Stability of Rifampin in SyrSpend SF

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ABSTRACT

Rifampin is a bactericidal antibiotic drug of the rifamycin group. It is a semi-synthetic drug produced from the bacterium *Streptomyces mediterranei*. Rifampin is commonly manufactured in capsule, tablet, and syrup dosage forms. Some patients, however, cannot tolerate solid dosage forms or oral solutions containing alcohol or sorbitol. The objective of this study was to determine the stability of rifampin in SyrSpend SF. The studied samples were compounded into 25-mg/mL suspensions and stored in low-actinic bottles at room temperature and refrigerated conditions. Samples were assayed at each time point out to 60 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 beyond-use date of the preparation is at least 60 days when refrigerated or stored at room temperature and protected from light.

INTRODUCTION

Rifampin (USAN), also referred to as Rifampicin (INN), is a broad spectrum antibiotic produced from the bacterium *Streptomyces mediterranei*. It is of the class known as rifamycins. Rifampin inhibits bacterial DNA-dependent RNA synthesis by inhibiting bacterial DNA-dependent RNA polymerase. It is the most commonly used member of its class because of its clinical indication for diseases such as tuberculosis, meningitis, and leprosy.

Rifampin is a red to orange powder. It is very slightly soluble in water, acetone, carbon tetrachloride, alcohol, and ether. It is freely soluble in chloroform and in dimethyl sulfoxide, and soluble in ethyl acetate, methyl alcohol, and tetrahydrofuran. 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 rifampin oral suspensions extemporaneously.

The objective of this study was to examine the stability of rifampin prepared in an oral suspension using SyrSpend SF. Two suspensions were compounded with rifampin raw powder in the SyrSpend SF suspension to a final concentration of approximately 25 mg/mL. The compounded suspensions were stored in low-actinic prescription bottles under two different storage conditions: *United States Pharmacopeia (USP)* refrigerated (2°C to 8°C) storage, and *USP* room temperature (18°C to 26°C) storage. Stability was assessed by percent recovery studies performed at varying time points over 60 days.

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MATERIALS AND METHODS

Chemical Reagents

Rifampin USP raw powder was purchased from Sigma (Lot 011M1159V; St. Louis, Missouri). High-performance liquid chromatographic (HPLC)-grade acetonitrile (Lot DG046; Burdick & Jackson, Muskegon, Michigan), monosodium phosphate monohydrate (Lot 113670; Fisher Chemical, Whippany, New Jersey), disodium phosphate heptahydrate (Lot 115824; Fisher Chemical), and 85% phosphoric acid (Lot 2011052000; CCI, Scottsburg, Indiana) were used in this study. HPLC-grade water was obtained by filtering deionized water from a Millipore (Billerica, Massachusetts) Elix through a Millipore Simplicity.

Equipment and Chromatographic Conditions

Two different types of HPLCs were used. The first, used for validation and the stability study, was a Perkin Elmer (Waltham, Massachusetts) 200-Series 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-mcL sample loop, and a 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 an 84-vial programmable autosampler with a 100-mcL sample loop and a 250-mcL 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 made using 600 mL of HPLC-grade water, 1.49 grams of monosodium phosphate monohydrate, 0.31 grams of disodium phosphate heptahydrate, and 400 mL of acetonitrile (to yield 1 liter), using 85% phosphoric acid to pH mobile phase to 5.87. The mobile phase was delivered at 1.2 mL/min. Chromatographic separation was achieved using a 150 × 4.6 mm Phenomenex (Torrence, California) Gemini C18 column with 5-mcm particle packing. The mobile phase was used as a solvent in diluting the standard and assay prepa-

rations to 100 mcg/mL. The assay was monitored at 254 nm following a 10-mcL injection.

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

Rifampin 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. Rifampin was diluted to 100 mcg/mL in a solution of acid (0.1M HCl), base (0.1 M NaOH), and hydrogen peroxide (3.5%), in addition to exposure to ultraviolet light at 365 nm and heat at 70°C. Time under each stressor varied due to the relative stability of rifampin to each individual degradation pathway. Any extraneous peaks found in the chromatogram were labeled, and the resolution, based on *USP* guidelines, was determined between the degradant and the rifampin. A resolution of 1.5 was considered full separation. Purity calculations were performed in Galaxie on the rifampin peak using the controlled unstressed standard as a reference.

Preparation of Rifampin Suspension Samples

Rifampin suspension was prepared by adding 5 grams of rifampin powder to a 250-mL amber bottle. While hand stirring to prevent air bubbles from forming in the suspension, 200 mL of SyrSpend were added to the bottle. The suspension was then divided into two bottles, each containing approximately 100 mL. One suspension was stored at *USP*-controlled refrigerated temperature and the other at *USP*-controlled room temperature for the duration of the stability study.

Stability Study

The rifampin samples suspended in SyrSpend SF at a concentration of 25 mg/mL were submitted for stability. One sample was packaged in a low-actinic flask and stored at *USP*-controlled refrigerated temperature (2°C to 8°C) using a laboratory refrigerator with digitally-controlled temperature from Forma Scientific (Edison, New Jersey). The other sample was packaged in low-actinic flasks and stored at *USP*-controlled room temperature condition (18°C to 26°C). Time points for the study were initial (T=0), 7 days (T=7), 14 days (T=14), 35 days (T=35), and 60 days (T=60). The evaluation parameter was percent recovery assay. The stability of rifampin in suspension was defined by the percent recovery with respect to T=0 using the validated HPLC method. The sample stock was prepared by adding 100 mcL of suspension with a Gilson positive displacement pipette to a 25-mL amber flask. The flask was brought to volume with the mobile phase. The average and standard deviation of all replicate injections at each time point was used to calculate the percent recovery.

RESULTS

The stability of rifampin in SyrSpend SF at room temperature is shown in Table 1. The stability of rifampin in SyrSpend SF at refrigerated temperature is shown in Table 2. The result of 25.07 mg/mL for the refrigerated and room temperature was set as the initial concentration for the study, and all subsequent time points were compared to this value. Figures 1 and 2 depict the data in terms of concentration of the suspension remained within the specification (90%<[rifampin]<110%) throughout the duration of the study.

DISCUSSION

The HPLC method was shown to be stability indicating by forcibly degrading rifampin and separating the degradant peaks from that of the main analyte. Degradation was seen with acid, base, light, heat, and oxidation. Additionally, validation parameters listed in Table 3 show that all system suitability results met acceptance criteria.

GALLIPOT SYRSPEND RIFAMPIN SUSPENSION

The initial potency of the rifampin suspensions was 25.07 mg/mL, as shown

TABLE 1. Stability of Rifampin in SyrSpend SF Stored at Room Temperature (18°C to 26°C) for 60 Days.

ELAPSED TIME	% RECOVERY
T=0	100 ± 0.873
T=7	99.83 ± 2.202
T=14	100.24 ± 1.259
T=35	101.94 ± 1.916
T=60	98.20 ± 1.33

TABLE 2. Stability of Rifampin in SyrSpend SF Refrigerated (2°C-8°C) for 60 Days.

ELAPSED TIME	% RECOVERY
T=0	100 ± 0.873
T=7	99.67 ± 1.794
T=14	100.74 ± 1.897
T=35	98.34 ± 4.635
T=60	98.33 ± 0.755

TABLE 3. Summary of the Validation Parameters for the High-performance Liquid Chromatographic Method Used in the Stability Study of Rifampin in SyrSpend SF.

VALIDATION PARAMETER	RESULTS
Peak tailing	1.183
Theoretical plates	4769.02
Linear range (254 nm)	10 mcg/mL to 200 mcg/mL (R^2=0.995)
Extraction precision *n*=6	% Relative standard deviation=0.18
Accuracy (20, 100, 160 mcg/mL)	%Target=98.14%, 99.00%, 99.79%
Specificity (resolution from main degradant peak)	Res (*USP*)=4.32

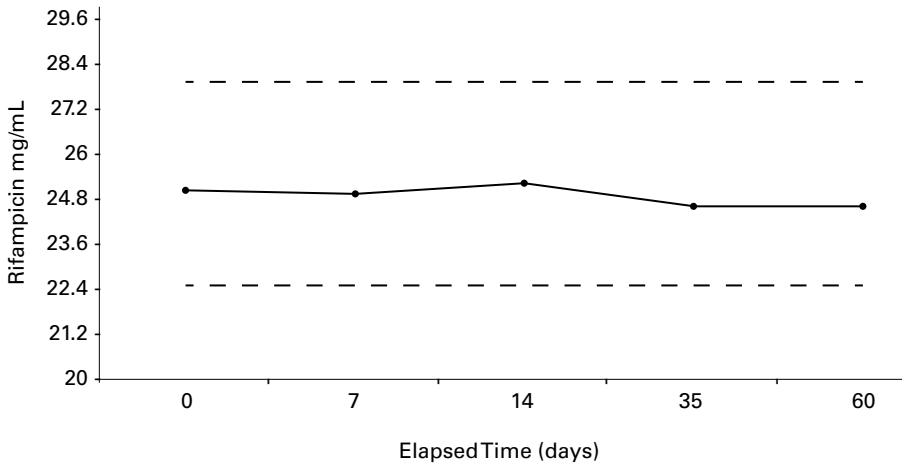
in Figures 1 and 2. This concentration was 100.29% (room temperature and refrigeration of the 25-mg/mL target concentration). The T=0 result was set as the baseline for all other time points. The assay results varied between 24.65 mg/mL (T=60) and 25.26 mg/mL (T=14) for the preparation stored at refrigerated temperature, and between 24.62 mg/mL (T=60) and 25.56 mg/mL (T=35) for the preparation stored at room temperature. All sample preparations at each time point were within specifications and all percent relative standard deviations (RSDs) were below 5.0%. Each replicate for every time point was clear of any degradant peaks and had the same chromatographic profile.

CONCLUSION

Rifampin was stable in SyrSpend SF for 60 days when stored under room temperature (18°C to 26°C) conditions. Rifampin was stable for 60 days when stored under refrigerated (2°C to 8°C) conditions. Concentrations of both storage conditions remained steady during the course of the study, and this data was used to obtain the beyond-use-date of 60 days.

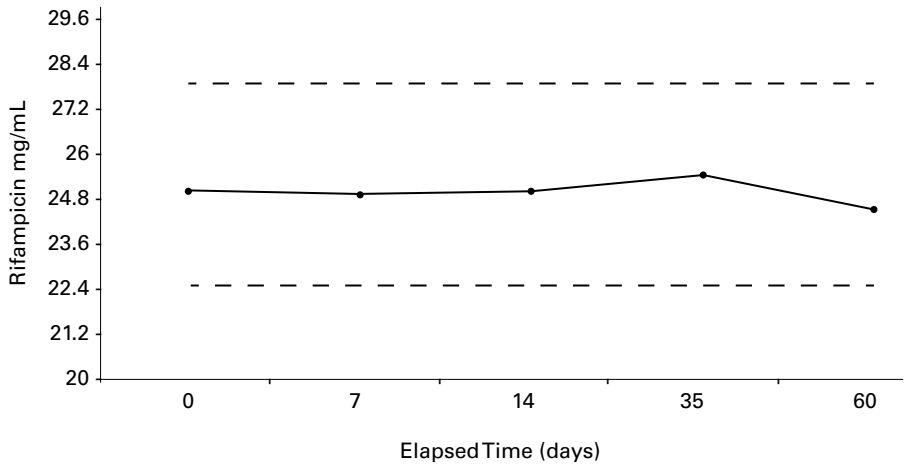
The findings of this study show that SyrSpend is an acceptable suspending vehicle for preparing individually-compounded rifampin formulations. This formulation is acceptable as an alcohol- and sorbitol-free suspension for use when the patient is unable to tolerate the solid dosage form or suspensions that contain alcohol or sorbitol.

FIGURE 1. Plot of refrigerated rifampin concentration in SyrSpend SF.



Note: Dashed lines represent upper and lower limits of rifampin specification.

FIGURE 2. Plot of room temperature rifampin concentration in SyrSpend SF.



Note: Dashed lines represent upper and lower limits of rifampin specification.

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