Stability of Commercially Available Grape and Compounded Cherry Oral Vancomycin Preparations Stored in Syringes and Cups

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ABSTRACT

The purpose of this study was to evaluate the stability of two preparations of vancomycin oral solution in two different storage containers, capped amber oral-dosing syringes and heat-sealed oral-dosing cups, stored under refrigerated conditions. Commercially available grape-flavored vancomycin oral preparation and compounded vancomycin for intravenous use in cherry syrup oral preparation were divided into 5-mL aliquots into heat-sealed plastic dosing cups and capped oral-dosing syringes. All samples were stored under refrigeration (2°C to 8°C) and evaluated at days 0, 3, 7, 14, 30, 60, and 90. For each evaluation, samples were visually inspected and analyzed for potency using a stability-indicating high-performance liquid chromatographic method with ultraviolet detection. Over the study period, at least 90% of the initial concentrations for the preparation and the product in both storage containers were retained at 60 days. The commercially available oral vancomycin further demonstrated stability within 90% out to 90 days in the syringe and the unit-dose cups. Visual inspection revealed no changes in the grape-flavored vancomycin oral preparation, but a detectable red-dye precipitate could be seen in the crevices of the dosing cups from the vancomycin in cherry syrup oral preparation after 60 days. Commercially available grape-flavored vancomycin oral preparation was stable up to 90 days, and compounded vancomycin for intravenous use in cherry syrup oral preparation maintained stability for 60 days when dispensed in capped amber polypropylene oral-dosing syringes and heat-sealed plastic dosing cups when stored at refrigerated conditions.

INTRODUCTION

Vancomycin is a glycopeptide antibiotic commonly used for treatment of gram-positive infections. When administered orally, insufficient quantities are systemically absorbed for use as a systemic antibiotic. As a result, oral vancomycin has carved its niche as the treatment for severe, severe complicated, or recurrent *Clostridium difficile* infection (CDI) as directed by the Infectious Diseases Society of America (IDSA) guidelines.[1] The American College of Gastroenterology (ACG) guidelines mirror the IDSA guidelines, but also state the oral vancomycin should be considered in patients who do not respond in 5 to 7 days to metronidazole, patients who are intolerant to metronidazole, or who are pregnant or breastfeeding.[2] Doses of oral vancomycin cited in these guidelines range from 125 mg to 500 mg orally every 6 hours.

When the IDSA guidelines were published in 2010, the only commercially available oral vancomycin product on the market was VANCOCIN in 125-mg and 250-mg capsules produced by ViroPharma.[3] VANCOCIN capsules are U.S. Food and Drug Administration (FDA)-indicated for the treatment of CDI. However, cost and other barriers to the capsules' use have led pharmacies to formulate and compound oral preparations using these capsules, the bulk vancomycin chemical, and generic lyophilized powder for intravenous (IV) use products as the source of the active pharmaceutical ingredient (API). These

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formulations frequently include sweetening vehicles or suspending agents such as cherry syrup to mask or lessen the undesirable taste reported by patients.[1] Without established beyond-use date (BUD) information for these formulations, pharmacists have empirically assigned BUDs to these formulations.

In 2014, CutisPharma introduced Vancomycin in their FIRST Compounding Kit, which contained the required components to prepare oral vancomycin solution in either 25-mg/mL or 50-mg/mL preparations. The package insert states that the product is stable for at least 30 days when compounded per the product's included instructions and stored at refrigerated temperature, protected from light, and tightly closed in the manufacturer supplied storage bottle.[4] Supply issues and lack of widespread knowledge of this product have limited the availability and use of this product.

The medication-use process often utilizes pharmacy informatics and automation to speed up and ensure more accurate delivery of safe and effective medications.[5] One of the strategies utilized in the medication-use-process is repackaging. Repackaging, as defined in the *FDA Draft Guidance* and representing FDA's current thinking on the topic, is the "act of taking a finished drug product from the container in which it was distributed by the original manufacturer and placing it into a different container without further manipulation of the drug."[6] The Joint Commission standard MM.03.01.01 element of performance 10 states that medications not commercially available in unit doses should be repackaged in ready-to-administer unit doses by the pharmacy or licensed repackager.[7]

Stability data pertaining to vancomycin oral preparations repackaged into individual dosage containers are lacking. The purpose of this study was to evaluate the long-term stability of a commercially available vancomycin solution as well as a compounded vancomycin solution in two different storage containers, capped amber oral-dosing syringes and heat-sealed oral-dosing cups, stored under refrigerated conditions.

MATERIALS AND METHODS

EQUIPMENT AND CHROMATOGRAPHIC CONDITIONS

Shimadzu ultra-fast liquid chromatography (UFLC) systems with ultraviolet (UV) and photo diode array (PDA) (Shimadzu Scientific, Kyoto, Japan) detection set at 280 nm were used for all chromatographic measurements. Each system was equipped with a column oven, in-line degasser, and auto-sampler. Gradient separation was completed on a Titan C18 (100 × 2.1mm id, 1.9 micron particle size) column (Supelco, St. Louis, Missouri), maintained at 50°C. The two components of the mobile phase for the high-performance liquid chromatographic (HPLC) method were component A; 50mM ammonium acetate in HPLC-grade water adjusted to pH 8.0 with concentrated ammonium hydroxide, and component B; HPLC-grade water/HPLC-grade methanol 65:35 v/v, delivered at a 0.150 mL/minute flow rate. The chromatographic gradient was as follows: initial conditions at 50%B; ramp to 65%B over 15 minutes; ramp to 100%B from 15 to 20 minutes; re-equilibrate at 50%B for 5 minutes between injections. All chemicals were of HPLC grade or higher (Fisher Scientific, Waltham, Massachusetts). The vancomycin hydrochloride (HCl) reference standard was supplied by the United States Pharmacopeial Convention, Inc. (USP) (Rockville, Maryland).

DEVELOPMENT AND VALIDATION OF A STABILITY-INDICATING HIGH-PERFORMANCE LIQUID CHROMATOGRAPHIC METHOD

The stability-indicating HPLC method development and validation was completed for system suitability, accuracy, repeatability, intermediate precision, specificity, linearity, and robustness. All tests were conducted in accordance with *United States Pharmacopeia (USP)* validation criteria set forth in *USP* General Chapter <1225>.[8]

PREPARATION OF VANCOMYCIN ORAL PREPARATIONS

A licensed pharmacist prepared two formulations of vancomycin oral preparations by means of standard compounding pharmacy protocols. The grape-flavored vancomycin oral preparation 50 mg/mL was prepared using the Vancomycin in the FIRST Grape Solution Compounding Kit (Lot E840 [Expiration 8/15]; CutisPharma, Inc., Wilmington, Massachusetts). The vancomycin in cherry syrup oral preparation 50 mg/mL was prepared by reconstituting a vancomycin generic lyophilized powder product intended for IV use in cherry syrup. The vancomycin for this preparation was obtained from Hospira (Lot 403603A [Expiration 1-1-16]; Hospira, Lake Forest, Illinois). Additionally, the cherry preparation required sterile water for injection (Lot 6113456 [Expiration 6/17]; Baxter, Deerfield, Illinois) and cherry syrup (Lot 545403 [Expiration 6/17]; Humco, Austin, Texas). The grape-flavored vancomycin preparation and vancomycin in cherry syrup preparation were divided into 5-mL aliquots into heat-sealed plastic dosing cups and capped amber polypropylene oral-dosing syringes and stored in the refrigerator at 4.9°C + 0.4°C.

CALIBRATION AND SAMPLING

On each sampling day, a 500-mcg/mL standard solution was prepared using the *USP* reference standard of vancomycin HCl dissolved in HPLC-grade water, and the concentrations of vancomycin in each study sample was calculated via recovery compared to the standard solution. Study samples were pulled from the refrigerator (n=3 in each sampling group on each day) and diluted with HPLC-grade water to achieve a target drug concentration of 500 mcg/mL. Samples were filtered using a 0.22-micron syringe filter immediately prior to HPLC injection. The temperature of the refrigerator was recorded each day using a digital thermometer probe. The concentrations of vancomycin in the calibration standards and samples were determined using a stability-indicating HPLC method described in the Equipment and Chromatographic Conditions section. Injection volume for all stability samples and reference standard was 10 microliters.

STABILITY INVESTIGATION

Assay results for vancomycin were based on the area under the curve of the chromatographic peak for vancomycin using a UV

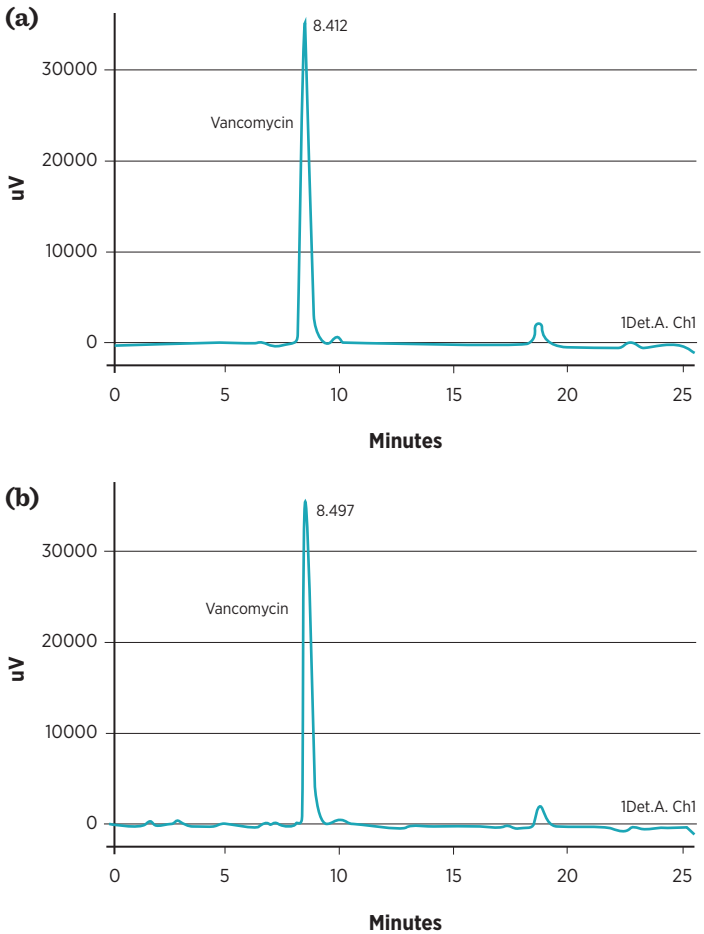
absorbance of 280 nm. The concentrations of vancomycin shown in the results have been corrected for dilution as well as corrected for use of the HCl salt to prepare the standard solution. The concentration-versus-time profiles for each bottle were evaluated using a two-way analysis of variance (ANOVA) with Bonferroni post-test (*P*-value of 0.05) using GraphPad Prism software (Version 5.03; GraphPad, San Diego, California). The column performance parameters (theoretical plates, tailing factor, resolution) were monitored throughout the study.

RESULTS

VALIDATION OF STABILITY-INDICATING HIGH-PERFORMANCE LIQUID CHROMATOGRAPHIC METHOD

All HPLC-UV method data passed *USP* validation criteria set forth in *USP* General Chapter <1225>. The target assay range was 400 mcg/mL to 600 mcg/mL, with 500 mcg/mL defined as the 100% or assay level concentration, as it represents a 100-fold dilution from the product concentration. The Figure shows a chromatogram of vancomycin on the day of compounding (day 0; target concentration of 500 mcg/mL in [a] grape-flavored preparation and [b] compounded preparation in cherry syrup). The results of these validation experiments are summarized in Table 1.

FIGURE. High-performance liquid chromatographic-ultraviolet chromatograms at 280 nm of (a) vancomycin in grape product at day 0; (b) vancomycin in cherry compounded preparation at day 0.



STABILITY INVESTIGATION

The column performance parameters (theoretical plates, tailing factor, resolution) remained within system suitability limits throughout the study period. Throughout the study, the chromatographic retention time of the API peak was consistent at around 8.2 to 8.6 minutes, with small variations associated with exact buffer pH. The appearance of the chromatogram did not differ between day zero and day 90 for either the samples or the standard solution.

Stability data for the grape-flavored vancomycin oral preparation are shown in Table 2. The vancomycin content from all initial samples fell within 90% to 110% of the label potency (45 mg/mL to 55 mg/mL). The response from the standard solution was highly reproducible throughout the duration of the study (4.34% RSD). The vancomycin concentrations found in each study sample from both the dosing cups and oral syringes remained within the 90% to 110% of label potency throughout the study, and were still within this range at 90 days. No statistically significant difference could be detected between the cup samples and syringe samples when evaluating concentration versus time profile using a 2-way ANOVA.

Stability data for vancomycin in cherry syrup oral preparation are shown in Table 3. The vancomycin content from all initial samples fell within 90% to 110% of the label potency (45 mg/mL to 55 mg/mL). The sampled vancomycin concentrations of the preparation stored in the oral syringes remained within the 90% to 110% of label potency throughout the study, and were still within this range at 90 days. The vancomycin concentrations of the preparation stored in the dosing cups decreased to 87% of the label claim by day 90 of the study; however, no statistically significant difference could be detected between cup and syringe samples using 2-way ANOVA. At day 60, a red film was visually detected in the crevice of the dosage cups after the vancomycin sample had been removed.

DISCUSSION

The purpose of this study was to provide stability data where data were lacking regarding repackaged vancomycin oral solutions. The stability and manufacturer's BUD cannot be applied to the preparations if the product has been taken from the container in which it was distributed by the original manufacturer and placed into a different container. This is because of factors such as adsorption of drug to the containers or leaching from the containers into the solution. Likewise, the stability of one formulation in one container does not guarantee a similar stability in another container. Both containers that were studied are frequently used per Joint Commission standards

as ready-to-administer unit doses and increase the external applicability of this study's results.

The dosing of oral vancomycin for CDI is relatively standardized and, as a result, oral vancomycin solutions are good candidates for repackaging in oral syringes, dosing cups, or any other ready-to-administer unit dosing. Available automated filling devices used in the repackaging of preparations often utilize heat-sealed cups as the ready-to-administer unit dosing to improve workflow. Syringes are best utilized for nonstandard doses or doses needing to be drawn up quickly and offer the advantage of less residual product remaining in the container after administration.

The application of this study's results may lead to the increased efficiency in pharmacy operations. Furthermore, the application also promotes the advantages of dispensing repackaged ready-to-administer unit dosing over dispensing bulk bottles. Doses can be drawn up to the individually prescribed dose allowing for easier and more accurate administration at the bedside. Barcodes can be added at the time of preparation to each individual unit dose allowing for bedside barcode scanning. Individual-unit doses can be loaded into automated dispensing cabinets with attached refrigerated sections allowing for immediate order validation, quicker administration, and inventory tracking. Finally, unit dosing helps reduce waste by allowing for batch dosing in advance of use and the return of unused doses to stock if proper storage can be verified. This becomes increasingly important in the current pharmaceutical industry challenged by constant drug shortages, decreased reimbursement rates, and limited opportunities for cost savings.

The study was limited to only two storage containers and only two formulations. The syringes smaller than the 5-mL syringe utilized in the study contained a higher surface area in contact with the liquid. This could allow for increased adsorption or leaching over time. Syringes larger than 5 mL are unlikely to be affected. The samples were also not tested in clear containers and exposed to light, which may increase degradation time. Finally, only one formula of compounded vancomycin was studied. This formula did not contain a suspending or solubilizing agent or preservatives, which may account for the shorter BUD compared to the commercially available product. It is unlikely that any of these factors would significantly affect the stability in the short term but may affect stability in the long term. The authors recommend that bulk repackaging be done in accordance to the study protocol. Dosages drawn up in containers not studied should be limited to immediate use.

TABLE 1. Method Validation Data for Determination of Vancomycin by High-performance Liquid Chromatographic-Ultraviolet at 280 nm.

TEST	RESULTS
SYSTEM SUITABILITY	Average Resolution (*n*=6) = 12.4
System suitability sample prepared at 500 mcg/mL level	Average Tailing Factor (*n*=6) = 1.0 Average Theoretical Plates (N) (*n*=6) =3668 Average %RSD (*n*=6) = 0.350 %
LINEARITY AND RANGE	
Calibration points = 400, 450, 500, 550, and 600 mcg/mL (*n*=3 of each point)	R^2 = 0.99928
ROBUSTNESS	
Included challenges of (a) decreased buffer pH (b) decreased flow rate (c) increased oven temperature, and (d) alternative column (*n*=9 for each challenge)	Average Resolution = 10.7 Average Tailing Factor = 1.3 Average N = 4103 Average %RSD = 0.566
ACCURACY	
Included vancomycin prepared in vehicle versus HPLC-grade water (*n*=9 at each concentration)	Average Recovery (80%) = 98.64% Average Recovery (100%) = 98.43% Average Recovery (120%) = 98.07%
REPEATABILITY	
n=9 at each concentration	%RSD (80%) = 1.27% %RSD (100%) = 0.51% %RSD (120%) = 0.32%
INTERMEDIATE PRECISION	
Included 5 injections of system suitability sample over 6 different days (*n*=30)	%RSD = 3.32 %
SPECIFICITY/FORCED DEGRADATION	
Utilized 10 mM sodium hydroxide (NaOH) and 20 mM perchloric acid ($HClO_4$) stored at room temperature for 48 hours	NaOH: Average Peak Purity Index = 0.9854 HClO4: Average Peak Purity Index = 0.9958
SOLUTION STABILITY	
Utilized 500 mcg/mL reference standard for 24 hours (intra-day) and for 3 days (inter-day)	**Intra-day: Recovery = 99.59%** **Intra-day: %RSD = 0.91%** **Inter-day: Recovery = 99.23%** **Inter-day: %RSD = 0.95%**

HPLC = high-performance liquid chromatographic; RSD = relative standard deviation

CONCLUSION

Two preparations of an oral vancomycin solution (50 mg/mL) were evaluated for vancomycin concentrations over a period of 90 days. These solutions were stored in oral syringes and oral-dosing cups at refrigerated temperatures. The data indicate that the commercially available grape preparation is stable out to 90 days when stored in these containers in the refrigerator. Additionally, the cherry compounded preparation is stable for 60 days in cups and syringes stored in refrigerated conditions. No statistically significant difference was detected between samples stored in cups versus syringes for either

TABLE 2. Stability Data for the Grape-flavored Vancomycin Oral Preparation Stored in Oral Syringes and Dosing Syringes for 90 Days Under Controlled Refrigerated Conditions (4.9°C + 0.4°C).

ORAL SYRINGES							
SPECIFICATION	**INITIAL**	**DAY 3**	**DAY 7**	**DAY 14**	**DAY 30**	**DAY 60**	**DAY 90**
mg/mL (*n*=3 for each day; shown as average + standard deviation)	52.48 + 0.79	53.38 + 0.28	52.81 + 0.77	52.47 + 0.89	50.34 + 3.04	49.50 + 0.84	49.41 + 0.22
% of labeled concentration (based on average concentration)	104.9	106.8	105.6	104.9	100.7	99.0	98.8
DOSING CUPS							
SPECIFICATION	**INITIAL**	**DAY 3**	**DAY 7**	**DAY 14**	**DAY 30**	**DAY 60**	**DAY 90**
mg/mL (*n*=3 for each day; shown as average + standard deviation)	52.88 + 0.70	53.26 + 0.50	52.72 + 0.50	53.33 + 0.35	51.75 + 1.11	49.14 + 0.65	48.94 + 0.64
% of labeled concentration (based on average concentration)	105.8	106.5	105.4	106.7	103.5	98.3	97.9

TABLE 3. Stability Data for Vancomycin in Cherry Syrup Oral Preparation Stored in Oral Syringes and Dosing Syringes for 90 Days Under Controlled Refrigerated Conditions (4.9°C + 0.4°C).

ORAL SYRINGES							
SPECIFICATION	**INITIAL**	**DAY 3**	**DAY 7**	**DAY 14**	**DAY 30**	**DAY 60**	**DAY 90**
mg/mL (*n*=3 for each day; shown as average + standard deviation)	48.54 + 1.03	47.30 + 0.14	48.94 + 0.41	48.37 + 0.42	46.60 + 1.73	46.29 + 0.61	45.38 + 0.72
% of labeled concentration (based on average concentration)	97.1	96.6	97.9	96.8	93.2	92.6	90.8
DOSING CUPS							
SPECIFICATION	**INITIAL**	**DAY 3**	**DAY 7**	**DAY 14**	**DAY 30**	**DAY 60**	**DAY 90**
mg/mL (*n*=3 for each day; shown as average + standard deviation)	48.68 + 0.99	48.03 + 1.13	48.11 + 0.99	49.01 + 0.06	47.56 + 0.16	95.97 + 0.38	43.77 + 0.33
% of labeled concentration (based on average concentration)	97.4	96.1	96.2	98	95.1	91.9	87.5

preparation. This work has the potential to assist pharmacy operations by allowing for bulk preparation of oral vancomycin products and storage in automated dispensing cabinets.

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