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 Hynovel, 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 mixing effect for the bitter taste, thereby increasing the palatability 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 (Patron 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 600804; Schaumburg, Illinois). High-performance liquid chromatographic (HPLC)-grade methanol (Lot D3 206; Honeywell, Michigan), sodium acetate trihydrate (Lot 107203; Fisher Chemical, New Jersey), and glacial acetic acid (Lot 8052205; Acros, Belgium) were used in this study. HPLC-grade water was supplied by filtering deionized water from a Millipore Elix through a Millipore Simplicity (Sillerton, 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-μL programmable autosampler with a Peltier tray, 800-μL sample loop, and 280-μL 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-μL programmable autosampler with a 100-μL sample loop, and a 280-μL syringe. The Perkin Elmer HPLC was operated and data was collected using Perkin Elmer Totalchrom chromatography software, while the Varian HPLC used Galaxia chromatography software. The mobile phase for the HPLC method was 70/30 methanol/acetic buffer, pH 5.2.