Stability of Omeprazole Oral Suspensions Compounded in Humco Flavor Sweet Sugar Free Product

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ABSTRACT:

Omeprazole oral suspension was prepared by compounding Omeprazole powder with Humco's Flavor Sweet Sugar Free™(FS-SF™) oral vehicle, with the pH of the solution adjusted to 7.5-8.5 with 8.4% sodium bicarbonate, at two Omeprazole concentrations: 1 mg/mL and 4 mg/mL. These two strengths of Omeprazole suspensions 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 90 days for their physical, chemical, and microbiological stability. Based on the stability data gathered over ten time-points for Omeprazole oral suspensions, both 1 mg/mL and 4 mg/mL strengths stored at controlled cold temperature were physically, chemically, and microbiologically stable for at least 90 days. Both strengths of the compounded suspensions stored at controlled room temperature were chemically stable up to 7-day time point.

KEYWORDS:

Omeprazole, Humco Flavor Products, Flavor Sweet Sugar Free™, Beyond-use Date, Stability of Omeprazole

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).

Omeprazole belongs to the group of drugs known as proton-pump inhibitors (PPIs) which are substituted pyridylmethylsulfinyl benzimidazole compounds. These compounds function by selectively and irreversibly inhibiting the stomach's parietal cells' H^+, K^+-ATPase [5]. Typically, Omeprazole suspension is used in pediatrics and to those who are unable to administer the Omeprazole tablets orally. Omeprazole has become a primary choice for the treatment of number of acid-reflux diseases including but not limited to, Zollinger-Ellison syndrome, gastroesophageal reflux disease (GERD), gastric ulcers, dyspepsia, and laryngopharyngeal reflux [6, 7]. 8.4% (w/v) sodium bicarbonate was added to the oral suspension vehicle prior to compounding it to the Omeprazole to bring the pH into the range of 7.5-8.5. Masking the bitter taste of Omeprazole, pH adjustment, and act as an antacid are the three key functions of added sodium bicarbonate in the Humco Flavor Sweet Sugar Free™ (FS-SF™) oral suspension. Omeprazole being an acid labile, tends to degrade much in the presence of gastric acid. Addition of sodium bicarbonate raises the pH of the oral suspension, which helps to protect Omeprazole from acid degradation [7]. The combination of sodium bicarbonate, Omeprazole, and Humco's Flavor Sweet-Sugar Free™ oral suspension is suitable for easy oral

administration to patients of any age. Flavor Sweet-SF™ is a sugar-free and alcohol-free cherry flavored syrup that is also ideal for diabetic preparations [8].

There are several published studies of Omeprazole oral suspensions compounded in different oral vehicles. The stability of Omeprazoleis found to be dependent on various factors including storage conditions, strengths, and oral vehicle itself [9, 10]. The strengths of Omeprazole in most of the studies are ranged from 0.65 – 4.0 mg/mL and the stability of Omeprazole are ranged from 30 days to 92 days under refrigerated conditions [9, 10, and 11]. Unlike these vehicles which either needs a complex preparation or reconstitution, Humco's Flavor Sweet-SF™ is ready-to-use oral suspension vehicle after addition of sodium bicarbonate. The objective of this study was to examine the stability of Omeprazole upon compounding in oral suspension using Humco's Flavor Sweet SF™ to determine the beyond-use-date (BUD).

EXPERIMENTAL:

In this study, the physical, chemical, and microbiological stability of Omeprazole compounded in a Humco Flavor Sweet-SF™ was conducted over the period of 90 days. The oral suspension was compounded at a high (4 mg/mL Omeprazole) and a low (1 mg/mL Omeprazole) concentration covering a range of concentrations that should bracket most prescriptions containing Omeprazole, and these two strengths were evaluated at two storage conditions: controlled cold (2 – 8 °C) and room temperature (25 °C and 60% RH). Flavor Sweet-SF™ as an oral suspension vehicle was measured out volumetrically, and the specified weight 8.4% (w/v) of sodium bicarbonate was added, followed by the addition of Omeprazole. A lab scale homogenizer was used to break up any agglomerations of active pharmaceutical ingredient (API) that might be present in the oral suspensions, and 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.

As a part of the physical testing, the description, visual appearance, odor were observed, and the pH and density measurements were conducted. Chemical testing identified 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 Omeprazole Oral Suspension. The USP assay method for Omeprazole was verified to be appropriate for the analysis of Omeprazole in the oral vehicle prior to the beginning of the stability study. The method verification was conducted according to the ICH Guidelines in publication Q2 (R1) 'Validation of Analytical Procedures', 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 Omeprazole 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 90) along with the intermediate of the study at day 63. Acceptance criteria for the microbiological testing are: TAMC ≤ 100 cfu/mL, TYAM ≤ 10 cfu/mL, and absence of *S. aureus* and *P. aeruginosa.* The Flavor Sweet-SF™ formulations, each formulated at 1 mg/mL and 4 mg/mL Omeprazole, prepared for this beyond-use-date (BUD) study are shown in Table 1.

Table 1: High and Low Concentrations of Omeprazole in Humco Flavor Sweet-SF™

Ingredient (s)	Amount
Omeprazole	-
For 1 mg/mL Oral Suspension	100 mg
For 4 mg/mL Oral Suspension	400 mg
Sodium Bicarbonate	8.4 g
Humco Flavor Sweet-SF™	QS to 100 mL

The physical and chemical testing were conducted at the initial time 0, followed by day 7, 14, 21, 28, 35, 43, 51, 63, and 90. 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 Omeprazole remaining at the given time point. The USP monograph sets a range of pH values

for Omeprazole oral suspension to be 7.5 – 8.5, and the acceptable specifications for chemical stability are set at 90-110% of the Omeprazole remaining from the original amount in the sample at the given time point.

Microbiological evaluations were performed at the initial time 0, day 63, and day 90, 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 Omeprazole samples is shown in Table 2.

Table 2: Testing Conducted for Omeprazole Oral Suspension formulations during the Stability/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
Omeprazole Potency/ Assay*	USP	90-110% of Initial Conc.	All Time Points
Identification by HPLC Omeprazole	USP	Sample peak matches that of the standard	All Time Points
pH $_{(neat)}$	pH Meter	7.5 – 8.5	All Time Points
Total Aerobic Microbial Count	USP <61>	≤ 100 cfu/mL	Days 0, 63, and 90
Total Combined Yeast & Mold	USP <61>	≤ 10 cfu/mL	Days 0, 63, and 90
Absence of *S. aureus* and *P. aeruginosa*	USP <62>	Absent	Days 0, 63, and 90

RESULTS AND DISCUSSIONS:

The results for the physical testing of the Omeprazole compounded oral suspensions formulas, at both the controlled cold temperature (2 – 8 °C) and controlled room temperature (25 °C and 60% RH), are shown in Tables3 and 4.

Table 3: Physical testing results for Omeprazoleformulas Stored at Controlled Cold Temperature (2 – 8 °C)

Controlled Cold Temperature (2 – 8 °C)				
Formulation Concentration	**Description**		**Density (mg/mL) Initial - Day 90**	**pH Range from Initial - Day 90**
	Initial (day 0)	**Days 7 - 90**		
1 mg/mL Omeprazole in FS-SF^{TM}	Light pink with cherry odor viscous liquid, smooth	Matches initial description. No separation upon shaking. No color change.	1.12	8.3 – 8.5
4 mg/mL Omeprazole in FS-SF^{TM}	Light pink with cherry odor viscous liquid, smooth	Matches initial description. No separation upon shaking. No color change.	1.13	8.3 – 8.5

Table 4: Physical testing results for Omeprazole Formulas Stored at Controlled Room Temperature (25 °C, 60% RH)

Controlled Room Temperature (25 °C, 60% RH)				
Formulation Concentration	**Description**		**Density (mg/mL) Initial - Day 90**	**pH Range from Initial - Day 90**
	Initial (day 0)	**Days 7 - 90**		
1 mg/mL Omeprazole in FS-SF™	Light pink with cherry odor viscous liquid, smooth	Started to change the color to purple/pink. Uniform upon shaking.	1.12	8.2 – 8.4
4 mg/mL Omeprazole in FS-SF™	Light pink with cherry odor viscous liquid, smooth	Started to change the color to purple/pink. Uniform upon shaking.	1.13	8.2 – 8.5

The results for physical testing show that both strengths of Omeprazole (1 mg/mL and 4 mg/mL) compounded in Humco in Flavor Sweet SF™ stored in a controlled cold temperature (CT) were stable in terms of description of the physical form, density, and pH. Upon shaking, the suspension became uniform with no separation, color change, non-homogeneity. Additionally, no change in appearance or organoleptic properties was observed in the Omeprazole formulations compounded in FS-SF™ over the study. However, samples placed in the room temperature (RT) were started to change the colors to purplish pink after day 7. The color change got more intense as time progressed. The physical observation for the controlled room temperature samples did not match the initial description beyond day 7.

The density of the samples remained constant, and the pH values varied slightly, but,according to the USP monograph for Omeprazole oral suspension, remained within acceptable limits (pH 7.5 – 8.5). The average pH of 1mg/mL CT, 4 mg/mL CT, 1 mg/mL RT, and 4 mg/mL RT formulations measured as 8.3 ± 0.1 (mean ± standard deviation, n = 10 time points), 8.4 ± 0.1, 8.3 ± 0.1, and 8.3 ± 0.1 respectively. The Omeprazole oral suspension formulations placed in the cold temperature met the criteria for physical testing for minimum of 90 days. The color changes of the formulations stored in room temperature at day 7 show that the refrigerated storage is required for Omeprazole in Flavor Sweet SF™ suspensions used for more than 7 days.The results for the chemical stability testing of the Omeprazole compounded in Flavor Sweet-SF™ formulas, at both the controlled cold temperature (2 – 8 °C) and controlled room temperature (25 °C and 60% RH), are shown in Tables5 and 6.

Table 5: Chemical stability of OmeprazoleOral Suspensions at Controlled Cold Temperature (2 – 8 °C)

Controlled Cold Temperature (2 – 8 °C)										
Formulation	**Omeprazole Assay**									
	Initial Potency (mg/mL)	**% of Initial Remaining**								
		Day 7	**Day 14**	**Day 21**	**Day 28**	**Day 35**	**Day 43**	**Day 51**	**Day 63**	**Day 90**
Omeprazole in Humco Flavor Sweet SF™	1.04	98.7	95.5	97.8	97.4	97.2	94.2	92.6	93.4	93.7
	4.13	102.8	95.7	98.7	95.4	99.4	97.5	97.1	99.3	95.7

Table 6: Chemical stability of Omeprazole Oral Suspensions at Controlled Room Temperature (25 °C and 60% RH)

Controlled Room Temperature (25 °C and 60% RH)										
Formulation	**Omeprazole Assay**									
	Initial Potency (mg/mL)	**% of Initial Remaining**								
		Day 7	**Day 14**	**Day 21**	**Day 28**	**Day 35**	**Day 43**	**Day 51**	**Day 63**	**Day 90**
Omeprazole in Humco Flavor Sweet SF™	1.04	93.5	80.5	75.7	66.9	56.3	47.2	47.5	29.3	11.9
	4.13	100.0	92.1	92.5	92.5	83.4	88.0	85.1	78.5	75.9

The results for chemical stability testing show that both concentrations (1 mg/mL and 4 mg/mL) of Omeprazolecompounded in Humco's Flavor Sweet-SF™ oral suspensions, were chemically stable for at least 90 days when stored in refrigerated conditions. However, Omeprazole oral suspensions formulations 1 mg/mL and 4 mg/mL did not meet the specification of 90 – 110% of the API remaining after day 7 and day 28 respectively. Shown graphically in Figure 1, Omeprazole formulation stored in room temperature tends to degrade faster with 11.9% and 75.9% percent of initial remaining concentration at day 90.

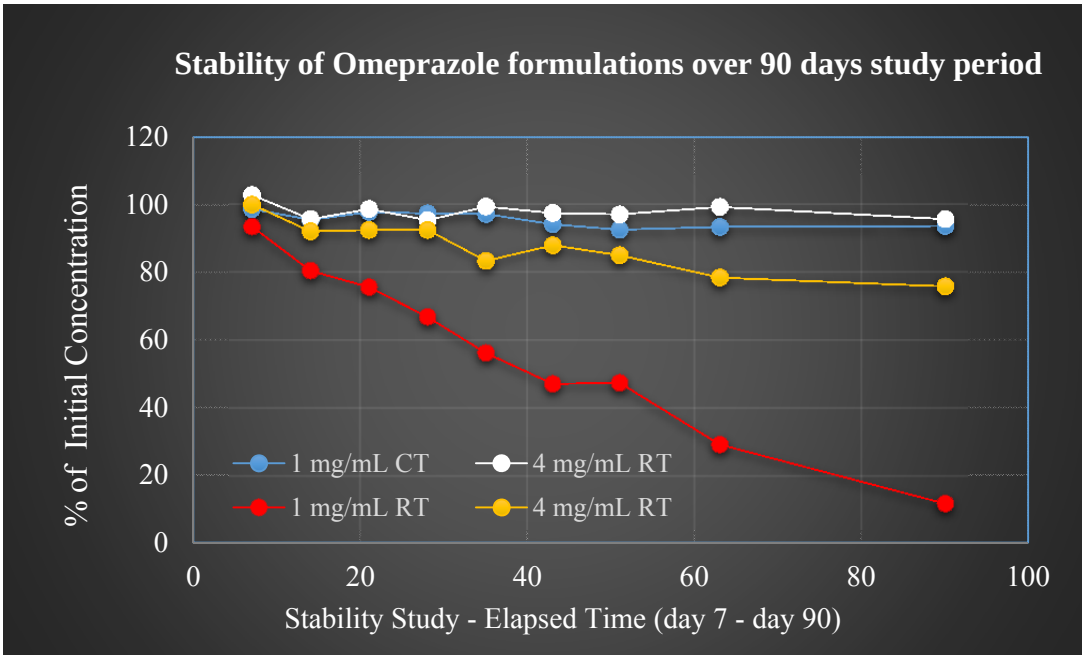

Figure 1. Percent Initial Omeprazole Remaining vs. Study Timepoints for Omeprazole FS-SF™ formulations at CT & RT

The microbiological evaluations for the Omeprazole oral suspensions, tested according to USP <61> and <62>, at Time 0 is shown in Table 7 and micro results at 90 Days are shown in Table 8.

Table 7: Microbiological results for Omeprazole Oral Suspensions from initial testing (time 0).

Storage Condition	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)	1 mg/mL	0 cfu/mL	0 cfu/mL	Negative	Negative
	4 mg/mL	0 cfu/mL	0 cfu/mL	Negative	Negative
Controlled Room Temperature (25 °C and 60% RH)	1 mg/mL	0 cfu/mL	0 cfu/mL	Negative	Negative
	4 mg/mL	0 cfu/mL	0 cfu/mL	Negative	Negative

Table 8: Microbiological results for Omeprazole Oral Suspensions at 63 Days and 90 Days

Storage Condition	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)	1 mg/mL	0 cfu/mL	0 cfu/mL	Negative	Negative
	4 mg/mL	0 cfu/mL	0 cfu/mL	Negative	Negative
Controlled Room Temperature* (25 °C & 60% RH)	1 mg/mL	0 cfu/mL	0 cfu/mL	Negative	Negative
	4 mg/mL	0 cfu/mL	0 cfu/mL	Negative	Negative

*Samples stored in controlled Room Temperature were not tested at day 90.

Each high and low concentration Omeprazole formulation, stored at both controlled cold temperature and controlled room temperature, were evaluated for microbiological growth and contamination. The micro testing time points Time 0 and Day 90 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 7 samples, micro testing of those samples was not conducted at day 90. All controlled cold temperature samples, however, met the specific criteria for micro testing at day 90.

CONCLUSIONS:

Overall, it can be concluded that the Omeprazole oral suspensions compounded in Humco's Flavor Sweet Sugar Free™ under refrigerated conditions had an excellent stability in terms of its physical, chemical, and microbiological attributes. Omeprazole API with the strengths of 1 mg/mL and 4 mg/mL compounded in FS-SF™ oral vehicle while adding 8.4% w/v Sodium Bicarbonate into the formulation have shown to have a beyond-use date of at least 90 days under controlled refrigerated conditions (2-8°C). In contrast, due to change in color and potency loss, samples placed in controlled room temperature found to be stable until day 7 Refrigerated storage is required for Omeprazole in Flavor Sweet SF™ suspensions used for more than 7 days. All Omeprazole suspensions in these specific formulations must be shaken before use.

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