Stability Study of Hydralazine HCl Oral Solutions Compounded in Humco Oral Vehicles to Determine a Beyond-use Date

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ABSTRACT:

Hydralazine HCl was compounded into three formulations, at two concentrations 1 mg/mL and 10 mg/mL, using Humco's oral compounding vehicles, and these formulations were evaluated for physical, chemical, and microbiological stability over a period of 9 weeks, in order to determine a beyond-use-date (BUD). The samples were stored at controlled room temperature (25 °C and 60% RH) and controlled cold temperature (2 – 8 °C), and after compiling the results for these samples over the time period, it was concluded that the samples compounded in Versa Free™ and 70% Sorbitol Solution (both 1 and 10 mg/mL) and Versa Free™ with 1% Carrageenan (10 mg/mL) were stable for at least 63 days when kept refrigerated. The 10 mg/mL Hydralazine HCl room temperature samples compounded in Versa Free™, 70% Sorbitol Solution, and Versa Free™ with 1% Carrageenan were also stable for at least 63 days.

KEYWORDS:

Hydralazine Hydrochloride, Versa Free™, Humco, Sorbitol 70%, Oral Solution, Pediatric Use

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).

Hydralazine HCl is an active pharmaceutical ingredient which is used with or without other medications to treat high blood pressure. Controlling the blood pressure helps to prevent strokes, heart attacks, and circulation issues in vascularized organs, among other cardiovascular ailments. Hydralazine HCl is a vasodilator, working by relaxing blood vessels so that blood can flow through the body with less resistance [5, 6]. There have been several studies of Hydralazine HCl compounded into oral solutions and studied at either controlled cold (2 - 8°C) or room temperature (25°C/60% relative humidity). With Hydralazine HCl, the stability varies greatly depending on the type of oral vehicle used. For instance, Hydralazine HCl is stable for only one day in some oral solution vehicles (namely Ora-Sweet) containing sucrose (or any aldose or ketose sugar) [7]. Osazones result from reaction of sugars like sucrose with Hydralazine HCl, and therefore, sugars cannot be used as sweetening agents in oral solutions containing Hydralazine HCl [8, 9]. Sorbitol solutions, containing the sugar alcohol (not an actual aldose or ketose sugar), provided stability up to 21 days at room temperature. Additionally, the USP stipulates that no flavors should be used with Hydralazine HCl oral preparations due to the reactivity of this compound with flavoring agents [6]. The present study data will provide a basis for adjusting the BUD in order to save both the patients' and the pharmacists' time and money on compounded oral prescriptions containing Hydralazine HCl.

EXPERIMENTAL:

This study examined the physical, chemical, and microbiological stability of the Hydralazine HCl for oral solutions compounded in Humco Versa Free™, Humco Versa Free™ /1% Carrageenan (1:1), and Humco Sorbitol 70% Solution (following the formulation stipulated in the USP monograph for Hydralazine HCl Compounded Oral Solutions). For the formulation compounded in Humco Versa Free™ /1% Carrageenan (1:1), the 1% Carrageenan suspension was made by heating the appropriate amount of purified water to 80°C and adding the 1% Carrageenan with stirring to dissolve. Upon cooling, the viscous solution is mixed in 1:1 proportions with Humco Versa Free™ to make the compounding vehicle.

Each oral solution was evaluated at a high (10 mg/mL Hydralazine HCl) and a low (1 mg/mL Hydralazine HCl) concentration covering a range of concentrations that should bracket most prescriptions containing Hydralazine HCl. Each oral vehicle was measured out volumetrically, and the specified weight of Hydralazine HCl was added to each oral vehicle formulation with constant stirring, yielding a very specific mass of Hydralazine HCl per unit volume of the oral compounding vehicle. A lab scale homogenizer was used to break up any agglomerations of API that might be present. A 4 oz. (120 mL) amber oval air tight prescription bottle was used as the unit container for the study. Each type of oral solution was evaluated in two storage conditions: controlled room temperature (25 °C and 60% RH) and controlled cold temperature (2 – 8 °C).

Physical evaluations of description, visual appearance, and odor, as well as solution pH and density measurements were conducted. Chemical evaluations identified the API and showed chemical stability of the API over time, and the chemical stability and identification was carried out using the assay method described in the USP monograph for Hydralazine Hydrochloride. The USP assay method for Hydralazine HCl was verified to be appropriate for the analysis of Hydralazine HCl in the oral vehicles prior to the beginning of the study, and ICH Guidelines in publication Q2 (R1) Validation of Analytical Procedures, with the exception of performing Forced Degradation of the Actives and Robustness evaluations. Linearity, accuracy, precision, and specificity were proven to meet acceptance criteria for the analysis of Hydralazine HCl in the studied formulations.

The microbiological evaluations included the Total Aerobic Microbe count, Total Yeast and Molds, and detection of *S. aureus* and *P. aeruginosa*, as detailed in the USP General Chapters <61> and <62>. Acceptance criteria for the microbiological testing are: Total Aerobic Microbes ≤ 100 cfu/mL, Total Yeast and Mold ≤ 10 cfu/mL, and absence of *S. aureus* and *P. aeruginosa.* The three Hydralazine HCl formulations, each prepared at a high concentration and a low concentration to cover a range of probable prescription strengths (1 mg/mL and 10 mg/mL Hydralazine HCl in this case), prepared for this beyond-use-date (BUD) study are shown in Tables 1, 2 and 3.

Table 1: High and Low Concentrations of Hydralazine HCl in 70% Sorbitol Solution*

Ingredients	Amount
Hydralazine Hydrochloride	-
For 1 mg/mL Oral Solution	100 mg
For 10 mg/mL Oral Solution	1000 mg
Humco Sorbitol Solution (70%)	40 g
Methylparaben	65 mg
Propylparaben	35 mg
Propylene Glycol	10 g
Aspartame	50 mg
Purified Water	QS to 100 mL

*(This table reproduced from USP Monograph for Hydralazine HCl for Oral Solution)

Table 2: High and Low Concentration of Hydralazine HCl in Versa Free ™

Ingredient	Amount
Hydralazine Hydrochloride	-
For 1 mg/mL Oral Solution	100 mg
For 10 mg/mL Oral Solution	1000 mg
Humco's Versa Free oral solution™	QS to 100 mL

Table 3: High and Low Concentration of Hydralazine HCl in Versa Free ™ /1% Carrageenan (1:1)

Ingredient	Amount
Hydralazine Hydrochloride	-
For 1 mg/mL Oral Solution	100 mg
For 10 mg/mL Oral Solution	1000 mg
Humco Versa Free ™ / 1% Carrageenan (1:1)	QS to 100 mL

The physical testing and chemical stability testing were conducted approximately weekly, and the evaluations were performed at the initial time 0, followed by Day 3, 7, 14, 21, 28, 35, 52, and 63. Physical data is shown as compared to the original freshly made sample, while chemical stability is represented as a percentage of the initial potency of the Hydralazine HCl remaining at the given time point. The USP monograph sets a range of pH values for Hydralazine HCl Oral Solutions to be 3.0 - 5.0, and the specifications for chemical stability are set at 90-110% of the Hydralazine HCl remaining from the original amount in the sample at the given time point.

Microbiological evaluations were performed at the initial time 0 and at day 63, and these data are presented as total cfu/gram 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 each element of the testing scheme for the Hydralazine HCl samples is shown in Table 4.

Table 4: Testing Conducted with Hydralazine HCl Compounded Oral Solutions during the BUD Study

Test	Method	Specification	Testing Interval
Description/Physical Form/Odor	Organoleptic	Must match initial description. No evident separation, stratification or non-homogeneity upon shaking.	All Time Points
Hydralazine HCl Potency Assay*	USP	90-110% of Initial Conc.	All Time Points
Identification by HPLC Hydralazine HCl	USP	Retention time of standard and sample peaks must match	All Time Points
pH $_{(neat)}$	pH Meter	Report	All Time Points
Total Aerobic Microbial Count	USP <61>	≤ 100 cfu/mL	Days 0 and 63
Total Combined Yeast & Mold	USP <61>	≤ 10 cfu/mL	Days 0 and 63
Absence of *S. aureus* and *P. aeruginosa*	USP <62>	Absent	Days 0 and 63

RESULTS AND DISCUSSIONS:

The results for the physical testing of the three Hydralazine HCl compounded oral solution formulas, at both the controlled cold temperature (2 – 8 °C) and controlled room temperature (25 °C and 60% RH), are shown in Table 5.

Table 5: Physical Testing Results for Hydralazine HCl Formulas Stored at Controlled Cold and Room Temperature

Formula	Conc.	Description		Density (mg/mL)	pH
		Initial	Days 3-63	Initial	Range from Initial - Day 63
70% Sorbitol (USP Compounded Oral Solution)	1 mg/mL	Clear, uniform, colorless flowable liquid with no odor	Matches Initial *Except Cold Temperature Days 52 and 63	1.10	7.3 - 7.7
	10 mg/mL	Clear, uniform, slightly yellow flowable liquid with no odor	Matches Initial *Except Cold Temperature Days 52 and 63	1.10	5.6 - 6.2
Humco Versa Free™	1 mg/mL	Clear, uniform, colorless flowable liquid with no odor	Matches Initial	1.07	4.8 - 5.0
	10 mg/mL	Clear, uniform, slightly yellow flowable liquid with no odor	Matches Initial	1.07	4.6 - 4.8
Humco Versa Free with 1% Carrageenan	1 mg/mL	Clear, uniform, colorless viscous liquid with no odor	Matches Initial	1.00	4.7 - 4.9
	10 mg/mL	Clear, uniform, slightly yellow viscous liquid with no odor	Matches Initial	1.00	4.6 - 4.7

The results for physical testing show that all three of the Hydralazine HCl Oral solutions compounded in Humco Versa Free and Versa Free with 1% Carrageenan oral vehicles, at 1 mg/mL and 10 mg/mL, were stable in terms of description of the physical form, density, and pH. There was no separation, color change, non-homogeneity, or change in appearance or organoleptic properties observed in the samples over the study period for samples compounded in those oral vehicles.

The 1 and 10 mg/mL samples compounded in 70% Sorbitol solution, as detailed in the USP monograph for Hydralazine HCl Oral Solutions, showed small yellow particulate matter when stored at Cold Temperature at 52 and 63 days. Since this formulation had acceptable potency (see Table 5) throughout the 63 day BUD study, this particulate matter is not expected to contain active ingredient. It is likely that these particulates are ingredients in the placebos that have precipitated out of solution at cold temperature, and this not expected to affect the overall safety or effectiveness of the oral solution.

The density of the samples remained constant, and the pH values varied slightly, but remained within ± 0.5 pH units of the original measured pH. Note that the USP monograph for Hydralazine HCl Compounded Oral Solutions mentions that the pH of the sample should be 3.0 - 5.0. The exact formulation listed in that monograph was followed, however, the pH values did not fall into that pH range (the pH's were 7.3 - 7.7 and 5.6 - 6.2 for the 1 mg/mL and 10 mg/mL solutions, respectively). The pH values were maintained within ± 0.5 pH units of the original measured pH. The three Hydralazine HCl samples, therefore, are concluded to be physically stable for at least 63 days.

The results for the chemical stability testing of the three Hydralazine HCl compounded oral solution formulas, at both the controlled cold temperature (2 – 8 °C) and controlled room temperature (25 °C and 60% RH), are shown in Tables 6 and 7, respectively.

Table 6: Chemical Stability of Hydralazine HCl Oral Solutions at Controlled Cold Temperature (2 – 8 °C)

Temperature Storage	Formula	Concentration	Hydralazine HCl Assay							
			Initial Potency (mg/mL)	% of Initial Remaining						
				Day 3	Day 7	Day 14	Day 21	Day 28	Day 35	Day 52	Day 63
Controlled Cold Temperature (2 – 8 °C)	70% Sorbitol (USP Compounded Oral Solution)	1 mg/mL	1.006	101.6	100.3	102.0	98.2	98.8	98.4	98.0	98.0
		10 mg/mL	9.989	100.9	95.7	103.4	97.9	99.4	100.3	100.0	99.0
	Humco Versa Free™	1 mg/mL	1.001	100.2	98.7	99.1	94.9	94.8	95.1	90.9	89.8*
		10 mg/mL	10.053	99.1	100.7	101.5	98.4	100.4	100.3	98.4	99.5
	Humco Versa Free with 1% Carrageenan	1 mg/mL	0.994	96.9	98.3	98.5	93.5	97.0	95.1	90.4	88.6
		10 mg/mL	9.482	104.0	100.1	100.0	96.3	96.8	97.9	95.9	95.7

* - Rounds to 90%

Table 7: Chemical Stability of Hydralazine HCl Oral Solutions at Room Temperature (25°C & 60% RH)

Temperature Storage	Formula	Concentration	Hydralazine HCl Assay							
			Initial Potency (mg/mL)	% of Initial Remaining						
				Day 3	Day 7	Day 14	Day 21	Day 28	Day 35	Day 52	Day 63
Controlled Room Temperature (25 °C and 60% RH)	70% Sorbitol (USP Compounded Oral Solution)	1 mg/mL	1.006	99.5	98.2	96.7	91.7	90.8	90.5	90.7	85.0
		10 mg/mL	9.989	96.6	99.6	100.0	96.6	98.2	97.9	93.8	96.1
	Humco Versa Free™	1 mg/mL	1.001	97.0	93.7	91.3	85.5	86.4	80.2	67.8	69.1
		10 mg/mL	10.053	101.0	100.4	100.9	97.4	99.1	98.6	90.1	92.0
	Humco Versa Free with 1% Carrageenan	1 mg/mL	0.994	95.8	90.9	85.4	77.9	74.5	71.9	60.0	55.2
		10 mg/mL	9.482	97.4	96.9	96.9	93.0	94.6	93.8	91.9	92.3

The results for chemical stability testing show that all two of the three Hydralazine HCl Oral solutions compounded in Humco oral vehicles - Versa Free and 70% Sorbitol solution - at 1 mg/mL and 10 mg/mL, were chemically stable for at least 63 days when stored in refrigerated conditions. The Versa Free with 1% Carrageenan 10 mg/mL Hydralazine HCl solution was also stable for at least 63 days under refrigerated conditions, but the 1 mg/mL Hydralazine HCl concentration with Versa Free and 1% Carrageenan failed to meet the specification of 90-110% of the API remaining after 63 days.

The study on the room temperature stability of the Hydralazine HCl formulations showed that the three formulas - Versa Free, Versa Free with 1% Carrageenan, and the 70% Sorbitol solution - were stable when the 10 mg/mL concentration was compounded, however, the low concentration 1 mg/mL samples failed to meet the specification 90-110% of the original amount of Hydralazine HCl at the 63 day time point. Apart from the naturally increased degradation kinetics that accompany a higher storage temperature, it also appears that the Carrageenan plays a role in degrading the API, since the 1 mg/mL sample barely met the specification at 7 days. Carrageenan, a natural complex carbohydrate, could undergo similar reactions with Hydralazine HCl as sucrose does, and further studies can determine the nature of the degradation kinetics. Suffice it to say that the Carrageenan would not be a good choice for a thickening agent for Hydralazine HCl oral solutions.

The microbiological evaluations for the Hydralazine HCl oral solutions, tested according to USP <61> and <62>, at Time 0 and Day 63 are shown in Tables 8 and 9, respectively.

Table 8: Microbiological Results for Hydralazine HCl Oral Solutions - Initial Testing Time 0

Formulation	Concentration	Total Aerobic Microbial Count	Total Yeast and Mold	Mannitol Test for *S. aureus*	Cetrimide Test for *P. aeruginosa*
Hydralazine HCl compounded in Humco 70% Sorbitol (USP Compounded Oral Solution)	1 mg/mL	0 cfu/mL	0 cfu/mL	Negative	Negative
	10 mg/mL	0 cfu/mL	0 cfu/mL	Negative	Negative
Hydralazine HCl compounded in Humco Versa Free™	1 mg/mL	0 cfu/mL	0 cfu/mL	Negative	Negative
	10 mg/mL	0 cfu/mL	0 cfu/mL	Negative	Negative
Hydralazine HCl compounded in Humco Versa Free with 1% Carrageenan	1 mg/mL	0 cfu/mL	0 cfu/mL	Negative	Negative
	10 mg/mL	0 cfu/mL	0 cfu/mL	Negative	Negative

Table 9: Microbiological Results for Hydralazine HCl Oral Solutions from Day 63

Storage Temperature	Formulation	Concentration	Total Aerobic Microbial Count	Total Yeast and Mold	Mannitol Test for *S. aureus*	Cetrimide Test for *P. aeruginosa*
Controlled Cold Temperature (2 – 8 °C)	Hydralazine HCl compounded in Humco 70% Sorbitol (USP Compounded Oral Solution)	1 mg/mL	0 cfu/mL	0 cfu/mL	Negative	Negative
		10 mg/mL	0 cfu/mL	0 cfu/mL	Negative	Negative
	Hydralazine HCl compounded in Humco Versa Free™	1 mg/mL	0 cfu/mL	0 cfu/mL	Inconclusive*	Negative
		10 mg/mL	0 cfu/mL	0 cfu/mL	Negative	Negative
	Hydralazine HCl compounded in Humco Versa Free with 1% Carrageenan	1 mg/mL	0 cfu/mL	0 cfu/mL	Negative	Negative
		10 mg/mL	0 cfu/mL	0 cfu/mL	Negative	Negative
Controlled Room Temperature (25 °C and 60% RH)	Hydralazine HCl compounded in Humco 70% Sorbitol (USP Compounded Oral Solution)	1 mg/mL	0 cfu/mL	0 cfu/mL	Negative	Negative
		10 mg/mL	0 cfu/mL	0 cfu/mL	Negative	Negative
	Hydralazine HCl compounded in Humco Versa Free™	1 mg/mL	0 cfu/mL	0 cfu/mL	Negative	Negative
		10 mg/mL	0 cfu/mL	0 cfu/mL	Negative	Negative
	Hydralazine HCl compounded in Humco Versa Free with 1% Carrageenan	1 mg/mL	10 cfu/mL	0 cfu/mL	Negative	Negative
		10 mg/mL	0 cfu/mL	0 cfu/mL	Negative	Negative

The three Hydralazine HCl oral formulas, each compounded at a high and low concentrations and stored at both controlled cold temperature and controlled room temperature were evaluated for microbiological growth and contamination. Both the Time 0 and Day 63 sample storage conditions showed little to no growth in terms of Total Aerobic Microbes, Total Yeast and Mold, and *S. aureus* and *P. aeruginosa*. The only sample that appeared to show any microbial growth was the Hydralazine in Versa Free kept at room temperature which showed 10 cfu/mL growth, which is far below the upper specification limit of 100 cfu/mL.

CONCLUSIONS:

Overall, it can be concluded that the Hydralazine HCl Oral Solutions compounded in Humco's Versa Free and Humco's 70% Sorbitol Solution had excellent stability in terms of its physical, chemical, and microbiological attributes. Samples compounded in these bases in a concentration range from 1 to 10 mg/mL can be said to have a BUD date of at least 63 days. Furthermore, it can be said that the 10 mg/mL sample in each of the 3 different formulas - Versa Free, 70% Sorbitol Solution, and the Versa Free with 1% Carrageenan - maintained their stability throughout the time of the study. Under the other conditions, a BUD cannot be guaranteed, but following this protocol a BUD of 63 days can be established for Hydralazine Hydrochloride.

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