Stability of Captopril in an Extemporaneously Compounded Humco's Oral Products

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ABSTRACT:

Captopril oral suspensions were prepared by compounding Captopril powder with Humco's Oral Products' (Flavor Sweet™ : Flavor Plus™ 1:1; and Flavor Sweet-Sugar Free™ : Flavor Plus™ 1:1), at two concentrations: 0.8 mg/mL and 4 mg/mL. These bracket concentrations of all Captopril formulations were stored in low-actinic plastic prescription bottles at controlled room temperature (25 °C and 60% RH) and controlled cold temperature (2 – 8 °C). These formulations were evaluated over 36 days for their physical, chemical, and microbiological stability. The chemical specification was set as 90% to 110% of initial concentration of the active. Based on the stability data gathered over 5 testing time points (day 0, 8, 13, 23, and 36) for Captopril oral suspension, both 0.8 mg/mL and 4 mg/mL strengths formulations stored at controlled cold temperature were physically, chemically, and microbiologically stable for at least 23 days. Furthermore, both strengths of the Captopril oral suspensions stored at controlled room temperature were chemically stable until the 8 day time point.

KEYWORDS:

Captopril, Humco Flavor Products, Flavor Sweet™, Flavor Sweet-Sugar Free™, Flavor Plus™, Beyond-use Date (BUD)

INTRODUCTION:

Liquid oral compounding vehicles are particularly useful when dosing medication to the very infirmed, the very old, or the very young. These groups of patients typically experience difficulty when attempting to swallow solid oral dosage forms, so compounding these medications into a more easily dosed form is advantageous both for the patient and the care-giver [1]. Use of commercially available liquid oral compounding vehicles, which can form either a solution or a suspension of a particular drug, can expedite the process of compounding for the pharmacist. An additional benefit of commercial liquid vehicles is that oral solutions and suspensions compounded in these products have the ability to taste-mask bitter drugs, improving patient compliance [2, 3]. Beyond-use-dating (BUD) is addressed in the USP chapter <795>, stating that for oral products "the BUD is not later than 14 days when stored at controlled cold temperatures" which applies in the absence of stability data on a specific drug in given preparation [4]. Practicality dictates that the stability of a drug should be assessed at room temperature over a longer period of time. Therefore, several studies have evaluated a variety of different classes of drugs for stability in liquid oral suspensions and solutions to determine the drug's beyond-use-dating (BUD).

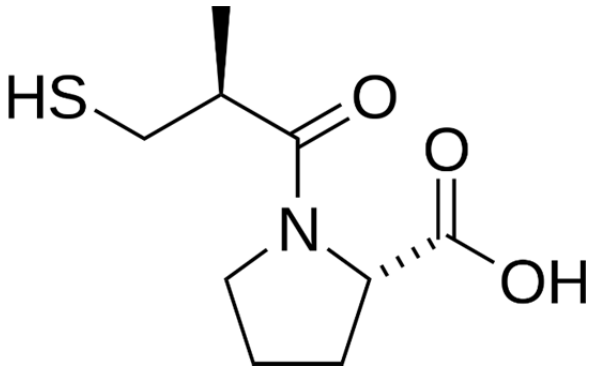

Figure 1. Captopril Chemical Structure

Captopril (figure 1) is an angiotensin-converting enzyme (ACE) inhibitor used primarily for the hypertension, congestive heart failure, myocardium, and kidney problems caused by diabetes [5]. Most common form of Captopril active is tablet; however, compounding pharmacist can extemporaneously prepare oral suspensions for the patients who are unable to administer tablets orally [6]. There are number of published studies of Captopril oral suspensions compounded in different oral vehicles. However, there is a lack of bracketed study of Captopril that is extemporaneously compounded in oral vehicles and conducting physical, chemical, and microbiological stability study over the specific time periods. The stability of Captopril in oral compounding syrup is dependent on various factors including storage conditions, storage medium, strengths, amount of aqueous phase and oral vehicle itself [7, 8, and 9]. The strengths of Captopril in most of the studies are ranged from 0.75 – 1 mg/mL and the stability of Captopril was found to be couple of weeks under refrigerated conditions. Unlike these vehicles which either need a complex preparation or don't have flavors or good taste, Humco's Flavor Products are ready-to-use oral suspension vehicles which are suitable for wide range of patients.

Humco's Flavor Sweet^{TM} (FS^{TM}) is a cherry-flavored syrup vehicle formulated to simplify the preparation of oral extemporaneous delivery systems. It may be used alone or in conjunction with other agents to give flavor and sweetness while increasing the suspensions' physical stability. Flavor Sweet^{TM} contains suitable preservatives and is buffered to a slightly acidic pH to provide a dependable and consistent vehicle [10]. Similarly, Flavor Sweet-Sugar Free^{TM} (FS-SF^{TM}) is a sugar – free and alcohol-free cherry flavored syrup. Flavor Plus^{TM} (FP^{TM}) is a unique flavor-free, aqueous based suspending vehicle used to simplify the process of compounding oral non-soluble suspensions. It is buffered to an acidic pH providing a uniform, consistent, and stable vehicle. It is recommended to use for hydrophilic, acid-stable and hydrophobic actives. It is ideal of diabetic preparations [10]. Being in an acidic pH, these vehicles are suitable for the preparation of Captopril oral suspension. The objective of this study was to examine the stability of Captopril while extemporaneously compounded in Humco's oral suspension vehicles (equal combination of Flavor Sweet- SF^{TM} and Flavor Plus^{TM}; and Flavor Sweet^{TM} and Flavor Plus^{TM}) to determine the beyond-use-date (BUD).

EXPERIMENTAL:

In this study, the physical, chemical, and microbiological stability of Captopril compounded in Humco's FS^{TM} : FP^{TM} (1:1) and FS-SF^{TM} : FP^{TM} (1:1) combination of oral products was conducted over the period of 36 days. The oral suspensions were compounded at a high (4 mg/mL) and a low (0.8 mg/mL) strengths covering a range of concentrations that should bracket most prescriptions containing Captopril. These two strengths of Captopril oral suspensions were evaluated at two storage conditions: controlled cold (2 – 8 °C) and room temperature (25 °C and 60% RH). The equal combination of two oral vehicles was measured out volumetrically for each formulation. Study was designed to cover wide array prescriptions and patients who might have sugar or sugar free preferences. A lab scale homogenizer was used to break up any agglomerations of active pharmaceutical ingredient (API) that might have present in the oral suspensions. Additionally, the suspensions were packaged with constant stirring to maintain a homogeneous mixture. A 4 oz. (120 mL) oval airtight low-actinic prescription bottle was used as the unit container for the study.

The description, visual appearance, odor, pH, and density measurements were conducted as a part of a Physical testing for the compounded formulations. Chemical testing identified and quantified the analyte of interest and showed the stability of the targeted API. The potency test for the determination of chemical stability and identification were carried out using the assay method described in the USP monograph for Captopril Oral Suspension. The USP assay method for Captopril was verified to be appropriate for the analysis of Captopril in the combination oral suspensions prior to the beginning of the study. ICH Guidelines in publication Q2 (R1) Validation of Analytical Procedures was followed to verify the analytical HPLC method with the exception of performing forced degradation of the active and robustness evaluations. Linearity, accuracy, precision, and specificity were proven to meet acceptance criteria for the analysis of Captopril in the studied formulations.

Furthermore, the microbiological testing that included the Total Aerobic Microbe Count (TAMC), Total Yeast and Molds (TYAM), and detection of *S. aureus* and *P. aeruginosa*, as detailed in the USP General Chapters <61> and <62> was conducted at the beginning of the study (day 0) and at the end of the study (day 36). Acceptance criteria for the microbiological testing are: TAMC ≤ 100 cfu/mL, TYAM ≤ 10 cfu/mL, and absence of *S. aureus* and *P. aeruginosa.* The FS^{TM} : FP^{TM} (1:1) and FS -SF^{TM} : FP^{TM} (1:1) formulations, each prepared at 0.8 mg/mL and 4 mg/mL Captopril prepared for this beyond-use-date (BUD) study are shown in Table 1.

Table 1: High and low concentrations of Captopril in Humco's oral products

Ingredient	Amount
Captopril	-
For 0.8 mg/mL Oral Suspension	80 mg
For 4 mg/mL Oral Suspension	400 mg
Flavor Sweet™ : Flavor Plus™ (1:1)	Qs to 100 mL
Flavor Sweet - SF™ : Flavor Plus™ (1:1)	QS to 100 mL

The physical and chemical testing were conducted at the initial time 0, followed by day 8, 13, 23, and 36. Physical observation each time point was compared to the original freshly made sample. pH data was recorded at each testing time points. Chemical stability is represented as a percentage of the initial potency of the Captopril remaining at the given time point. The USP monograph recommend a range of pH values for Captopril oral suspension to be in acidic end (3.8 – 4.3), and the acceptable specifications for chemical stability are set at 90-110% of the Captopril remaining from the original amount in the sample at the given time point.

Microbiological evaluations were performed at the initial time 0 and at the end of the study (day 36), and these data are presented as total cfu/mL for aerobic microbes, yeasts, and molds, and a positive or negative result for detection of *Staphylococcus aureus* or *Pseudomonas aeruginosa*. The testing scheme and specifications for testing the Captopril samples is shown in Table 2.

Table 2: Testing conducted with Captopril oral suspensions during the BUD study

Test	Method	Specification	Testing Interval
Description/Physical Form/Odor	Organoleptic	Must match initial description. No separation, stratification or non-homogeneity upon shaking.	All Time Points
Captopril Assay*	USP	90-110% of Initial Conc.	All Time Points
ID by HPLC Captopril	USP	peak matches that of the standard	All Time Points
pH $_{(neat)}$	pH Meter	Report only	All Time Points
Total Aerobic Microbial Count	USP <61>	≤ 100 cfu/mL	Days 0 and 36
Total Combined Yeast & Mold	USP <61>	≤ 10 cfu/mL	Days 0 and 36
Absence of *S. aureus* and *P. aeruginosa*	USP <62>	Absent	Days 0 and 36

RESULTS AND DISCUSSIONS:

The results for the physical testing of the Captopril oral suspensions, at the controlled cold temperature (CT; 2 – 8 °C) are shown in Table 3. Physical properties appeared to be the same for the Controlled Room Temperature samples. Controlled Room Temperature (RT) samples were not tested at day 36.

Table 3: Physical testing results for Captopril formulations stored at controlled CT (2 – 8 °C)

Controlled Cold Temperature (2 – 8 °C)				
Formulation Concentration	**Description**		**Density (mg/mL) Initial – 36 D**	**pH Range from Initial - Day 36**
	Initial (day 0)	**8 – 36 Days**		
0.8 mg/mL **Captopril in FS™: FP™**	Light pink with cherry odor viscous liquid, smooth	Matches initial description. Uniform. No separation or color change.	1.14	4.0 – 4.1
4 mg/mL **Captopril in FS™: FP™**	Light pink with cherry odor viscous liquid, smooth	Matches initial description. Uniform. No separation or color change.	1.14	3.5 – 3.6
0.8 mg/mL **Captopril in FS-SF™: FP™**	Light pink/orange with cherry odor viscous liquid, smooth	Matches initial description. Uniform. No separation or color change.	1.01	4.1 – 4.2
4 mg/mL **Captopril in FS-SF™: FP™**	Light pink/orange with cherry odor viscous liquid, smooth	Matches initial description. Uniform. No separation or color change.	1.02	3.7 – 3.9

The results for physical testing show that both strengths of Captopril (0.8 mg/mL and 4 mg/mL) compounded in Humco's oral combinations - Flavor Sweet™ : Flavor Plus™ (1:1) and Flavor Sweet-SF™ : Flavor Plus™ (1:1) stored in a controlled cold temperature (CT) and controlled room temperature were stable in terms of description of the physical form, density, and pH. No unusual changes were noticed while observing the formulations visually throughout the study period. The suspension met the initial description of the compounded sample: uniform with no separation, no color change, no non-homogeneity, and there was no change in appearance or organoleptic properties observed in the samples over the study period for samples compounded in those formulations.

The density of the samples remained constant, and the pH values varied negligibly remaining in acidic environment. The Captopril oral suspension formulations placed in the cold temperature met the criteria for physical testing for minimum of 36 days. The results for the chemical stability testing of the Captopril compounded oral formulations, at both the controlled cold temperature (2 – 8 °C) and controlled room temperature (25 °C and 60% RH), are shown in Tables 4 and 5.

Table 4. Potency data for Captopril in FS™ : FP™ (1:1) at CT and RT storage condition

Strength	**Conc. (mg/mL)**	**Flavor Sweet™ : Flavor Plus™ (1:1) Controlled CT (2-8°C)** % Recovery of Initial Conc. of Captopril (Spec: 90 – 110%)			
	Day 0	**Day 8**	**Day 13**	**Day 23**	**Day 36**
0.8 mg/mL	0.780	99.6%	97.7%	93.5%	85.4%
4 mg/mL	3.942	101.6%	100.8%	93.5%	92.5%
	Controlled RT (25°C 60% RH)				
0.8 mg/mL	0.780	90.3%	84.9%	76.0%	Not Tested
4 mg/mL	3.942	97.7%	92.2%	81.2%	

Table 5. Potency data for Captopril FS-SF™ : FP™ (1:1) at CT and RT Storage Condition

Strength	Conc. (mg/mL)	Flavor Sweet-Sugar Free™ : Flavor Plus™ Controlled CT (2-8°C) % Recovery of Initial Conc. of Captopril (Spec: 90 – 110%)			
	Day 0	**Day 8**	**Day 13**	**Day 23**	**Day 36**
0.8 mg/mL	0.756	99.3%	95.6%	91.5%	92.4%
4 mg/mL	3.965	99.8%	94.8%	90.2%	87.8%
		Controlled RT (25°C 60% RH)			
0.8 mg/mL	0.756	90.6%	82.7%	75.8%	Not Tested
4 mg/mL	3.965	95.7%	89.3%	79.1%	

The results for chemical stability testing show that both concentrations (0.8 mg/mL and 4 mg/mL) of Captopril compounded in Humco's FS™ : FP™ (1:1) and FS-SF™ : FP™ (1:1) oral suspensions, were chemically stable for at least 23 days when stored in refrigerated conditions. However, Captopril oral suspensions formulations 0.8 mg/mL and 4 mg/mL did not meet the specification of 90 – 110% of the API remaining after day 8 (at least one of the bracket of each formulation was below the specification).

The microbiological evaluations for the Captopril oral suspensions, tested according to USP <61> and <62>, at Time 0 is shown in Table 6 and micro results at 36 Days are shown in Table 7.

Table 6: Microbiological results for Captopril oral suspensions from initial testing time 0.

Oral Vehicle Combination	Concentration	Total Aerobic Microbial Count	Total Yeast and Mold	Mannitol Test for *S. aureus*	Cetrimide Test for *P. aeruginosa*
Captopril in FS™: FP™	0.8 mg/mL	0 cfu/mL	0 cfu/mL	Negative	Negative
	4 mg/mL	0 cfu/mL	0 cfu/mL	Negative	Negative
Captopril in	0.8 mg/mL	0 cfu/mL	0 cfu/mL	Negative	Negative
FS-SF™: FP™	4 mg/mL	0 cfu/mL	0 cfu/mL	Negative	Negative

Table 7: Microbiological results for Captopril oral suspensions at 36 Days (Cold Temp) *

Oral Vehicle Combination	Concentration	Total Aerobic Microbial Count	Total Yeast and Mold	Mannitol Test for *S. aureus*	Cetrimide Test for *P. aeruginosa*
Captopril in FS™: FP™	0.8 mg/mL	0 cfu/mL	0 cfu/mL	Negative	Negative
	4 mg/mL	0 cfu/mL	0 cfu/mL	Negative	Negative
Captopril in	0.8 mg/mL	0 cfu/mL	0 cfu/mL	Negative	Negative
FS-SF™: FP™	4 mg/mL	0 cfu/mL	0 cfu/mL	Negative	Negative

**Samples stored in controlled room temperature were not tested at day 36.*

Each high and low concentration of Captopril formulation in both combo vehicles were evaluated for microbiological growth and contamination. The micro testing time points Time 0 and Day 36 showed no growth in terms of Total Aerobic Microbes, Total Yeast and Mold, and *S. aureus* and *P. aeruginosa*. Since samples stored at room temperature did not meet specifications past day 8 samples, micro testing of those

samples was not conducted at day 36. All controlled cold temperature samples, however, met the specific criteria for micro testing at day 36.

CONCLUSIONS:

Overall, it can be concluded that the Captopril active compounded in Humco's oral products Flavor Sweet™ : Flavor Plus™ (FS™ : FP™ ; 1:1) and Flavor Sweet-Sugar Free™ : Flavor Plus™ (FS-SF™ : FP™ 1:1) combo formulations under refrigerated conditions had the good stability in terms of its physical, chemical, and microbiological attributes. Captopril API with the strengths of 0.8 mg/mL and 4 mg/mL compounded in FS™ : FP™ (1:1) and FS-SF™ : FP™ (1:1) oral vehicle formulations have shown to have a beyond-use date of at least 23 days under controlled refrigerated conditions (2-8°C). In contrast, due to loss in potency below specification, Captopril samples placed in controlled room temperature found to be unstable beyond day 8. Refrigerated storage is required for Captopril oral suspensions if used for more than 8 days. All Captopril oral suspensions must be shaken before use.

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