



# Stability of Vancomycin in SyrSpend SF

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## INTRODUCTION

Vancomycin hydrochloride (HCl) is a glycopeptide antibiotic used in the treatment of infections caused by Gram-positive bacteria. An oral form of vancomycin HCl was originally approved by the U.S. Food and Drug Administration for the treatment of *Clostridium difficile* (*C. difficile*)-induced pseudomembranous colitis.<sup>1</sup> It is not orally absorbed into the blood and remains in the gastrointestinal tract to eradicate *C. difficile*. Vancomycin is also used for the treatment of enterocolitis caused by *Staphylococcus aureus* (including methicillin-resistant strains).

Vancomycin HCl is a white crystalline solid with a very bitter taste. The bitter taste presents an issue for patients who are incapable of swallowing the capsules whole. An oral preparation formulation containing a sweetener would provide a masking effect for the bitter taste, thereby increasing the palatability of an oral dose form as a way to increase therapeutic compliance. SyrSpend SF (Fagron US [formerly Gallipot], St. Paul, Minnesota) is a sugar- and sorbitol-free suspending agent which could serve as an alternative for formulating vancomycin HCl oral suspensions.

The objective of this study was to examine the stability of vancomycin HCl prepared in an oral suspension using SyrSpend SF. The decision was made to compound two suspensions, one compounded with vancomycin HCl raw powder and the second compounded with commercially available sterile pharmacy bulk product. The suspensions were stored in low-actinic plastic, amber bottles at a concentration of 50 mg/mL under *United States Pharmacopeia* (USP) refrigerated (2°C to 8°C) storage conditions. Stability was assessed by percent recovery studies performed at varying time points throughout 90 days.

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## ABSTRACT

Vancomycin is administered orally for the treatment of pseudomembranous colitis induced by *Clostridium difficile*. Vancomycin is marketed for this purpose by ViroPharma as VANCOCIN in 125-mg and 250-mg capsules. The need for other dose form options for those patients who cannot take capsules has led compounding pharmacies to seek other alternatives, namely oral solutions and suspensions. Additionally, some patients are unable to use suspending agents containing alcohol or sorbitol. The objective of this study was to determine the stability of vancomycin in SyrSpend SF, a suspending agent containing neither sorbitol nor alcohol. The studied sample was compounded into a 50-mg/mL suspension and stored in a low-actinic plastic bottle at temperatures between 2°C and 8°C. Six samples were assayed at each time point out to 90 days by a stability-indicating high-performance liquid chromatography method. The method was validated for its specificity through forced-degradation studies. The sample remained within 90% to 110% of the initial concentration throughout the course of the study. Based on data collected, the shelf life of this product is at least 90 days when refrigerated and protected from light. Based on the final potency data at day 90, the beyond-use date may be longer, but 90 days was the limit of this study.

## MATERIALS AND METHODS

### Chemical Reagents

Vancomycin HCl raw powder was purchased from [Fagron] Gallipot Inc. (Lot 1103457J12; St. Paul, Minnesota). Sterile Vancomycin HCl USP raw powder was purchased from Hospira (Lot 903003A; Lake Forest, Illinois). High-performance liquid chromatographic (HPLC)-grade acetonitrile (Lot CZ629; Burdick and Jackson, Kalamazoo, Michigan), triethylamine (Lot B0521038; Acros Organics, Geel, Belgium), tetrahydrofuran (Lot 2AH0452; Spectrum Chemical, New Brunswick, New Jersey), and 85% phosphoric acid ACS-grade (Lot 201103115; CCI, New Delhi, India) 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

Two different types of HPLCs were used. The first, used for validation and the stabil-

ity study, was a Perkin Elmer 200-Series (Waltham, Massachusetts) equipped with a quaternary gradient solvent delivery system, a dual wavelength UV/VIS detector, and a 100-vial programmable autosampler with a Peltier tray, 200-mL sample loop, and 250-mL syringe. The second HPLC system, used for forced-degradation studies, was a Varian Prostar (Palo Alto, California), equipped with a tertiary gradient solvent delivery system, a photodiode array detector, and a 84-vial programmable autosampler with a 100-mL sample loop, and 250-mL syringe. The Perkin Elmer HPLC was operated and data was collected using Perkin Elmer Totalchrom chromatography software while the Varian HPLC used Galaxie chromatography software. The mobile phase for the HPLC method was water, acetonitrile, triethylamine, tetrahydrofuran (4500:300:7:50). The mobile phase's pH was adjusted to 3.00 with 85% phosphoric acid and was delivered at 1.8 mL/min. Chromatographic separation was achieved using a 150 × 4.6 mm Phenomenex (Tor-

rence, California) Gemini C18 column with 5 µm particle packing. The mobile phase was used as solvent in diluting the standard and assay preparations to 50 mcg/mL. The assay was monitored at 280 nm following a 100-µL injection.

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

Vancomycin HCl samples were stressed and assayed to determine the specificity of the HPLC method to any possible degradation product produced during storage of an oral suspension. Vancomycin was diluted to 50 mcg/mL in solutions of base (0.1N NaOH), acid (0.1M HCl), hydrogen peroxide (3.5%), in addition to exposure to UV light at 365 nm and heat at 70°C. Time under each stressor varied due to the relative stability of vancomycin to each individual degradation pathway. The time was tailored to provide approximately 15% degradation when compared to a controlled, unstressed standard. Any extraneous peaks found in the chromatogram were labeled and the resolution (*USP*) was determined between the degradant and the vancomycin. A resolution of 1.5 was considered full separation. Purity calculations were performed in Galaxie on the vancomycin peak using the controlled, unstressed standard as a reference.

### Preparation of Vancomycin Hydrochloride Suspension Samples

The first vancomycin HCl suspension was prepared by adding 250 mg of vancomycin HCl powder to a 500-mL volumetric flask, followed by 100 mL of SyrSpend SF. The contents were stirred on a stir plate while adding another 300 mL of SyrSpend SF. The flask was brought to volume with SyrSpend SF and then stirred until a homogenous preparation was achieved. The second vancomycin HCl suspension was prepared by adding 250 mg of vancomycin HCl sterile pharmacy bulk product to a 500-mL volumetric flask, followed by 100 mL of SyrSpend SF. The contents were stirred on a stir plate while adding another 300 mL of SyrSpend SF. The flask was brought to volume with SyrSpend SF and then stirred until a homogenous preparation

**TABLE 1. Stability of Vancomycin Hydrochloride in SyrSpend SF Refrigerated (2°C to 8°C) for 90 days.**

Elapsed Time	% Recovery (Raw Powder)	% Recovery (Sterile Raw Powder)
T=0	100.00	100.00
T=6	107.47 ± 0.39%	105.62 ± 0.77%
T=7	101.74 ± 3.22%	104.09 ± 0.87%
T=14	101.00 ± 1.18%	102.09 ± 0.84%
T=30	99.64 ± 2.84%	101.82 ± 1.61%
T=63	106.47 ± 2.41%	106.72 ± 2.15%
T=90	105.46 ± 3.27%	107.67 ± 2.00%

was achieved. The contents of each flask were poured into 60-mL amber prescription bottles and stored at *USP*-controlled refrigerated temperature (2°C to 8°C) for the stability study.

### Stability Study

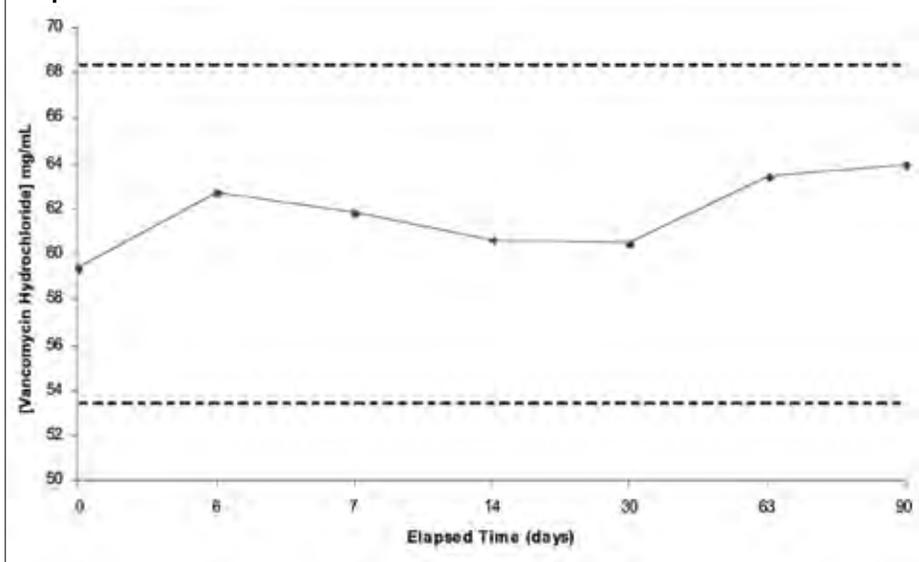
The samples of vancomycin HCl suspended in SyrSpend SF at a concentration of 50 mg/mL were submitted for stability. The samples were packaged in 60-mL low-actinic plastic prescription bottles, and stored at *USP*-controlled refrigerated temperature (2°C to 8°C) using a digitally controlled laboratory refrigerator from Forma Scientific (Edison, New Jersey). Time points for the study were initial (T=0), 6 days (T=6), 7 days (T=7), 14 days (T=14), 30 days (T=30), 63 days (T=63), and 90 days (T=90). The evaluation parameter was per-

cent recovery assay. The stability of vancomycin HCl in suspension was defined by the percent recovery with respect to T=0 using the validated HPLC method. The sample stock was prepared six times by adding 5 mL of suspension with a volumetric pipette to 100 mL with water. Each sample stock was further diluted by adding 1 mL of stock to 25 mL with water. The average and standard deviation of all replicate injections at each time point were used to calculate the percent recovery.

### RESULTS

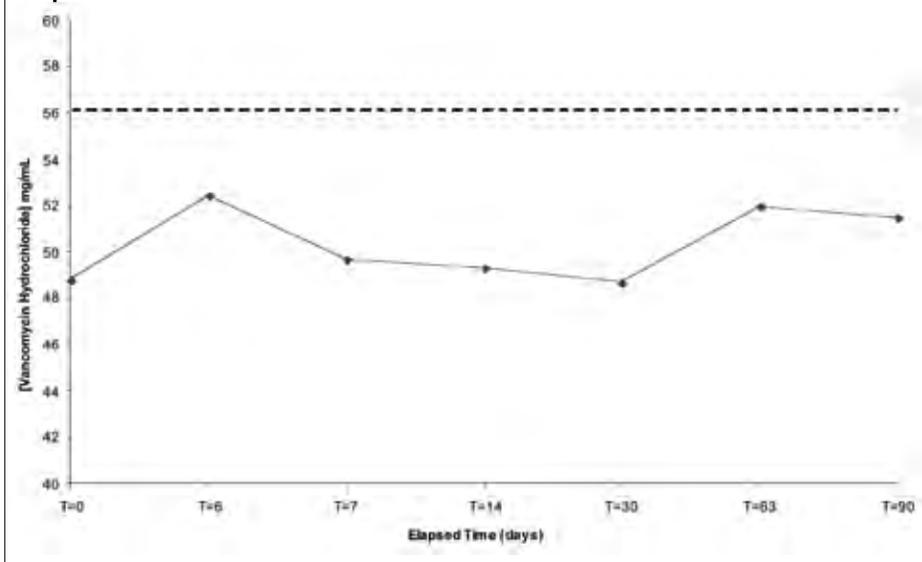
The stability of vancomycin HCl in SyrSpend SF is shown in Table 1. For the suspension compounded with raw powder, the result of 48.82 mg/mL at T=0 was set as the initial concentration for the study, and all subsequent time points were compared

**FIGURE 1. Plot of vancomycin hydrochloride concentration (raw powder) in SyrSpend SF Suspension.**



Note: Dashed lines represent upper and lower limits of vancomycin hydrochloride specifications.

**FIGURE 2. Plot of vancomycin hydrochloride concentration (sterile raw powder) in SyrSpend SF Suspension.**



Note: Dashed lines represent upper and lower limits of vancomycin hydrochloride specifications.

to this value. For the suspension compounded with sterile raw powder, the result of 59.41 mg/mL at T=0 was set as the initial concentration for the study, and all subsequent time points were compared to this value. Figures 1 and 2 show the data in terms of concentration and show that the concentration of each suspension remained within the specification (90% < [vancomycin HCl] < 115%) throughout the duration of the study.

## DISCUSSION

The HPLC method was shown to be stability-indicating by forcibly degrading vancomycin HCl and separating the degradant peaks from that of the main analyte. Vancomycin HCl was stable to acid and ultraviolet light; however heat, base, and oxidizer created significant degradation. The degradants present in the base, heat, and oxidation were all completely separated from the analyte with acceptable resolution. Additionally, validation parameters listed in Table 2 show that all system suitability results met acceptance criteria.

### Vancomycin Hydrochloride USP Raw Powder (Fagron US [formerly Gallipot]) in SyrSpend SF Suspension

The initial potency of the Vancomycin HCl USP (raw powder) in SyrSpend SF suspension was 48.82 mg/mL, which is shown in Figure 1. This concentration was 97.6% 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 varied between 48.65 mg/mL (T=30) and 52.46 mg/mL

**TABLE 2. Summary of the Validation Parameters for the High-Performance Liquid Chromatographic Method Used in the Stability Study of Vancomycin Hydrochloride in SyrSpend SF.**

Validation Parameter	Results
Peak tailing	0.984 % RSD = 1.53
Theoretical plates	1983.0 % RSD = 1.40
Linear range (254 nm)	40 to 200 mcg/mL R <sup>2</sup> = 0.9997
Extraction precision SyrSpend SF) n=6	% RSD = 1.88
Accuracy (20, 100, 160 mcg/mL)	% Target = 100.9%, 100.3%, 99.6%
Specificity (resolution between main degradant peaks)	Res (USP) = 4.39 Res (USP) = 2.21

(T=6). All sample preparations at each time point were within specification, with a high % RSD of 3.27% (T=90). Every replicate chromatogram for every time point was clear of degradant peaks and had the same chromatographic profile.

### Vancomycin Hydrochloride USP Sterile Raw Powder (Hospira) in SyrSpend SF Suspension

The initial potency of the Vancomycin HCl USP (sterile raw powder) in SyrSpend SF suspension was 59.41 mg/mL, which is shown in Figure 2. This concentration was 118.8% 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 varied between 59.41 mg/mL (T=0) and 63.97 mg/mL (T=90). All sample preparations at each time point were within specification with a high % RSD of 2.15% (T=83). Every replicate chromatogram for every time point was clear of the degradant peaks and had the same chromatographic profile.

## CONCLUSION

Vancomycin HCl was stable in SyrSpend SF for 90 days when stored under refrigerated (2°C to 8°C) conditions when compounded from either the raw powder or sterile raw powder. The samples were still within specification at day 90; however, no general trend was observed during the course of the study. Therefore, the beyond-use date is concluded to be 90 days. The findings of this study show that SyrSpend SF is an acceptable oral syrup and suspending vehicle for preparing individual compounded vancomycin HCl formulations. This formulation has the added advantage of helping to mask the bitter taste while remaining alcohol-, sorbitol-, and sugar-free. The formulations would be viable alternatives to commercially available capsules when that dosage form is found to be inappropriate.

## REFERENCE

1. Vancocin HCl (vancomycin hydrochloride) capsules [product information]. Exton, PA: ViroPharma Incorporated; October 2005. [ViroPharma Incorporated Website.] Available at: [www.viopharma.com/physicians/vancocin%20overview/vancocin%20package%20insert.aspx](http://www.viopharma.com/physicians/vancocin%20overview/vancocin%20package%20insert.aspx). Accessed January 12, 2011. ✓