Stability of Midazolam in SyrSpend SF and SyrSpend SF Cherry

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ABSTRACT

Midazolam is a short-acting benzodiazepine central nervous system depressant available as an injection, tablet, or oral syrup. The need for alternative dosage form options for patients unable to take tablets and shortages of other forms of the drug have led compounding pharmacies to seek alternatives, mainly 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 midazolam in sorbitol-free, alcohol-free SyrSpend SF and SyrSpend SF Cherry suspending agents. The studied samples were compounded into a 1-mg/mL suspension and stored in low-actinic plastic bottles at temperatures between 2°C to 8°C and at room temperature conditions. Six samples were assayed at each time point out to 58 days by a stability-indicating high-performance liquid chromatography method. The method was validated for its specificity through forced-degradation studies. The samples remained within 90% to 110% of the initial concentration throughout the course of the study. Based on the data collected, the beyond-use date of these preparations is at least 58 days when protected from light at both refrigerated and room temperature storage conditions.

INTRODUCTION

Midazolam, a short-acting drug in the benzodiazepine class, is used for treatment of acute seizures, moderate to severe insomnia, and for inducing sedation and amnesia before medical procedures. Midazolam is marketed under the trade names Versed, Dormicum, and Hypnovel and is also available generically from several manufacturers.[1]

Midazolam is a very bitter white or yellowish powder. It is available as an injection, tablet, and oral syrup.[2] An oral preparation formulation containing a sweetener would provide a masking effect for the bitter taste, thereby increasing the palpability of an oral dose form. However, the inclusion of alcohol or sorbitol in a vehicle especially for elderly or pediatric patients can pose concerns about drug-drug and drug-disease state interactions, as well as complications for a patient's activities of daily living. SyrSpend SF (Fagron US [formerly Gallipot], St. Paul, Minnesota) is a sugar- and sorbitol-free suspending vehicle which could serve as an alternative for formulating midazolam oral suspensions.

The objective of this study was to examine the stability of midazolam prepared in oral suspensions using SyrSpend SF and SyrSpend SF Cherry. The suspensions were stored in low-actinic plastic bottles at a concentration of 1 mg/mL under *United States Pharmacopeia (USP)* refrigerated (2°C to 8°C) storage conditions and at room temperature conditions. Stability was assessed by percent recovery studies performed at varying time points throughout 58 days.

MATERIALS AND METHODS

Chemical Reagents

Midazolam hydrochloride (HCl) injection was purchased from APP Pharmaceuticals (Lot 6003904; Schaumburg, Illinois). High-performance liquid chromatographic (HPLC)-grade methanol (Lot DG 295; Honeywell, Michigan), sodium acetate trihydrate (Lot 107503; Fisher Chemical, New Jersey), and glacial acetic acid (Lot B0522653, Acros, Belgium) were used in this study. HPLC-grade water was supplied by filtering deionized water from a Millipore Elix through a Millipore Simplicity (Billerica, Massachusetts).

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Equipment and Chromatographic Conditions

Two different types of HPLCs were used. The first, used for validation and the stability 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-mcL sample loop, and 250-mcL 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-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 70/30 methanol/acetate buffer, pH 5.2,

delivered at 1.5 mL/min. Chromatographic separation was achieved using a 150 × 4.6 mm Phenomenex (Serial No. 649739-2; Torrence, California) Gemini C18 column with 5 mcm particle packing. The mobile phase was used as a solvent in diluting the standard and assay preparations to 20 mcg/mL. All preparations were filtered prior to injection. The assay was monitored at 221 nm following a 25-mcL injection.

Validation of Forced-degradation Studies to Determine Stability-indicating Characteristics of High-Performance Liquid Chromatographic Method

Midazolam 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. Midazolam was diluted to 20 mcg/mL in solutions of base (0.1N NaOH), acid (0.1M HCl), and hydrogen peroxide (7%), in addition to exposure to ultraviolet light at 365 nm and heat at 70°C. Time under each stressor was three hours and was 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 midazolam. A resolution of 1.5 was considered full separation. Purity calculations were performed in Galaxie on the midazolam peak using the controlled, unstressed standard as a reference.

Preparation of Midazolam Suspension Samples

The first midazolam suspension was prepared by adding 10 mL of a 5-mg/mL midazolam HCl pharmaceutical preparation and 15 mL HPLC grade water to a 50-mL "to contain" graduated cylinder. The cylinder was brought to volume using SyrSpend SF. The cylinder was inverted to mix until a homogenous preparation was achieved with a final concentration of 1 mg/mL. The contents were split between two plastic amber bottles and one stored at *USP*-controlled refrigerated temperatures (2°C to 8°C) and one stored at room temperatures for the stability study. The preparation was repeated using SyrSpend SF Cherry.

Stability Study

The samples of midazolam suspended in SyrSpend SF and SyrSpend SF Cherry at a concentration of 1 mg/mL were submitted for stability. The samples were packaged in low-actinic plastic 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) and at room temperature. Time points for the study were initial (T=0), 7 days (T=7), 14 days (T=14), 30 days (T=30), 42 days (T=42), and 58 days (T=58). The evaluation parameter was percent recovery assay. The stability of midazolam 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 200 mcL with a Gilson pipette to 10 mL with mobile phase. The average and standard deviation of all replicate injections at each time point were used to calculate the percent recovery.

RESULTS

The stability of midazolam in SyrSpend SF and SyrSpend SF Cherry is shown in Table 1 and Table 2, respectively. For the suspension compounded with SyrSpend SF, the result of 1.02542 mg/mL at T=0 was set as the initial concentration for the study, and all subsequent time points were compared to this value. For the suspension compounded with SyrSpend SF Cherry, the result of 1.0333 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%<[midazolam]<110%) throughout the duration of the study at both refrigerated and room temperature conditions.

DISCUSSION

The HPLC method was shown to be stability indicating by forcibly degrading midazolam and separating the degradant peaks from that of the main analyte. Midazolam was stable to acid, oxidizer, and heat. Base and light caused slight degradation. Additionally, validation parameters listed in Table 3 show that all system suitability results met acceptance criteria.

TABLE 1. Stability of Midazolam in SyrSpend SF for 58 Days.

ELAPSED TIME	% RECOVERY AT ROOM TEMPERATURE	% RECOVERY AT 2°C - 8°C
T=0	100.00	100.00
T=7	100.25 ± 1.01	99.36 ± 2.10
T=14	93.79 ± 1.07	97.71 ± 0.41
T=30	98.86 ± 0.93	99.14 ± 0.66
T=42	100.09 ± 0.702	99.80 ± 0.54
T=58	99.29 ± 1.81	99.13 ± 0.70

TABLE 2. Stability of Midazolam in SyrSpend SF Cherry for 58 Days.

ELAPSED TIME	% RECOVERY AT ROOM TEMPERATURE	% RECOVERY AT 2°C - 8°C
T=0	100.00	100.00
T=7	99.83 ± 1.41	100.92 ± 1.11
T=14	93.83 ± 0.97	98.53 ± 0.95
T=30	99.51 ± 0.65	99.18 ± 0.53
T=42	99.07 ± 1.63	98.48 ± 2.19
T=58	99.59 ± 1.77	99.91 ± 1.46

Midazolam Hydrochloride Injection in SyrSpend SF Suspension

The initial potency of the midazolam in SyrSpend SF suspension was 1.02542 mg/mL, which is shown in Figure 1. This concentration was 102.54% of the compounding target of 1.0 mg/mL. The T=0 result was set as the baseline for all other time points tested. The assay results varied between 0.96 mg/mL (T=14) and 1.03 mg/mL (T=7) for room temperature storage conditions. The assay results varied between 1.00 mg/mL (T=14) and 1.03 mg/mL (T=0) for refrigerated conditions. All sample preparations at each time point were within specifications, with a high relative standard deviation of 1.81% (T=58) for room temperature conditions and 2.10% (T=7) for refrigerated conditions. Every replicate chromatogram for every time point was clear of degradant peaks and had the same chromatographic profile.

FIGURE 1. Plot of midazolam concentration in SyrSpend SF Suspension.

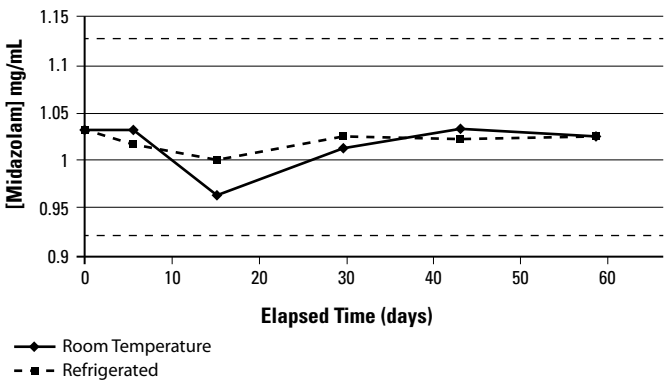

FIGURE 2. Plot of midazolam concentration in SyrSpend SF Cherry Suspension.

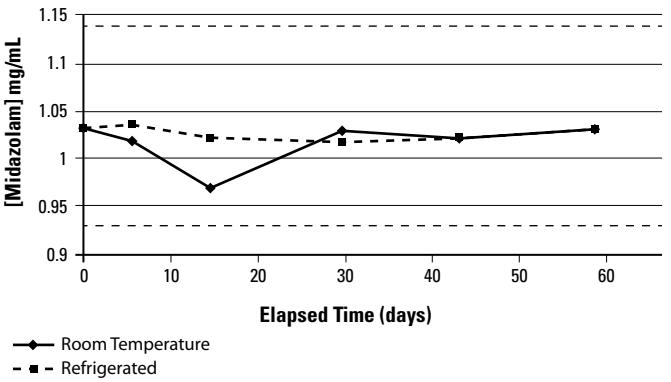

TABLE 3. Summary of the Validation Parameters for the High-performance Liquid Chromatographic Method Used in the Stability Study of Midazolam.

VALIDATION PARAMETER	RESULTS
Peak tailing	1.11 % RSD = 0.43
Theoretical plates	4445.73 % RSD = 0.58
Linear range	2.62 to 73.42 mcg/mL R^2 = 1.000
Extraction precision (SyrSpend SF) *n*=6	% RSD = 1.26
Accuracy (mcg/mL)	%Target = 101

Midazolam Hydrochloride Injection in SyrSpend SF Cherry Suspension

The initial potency of the midazolam in SyrSpend SF Cherry suspension was 1.0333 mg/mL, which is shown in Figure 1. This concentration was 103.33% of the compounding target of 1.0 mg/mL. The T=0 result was set as the baseline for all other time points tested. The assay results varied between 0.97 mg/mL (T=14) and 1.03 mg/mL (T=0) for room temperature storage conditions. The assay results varied between 1.02 mg/mL (T=42) and 1.04 mg/mL (T=7) for refrigerated conditions. All sample preparations at each time point were within specifications, with a high relative standard deviation of 1.766% (T=58) for room temperature conditions and 2.19% (R=42) for refrigerated conditions. Every replicate chromatogram for every time point was clear of degradant peaks and had the same chromatographic profile.

CONCLUSION

Midazolam was stable in SyrSpend SF and SyrSpend SF Cherry for 58 days when stored under both refrigerated (2°C to 8°C) conditions and at room temperature conditions when compounded from midazolam HCl injection. The samples were still within specifications at day 58; therefore, the beyond-use date is concluded to be 58 days. The findings of this study show that SyrSpend SF and SyrSpend SF Cherry is an acceptable oral syrup and suspending vehicle for preparing individual compounded midazolam 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 tablets when that dosage form is found to be inappropriate.

REFERENCE

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