# Stability of Verapamil Hydrochloride in SyrSpend SF Compared to Sorbitol Containing Syrup and Suspending Vehicles

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## ABSTRACT

**Verapamil hydrochloride is widely prescribed to treat multiple cardiovascular diseases. There are a number of generic manufacturers of verapamil tablets and injectables. The need for other administration options for patients who cannot take tablets has led compounding pharmacies to seek other alternatives, namely, oral solutions and suspensions. The stability of these compounded verapamil oral liquid preparations is a concern to anyone making them. The objective of this study was to determine the stability of verapamil hydrochloride in SyrSpend SF in comparison to stability of verapamil hydrochloride in Ora-Sweet SF:Ora-Plus (1:1). The two samples were compounded in 50-mL batches and stored in amber 60-mL plastic prescription bottles at United States Pharmacopeia refrigerated conditions. Five replicates at each pre-defined time point were assayed by a stability-indicating high performance liquid chromatographic method with an end date of 60 days. No degradation peaks were seen in the chromatograms for either preparation at any time point and the recovery of verapamil hydrochloride was within 90% to 110% of the initial concentration for all replicates. Verapamil hydrochloride is stable in amber plastic prescription bottles for 60 days when refrigerated for both SyrSpend SF and Ora-Sweet SF:Ora-Plus (1:1).**

## INTRODUCTION

Verapamil hydrochloride (HCl) is a phenylalkylamine calcium channel blocker which was introduced in 1962 as an antiarrhythmic and antianginal agent.[1] Although verapamil is mainly used in cardiovascular diseases, it has become a regularly prescribed high-dose prophylactic treatment of both episodic and chronic cluster headaches.[2] It has also been shown to be an effective therapeutic agent for the treatment of hypertrophic cardiomyopathy in children.[3]

Due to the varying uses of verapamil, it is prescribed to a large cross-section of the population ranging from pediatrics to geriatrics. Although the vast majority of patients' cluster headache onset tends to be in the late 20s and early 30s,[4] chronic cluster headaches tend to last upwards of 20 to 30 years, which would place them in an elderly demographic. Additionally, Fields et al studied adult hypertension, for which verapamil is an effective treatment, between 1999 and 2000 and found increasing percentages of hypertension at increased ages (18 to 34 6.00%, 35 to 44 16.00%, 45 to 54 31.00%, 55 to 64 58.00%, 65 to 74 65.10%, and 75+ 77.60%).[5]

Verapamil is currently commercially supplied as intravenous injections and both immediate- and slow-release tablets. With the increasing ages of patients requiring verapamil and its uses in pediatrics, additional dosage delivery forms are necessary for patients that cannot administer oral tablets because they might be incapable of swallowing the tablets.[6]

Verapamil is a white crystalline solid that has a bitter taste which benefits from a sweetener in oral preparation formulations. Stability studies in Ora-Sweet SF:Ora-Plus (Paddock Laboratories Inc., Minneapolis, Minnesota) (1:1) have been completed and showed refrigerated stability of verapamil out 60 days.[7] Ora-Sweet SF and Ora-Plus suspending vehicles both contain sorbitol, which increases the osmolality of the verapamil solutions, possibly leading to negative patient side effects. Sorbitol can also cause nausea, which is already a potential side effect of verapamil treatment, and could exacerbate the reaction.

SyrSpend SF (Gallipot, St. Paul, Minnesota) is a sugar- and sorbitol-free suspending agent with a low osmolality. The cherry flavored variety provides a masking effect for the bitter verapamil and could be an alternative for creating verapamil oral solutions or suspensions.

The objective of this study was to compare the stability of verapamil HCl oral solutions using either Ora-Sweet SF:Ora-Plus (1:1) or SyrSpend SF as solution vehicles and stored in amber prescription vials at a concentration of 50 mg/mL stored at United States Pharmacopeia (USP) refrigerated conditions (2°C to 8°C). Stability was assessed by percent recovery studies at varying time points throughout 60 days.

## MATERIALS AND METHODS

### Chemical Reagents

Two separate lots of Verapamil HCl were purchased from two separate vendors; Spectrum Chemical (Lot YR3110; Gardena, California) and Sigma Aldrich (Lot 118K1197; St. Louis, Missouri). High-performance liquid chromatographic (HPLC)-grade acetonitrile (Lot CZ629; Burdick & Jackson, Kalamazoo, Michigan) and methanol (Lot 09253-74; Pharmco-Aaper, Brookfield, Connecticut), anhydrous sodium acetate (Lot 46177843;

EMD, Gibbstown, New Jersey), and Glacial Acetic Acid (Lot 067970; Fairlawn, New Jersey) were used in the study. HPLC-grade water was supplied by filtering deionized water from a Millipore Elix through a Millipore Simplicity (Billerica, Massachusetts).

### Equipment and Chromatographic Conditions

The HPLC instrument was a Varian Prostar (Palo Alto, California) equipped with a model 230 tertiary gradient solvent delivery system, a model 335 photodiode array detector, and a model number 410 programmable autosampler fitted with a 100-mcL sample injection loop and 250-mcL syringe. The HPLC was operated and data was quantitated using Galaxie software from Varian. The mobile phase for the system was 50 mM sodium acetate, acetonitrile, methanol (540:360:100), adjusted to a pH of 4.25 with glacial acetic acid and delivered at 1.5 mL/minute. Chromatographic separation was achieved using a 150 mm × 4.6 mm Phenomenex (Torrance, California) Gemini C18 column with 5-mcm particle packing. The mobile phase was used as solvent in diluting the standard and assay preparations to 25 mcg/mL. Assay and standard preparations were monitored at 271 nm following 100-mcL full-sample loop injections.

### Validation of Forced-degradation Studies to Determine Stability-indicating Characteristics of the High-performance Liquid Chromatographic Method

Verapamil HCl samples were stressed and assayed to determine the sensitivity of the HPLC method regarding the analyte of interest and any possible degradant or impurities. Verapamil HCl was diluted to 25 mcg/mL in solutions of base (0.1N NaOH), acid (0.1N HCl), and hydrogen peroxide (3.5%), in addition to exposure to ultraviolet (UV) light at 365 nm and heat at 70°C. Time under these stressors varied due to the relative stability of verapamil to each individual condition. Additional peaks found in the chromatograms were labeled and the resolution (USP) was determined between the degradant and the verapamil. A resolution of 1.5 was considered full separation. Peak purity calculations were performed on verapamil based on an external reference spectrum and on the peak's apex.

### Preparation of Verapamil Hydrochloride Suspension Samples

The compounding of the samples was loosely based on a formulation that was written by Dr. Loyd V. Allen Jr. and published in the *International Journal of Pharmaceutical Compounding*.[8]

Verapamil HCl in Ora-Sweet SF:Ora-Plus (1:1) was prepared by adding an appropriate amount of verapamil HCl (Sigma Aldrich) into a [ceramic] mortar and grinding into a uniform powder. To a 50-mL volumetric flask, 2.5 g of powder was added, followed by 10 mL of Ora-Sweet SF using a volumetric pipette. The flask contents were stirred on a stir plate while adding another 15 mL of Ora-Sweet SF. To bring the contents of the flask to volume, 25 mL of Ora-Plus was used, and it was stirred until a homogeneous preparation was achieved. The contents of the flask were poured into a 60-mL amber prescription bottle and stored for stability studies. After approximately 15 minutes of stirring, extra solid precipitate appeared in the suspension. This precipitate was not identified.

Verapamil HCl in SyrSpend SF was prepared similarly to the previous solution. After weighing 2.5 g of uniform powder to a 50-mL volumetric flask, 25 mL of SyrSpend SF was added and stirred. The preparation was brought to volume with SyrSpend SF, stirred until homogenous, placed into a 60-mL amber plastic prescription bottle, and stored for stability studies.

### Stability Study

Two different samples were submitted for stability: verapamil HCl 50-mg/mL suspension in Paddock Laboratories Ora-Sweet SF:Ora-Plus (1:1) (Lot 9439089 and 9499528, respectively) and verapamil HCl 50-mg/mL suspension in Gallipot Inc. SyrSpend SF (Lot 0909185J12). The samples were packaged in 60-mL low actinic plastic prescription bottles, each containing 50 mL suspension and stored at USP controlled refrigerated temperature (2°C to 8°C) using a digitally controlled laboratory refrigerator from Forma Scientific (Edison, New Jersey). Time points for the study were initial (T=0), 1 day (T=1), 7 days (T=7), 11 days (T=11), 14 days (T=14), 28 days (T=28), 36 days (T=36), 47 days (T=47), and 60 days (T=60). The evaluation parameter was percent recovery assays. The stability of verapamil HCl in each of the suspensions was defined by the percent recovery with respect to T=0 using the validated HPLC method. The samples were prepared five times by adding 0.5 mL of suspension with a volumetric pipette to 1000 mL mobile phase for a 1:2000 total dilution and calculating the averages and standard deviations for all replicate injections.

## RESULTS

The stability of verapamil HCl in either Ora-Sweet SF:Ora-Plus (1:1) or SyrSpend SF is shown in Table 1. The beginning analyses of 50.32 mg/mL for Ora-Sweet SF:Ora-Plus (1:1) and 46.14 mg/mL for SyrSpend SF at T=0 were set as the initial concentrations of the study and all subsequent time points were compared to these values. Figures 1 and 2 show the data in terms of concentration and show that both suspensions remained within specifications (90%< [verapamil HCl] <110%) throughout the duration of the study.

**TABLE 1. Stability of Verapamil Hydrochloride in Ora-Sweet SF:Ora-Plus (1:1) and SyrSpend SF Refrigerated (2°C to 8°C) for 60 Days.**

| Elapsed Time | Ora-Sweet SF:Ora-Plus (1:1) % Recovery | SyrSpend SF % Recovery |
|---|---|---|
| T=0 | 100 | 100 |
| T=1 | 100.86 | 99.79 |
| T=7 | 101.47 | 104.06 |
| T =11 | 95.33 | 98.99 |
| T=14 | 97.66 | 96.6 |
| T=28 | 98.95 | 96.54 |
| T=36 | 102.75 | 94.18 |
| T=47 | 104.08 | 104.47 |
| T=60 | 101.92 | 102.52 |

## DISCUSSION

The HPLC method was shown to be stability-indicating by forcibly degrading verapamil HCl and separating the degradant peaks from that of the main analyte. Verapamil HCl was stable to heat, UV light, acid and base; however, oxidizer created an initial degradant peak.

**FIGURE 1. Plot of verapamil hydrochloride concentration in Ora-Sweet SF: Ora Plus (1:1) Suspension.**
**(Dashed lines represent upper and lower limits of verapamil hydrochloride specifications.)**

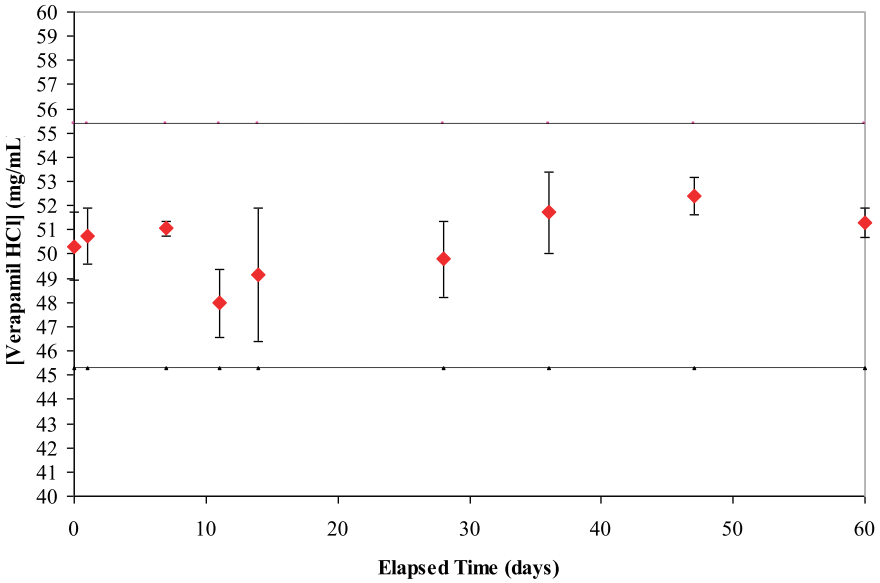


**FIGURE 2. Plot of verapamil hydrochloride concentration in SrySpend SF Suspension.**
**(Dashed lines represent upper and lower limits of verapamil hydrochloride specifications.)**

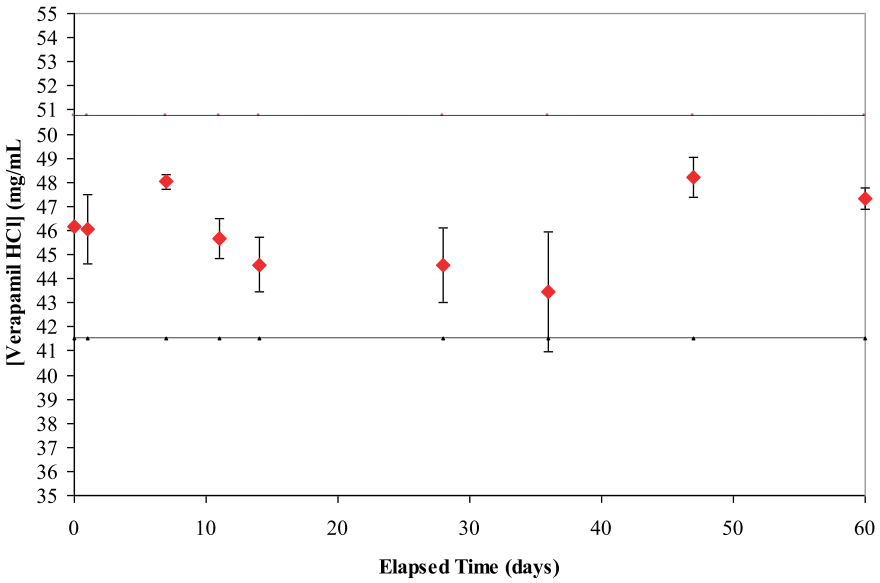


Figure 3 shows a standard unstressed verapamil sample overlaid with an oxidized stressed verapamil sample. The main degradant was completely separated from the analyte with acceptable resolution. Additionally, validation parameters listed in Table 2 show that all system suitability results met acceptance criteria.

### Paddock Laboratories Inc. Ora-Sweet SF:Ora-Plus (1:1) Verapamil Hydrochloride Suspension

Table 1 and Figure 1 show the stability data for a verapamil in Ora-Sweet SF:Ora-Plus (1:1) suspension stored refrigerated and light-protected for 60 days. The sample's potency began at 50.32 mg/mL, which was 100.64% of the compounding target of 50 mg/mL. This value was set as the baseline for all the subsequent time points. All of the time points had consistent chromatographic profiles as T=0, and no degradant peaks were visualized throughout the study. The data followed no specific concentration profile or general trend and appeared to remain constant with all results falling within two T=0 standard deviations from the initial concentration. At no time in the study did the standard deviation from any time point place the sample outside of the acceptable limits.

### Gallipot SyrSpend SF Verapamil Hydrochloride Suspension

The initial potency of the verapamil HCl SyrSpend SF suspension was 46.14 mg/mL, which is shown in Figure 2. This concentration was 92.3% of the compounding target of 50 mg/mL. The T=0 result was set as the baseline for all other time points tested. The assay results were congruent with the Ora-Sweet SF:Ora-Plus (1:1) suspension results because they vary at time points and do not follow any discernable trend. The assay results varied between 43.45 mg/mL (T=36) and 48.01 mg/mL (T=7). Day 36, the time point with the lowest results, did have a standard deviation (results of 42.22 mg/mL, 42.29 mg/mL, 47.85 mg/mL, 41.95 mg/mL, and 42.96 mg/mL) that could place the sample just out of specification, although every sample replicate and the average were above the acceptable limits. Every replicate chromatogram for every time point was clear of degradant peaks and had the same chromatographic profiles.

**FIGURE 3. Chromatograms of verapamil hydrochloride.**

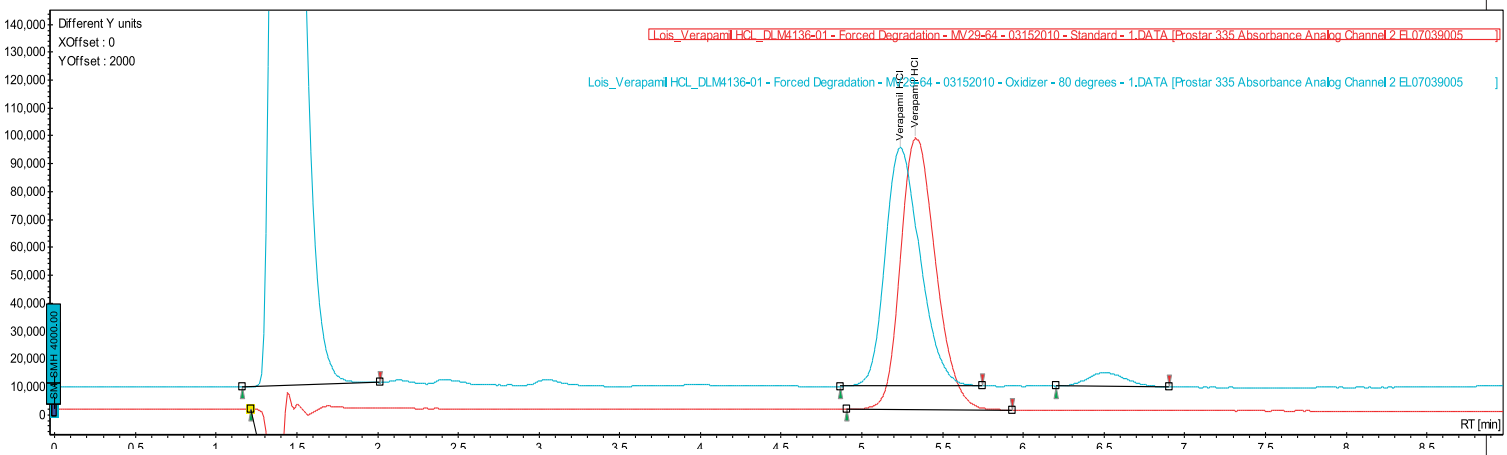


**TABLE 2. Summary of the Validation Parameters for the High-performance Liquid Chromatographic Method Used in the Stability Study of Verapamil Hydrochloride.**

| Validation Parameter | Results |
|---|---|
| Peak Tailing | 1.29 %RSD = 1.5 |
| Theoretical Plates | 2248.8 %RSD = 0.8 |
| Linear Range (271 nm) | 6-115 mcg/mL $R^2$ = 0.9997 |
| Extraction Precision Ora-Sweet SF:Ora-Plus (1:1) *n*=6 | %RSD = 0.5 |
| Extraction Precision (SyrSpend SF) *n*=6 | %RSD = 0.37 |
| LOQ and LOD | 3.7 mcg/mL and 0.7 mcg/mL |
| Accuracy (105, 60, 25 mcg/mL) | %Target = 99.9%, 100.0%, 100.4% |
| Ruggedness (2 days, 2 analysts, 2 instruments) | %RSD = 0.3 %Target = 100.0% |
| Ruggedness (10% change in % organic and pH) | %RSD = 1.7 %Target = 99.8% |
| Specificity (Resolution between main degradant peak) | RT = 6.51 Res(USP) = 2.95 |

## CONCLUSION

Previous studies have shown that verapamil HCl is stable for 60 days in Ora-Sweet SF:Ora-Plus (1:1) which lends support to the findings in this study.[7] Verapamil HCl was stable in Ora-Sweet SF:Ora-Plus (1:1) and SyrSpend SF for 60 days when refrigerated. The shelf-life could not be extended past 60 days with the data acquired since there was no general trend within the 60 days. Varying temperatures were also not addressed in this study.

The findings of this study show that SyrSpend SF is an acceptable oral syrup and suspending vehicle for preparing individual compounded verapamil HCl formulations that are alcohol-, sorbitol-, and sugar-free, while still masking the bitter taste of the raw powder. The formulations would be possible alternatives to injections and tablets when these commercially-available dosage forms are inappropriate for pediatric, geriatric, and other special-needs patient populations.

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