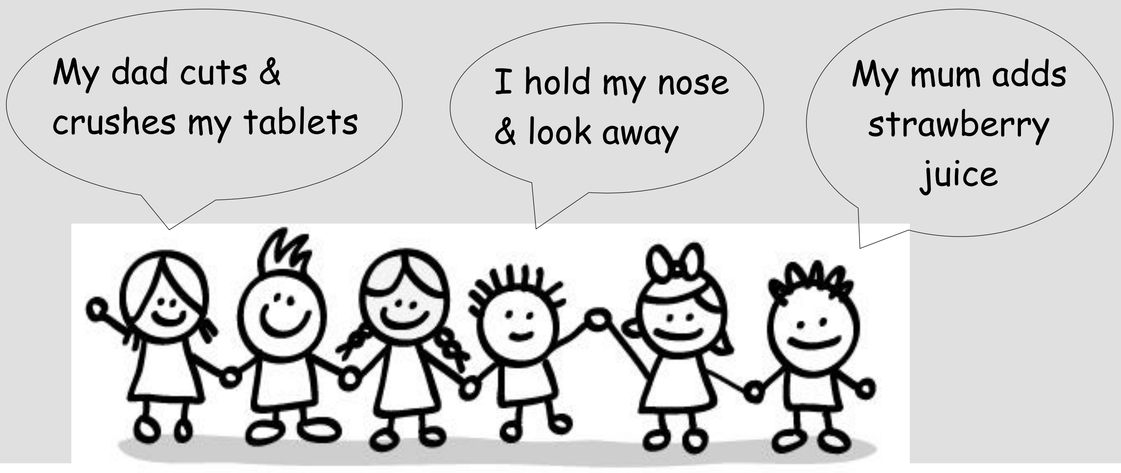

INTRODUCTION:

The purpose of this study was to investigate the physicochemical and microbiological stability of three compounded pediatric oral cardiovascular suspensions: captopril (1 mg/mL and 5 mg/mL), hydrochlorothiazide (5 mg/mL and 10 mg/mL), and metoprolol (1 mg/mL and 10 mg/mL) formulated with a commercial oral suspending vehicle (PCCA SuspendIt). These active ingredients belong to different pharmacological groups and are used to treat a variety of cardiovascular conditions. Commercial pharmaceutical forms of these drugs are not available for pediatric patients, leaving a gap in dosing options. Therefore, the primary means of serving this population is through extemporaneous compounding of oral suspensions.

METHOD:

Ultra-high-performance liquid chromatography (UHPLC) methods were developed and validated for the determination of the chemical stability of captopril, hydrochlorothiazide and metoprolol in the oral suspending vehicle. Various forced degradation conditions were employed, including acidic, basic, oxidative, and heat degradation. The results revealed that potential interfering degradants do not affect the analytical peaks of the drug substance, and the factors contributing to the significant degradation of the drug substance in the suspension were identified. Test suspensions were prepared for each active ingredient (two concentrations) and evenly distributed into 4 oz prescription oval amber plastic bottles. Hydrochlorothiazide and metoprolol test suspensions were stored in an environmentally controlled chamber at a relative humidity of 60±5 %, temperature of 25±2°C. Captopril test suspensions were stored in a laboratory refrigerator at a temperature of 5±3°C. For the stability study of the suspensions, one test bottle was taken from the place of storage at predetermined time points: 0, 7, 14, 30, 60, 90, and 180 days. Physical properties such as pH, color/appearance and odor were also observed. All measurements were performed in duplicate. The determinations obtained on day 0 were set as baseline for comparison purposes. Antimicrobial efficacy tests were performed to control microbial growth during storage. This test was conducted on 0, 90 and 180 days of storage, in accordance with the USP Chapter <51> Antimicrobial Effectiveness Test.

RESULTS:

Captopril showed a degradation of 20.04% under the influence of heat, which indicates sensitivity to elevated temperatures and justifies the choice of refrigerator as storage condition. Captopril also showed susceptibility to oxidative conditions, which emphasizes the need to use a tightly sealed closure system. Hydrochlorothiazide showed a degradation of 20.31% under acidic conditions, which emphasizes the need to control the pH in the formulation during extemporaneous compounding.

This study demonstrates the robust stability of the compounded pediatric oral cardiovascular suspensions formulated with the commercial oral suspending vehicle. The chemical stability of the captopril, hydrochlorothiazide, and metoprolol suspensions remained within the acceptable range of 90-110 %. All suspensions kept their organoleptic characteristics, namely color/appearance and odor. The pH measurements were all within the expectations, as follows: 3.07-3.28 for captopril; 3.14-3.46 for hydrochlorothiazide; and 3.81-4.09 for metoprolol. Antimicrobial susceptibility test results (*Aspergillus brasiliensis, Candida albicans, Pseudomonas aeruginosa, Staphylococcus aureus, and Escherichia coli*) were consistently approved (pass) for the three active ingredients. These results underscore the versatility of using a suspending vehicle in the formulation of pediatric oral cardiovascular suspensions, providing compounded alternatives for captopril, hydrochlorothiazide, metoprolol tartrate at various strengths with a beyond-use-date that meets desired stability criteria.

Sample Name	Time	Appearance	pH	C, mg/mL	Potency, %	USP 51 Antimicrobial Effectiveness Test				
						Aspergillus brasiliensis	*Candida albicans*	*Pseudomonas aeruginosa*	*Staphylococcus aureus*	*Escherichia coli*
Captopril 1 mg/mL Oral Suspension (SuspendIt®) Storage Conditions: 5±3°C	Day 0	Clear susp.	3.28	0.995	99.5	pass	pass	pass	pass	pass
	Day 14	Clear susp.	3.23	0.984	98.4	-	-	-	-	-
	Day 30	Clear susp.	3.19	0.942	94.2	-	-	-	-	-
	Day 60	Clear susp.	3.18	0.949	94.9	-	-	-	-	-
	Day 90	Clear susp.	3.20	0.916	91.6	pass	pass	pass	pass	pass
	Day 180	Clear susp.	3.23	0.908	90.8	pass	pass	pass	pass	pass
Captopril 5 mg/mL Oral Suspension (SuspendIt®) Storage Conditions: 5±3°C	Day 0	Clear susp.	3.13	5.03	100.6	pass	pass	pass	pass	pass
	Day 14	Clear susp.	3.12	4.93	98.6	-	-	-	-	-
	Day 30	Clear susp.	3.07	4.89	97.8	-	-	-	-	-
	Day 60	Clear susp.	3.13	4.96	99.2	-	-	-	-	-
	Day 90	Clear susp.	3.10	4.82	96.4	pass	pass	pass	pass	pass
	Day 180	Clear susp.	3.21	4.78	95.6	pass	pass	pass	pass	pass
Hydrochlorothiazide 5 mg/mL Oral Suspension (SuspendIt®) Storage Conditions: 25±2°C	Day 0	Light pink susp	3.4	5.18	103.6	pass	pass	pass	pass	pass
	Day 14	Light pink susp	3.46	5.42	108.4	-	-	-	-	-
	Day 30	Light pink susp	3.39	5.42	108.4	-	-	-	-	-
	Day 60	Light pink susp	3.31	4.95	99.0	-	-	-	-	-
	Day 90	Light pink susp	3.30	4.88	97.6	pass	pass	pass	pass	pass
	Day 180	Light pink susp	3.27	5.11	102.2	pass	pass	pass	pass	pass
Hydrochlorothiazide 10 mg/mL Oral Suspension (SuspendIt®) Storage Conditions: 25±2°C	Day 0	Light pink susp	3.3	9.91	99.1	pass	pass	pass	pass	pass
	Day 14	Light pink susp	3.35	10.0	100.0	-	-	-	-	-
	Day 30	Light pink susp	3.29	10.3	103.0	-	-	-	-	-
	Day 60	Light pink susp	3.24	9.71	97.1	-	-	-	-	-
	Day 90	Light pink susp	3.28	9.77	97.7	pass	pass	pass	pass	pass
	Day 180	Light pink susp	3.14	10.4	104.0	pass	pass	pass	pass	pass
Metoprolol Tartrate 1 mg/mL Oral Suspension (SuspendIt®) Storage Conditions: 25±2°C	Day 0	Clear susp.	3.81	0.994	99.4	pass	pass	pass	pass	pass
	Day 14	Clear susp.	3.87	0.994	99.4	-	-	-	-	-
	Day 30	Clear susp.	3.83	0.993	99.3	-	-	-	-	-
	Day 60	Clear susp.	3.87	1.02	102.0	-	-	-	-	-
	Day 90	Clear susp.	3.93	1.03	103.0	pass	pass	pass	pass	pass
	Day 180	Clear susp.	3.85	1.01	101.0	pass	pass	pass	pass	pass
Metoprolol Tartrate 10 mg/mL Oral Suspension (SuspendIt®) Storage Conditions: 25±2°C	Day 0	Clear susp.	3.97	9.88	98.8	pass	pass	pass	pass	pass
	Day 14	Clear susp.	4.02	9.91	99.1	-	-	-	-	-
	Day 30	Clear susp.	3.92	9.95	99.5	-	-	-	-	-
	Day 60	Clear susp.	3.89	10.2	102.0	-	-	-	-	-
	Day 90	Clear susp.	4.09	10.3	103.0	pass	pass	pass	pass	pass
	Day 180	Clear susp.	3.99	9.98	99.8	pass	pass	pass	pass	pass

CONCLUSION:

This study demonstrates that the compounded pediatric oral cardiovascular suspensions are physically, chemically and microbiologically stable for 180 days for captopril (refrigerator), and hydrochlorothiazide and metoprolol tartrate (room temperature). This study provides a viable compounded alternative for hydrochlorothiazide, metoprolol tartrate and captopril in a liquid dosage form with an adequate beyond-use-date date to meet patient needs. The study's documentation of stability over a bracketed concentration range for each formulation increases flexibility for compounding pharmacists in customizing pediatric cardiovascular suspensions. This flexibility ensures that healthcare providers can tailor formulations to meet specific patient needs while maintaining required stability and safety standards.