Stability of Ursodiol in SyrSpend SF Cherry Flavored

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ABSTRACT

Ursodiol is used in the treatment and prevention of certain types of gallstones and for patients with primary biliary cirrhosis. Ursodiol is marketed for this purpose by Watson Pharma, Inc. as ACTIGALL, by Axcan Scandipharm Inc. as URSO 250 and URSO Forte, and by a number of generic manufacturers. Ursodiol is available as capsules of varying strengths. 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 tolerate suspending agents containing alcohol or sorbitol. The objective of this study was to determine the stability of ursodiol in SyrSpend SF Cherry Flavored which does not contain sorbitol or alcohol. The studied sample was compounded into a 30-mcg/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 66 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. The beyond-use-date of this product is at least 66 days, based on data collected when refrigerated and protected from light.

INTRODUCTION

Ursodiol is a naturally occurring bile acid found in small quantities in normal human bile and in the biles of certain other mammals. An oral form of ursodiol is approved for use for patients with radiolucent, noncalcified gallbladder stones at surgical risk and for the prevention of gallstone formation in obese patients experiencing rapid weight loss.[1]

Ursodiol is a bitter-tasting white crystalline powder. The bitter taste presents an issue for patients who are incapable of swallowing the capsules whole. A suspending agent containing a sweetener would provide a masking effect for the bitter taste, increasing the palatability of an oral dose form to increase therapeutic compliance. SyrSpend SF Cherry Flavored (Fagron US—formerly Gallipot, St. Paul, Minnesota) is an alcohol- and sorbitol-free suspending agent which could serve as a suitable alternative for compounding ursodiol oral suspensions.

The objective of this study was to examine the stability of ursodiol in an oral suspension using SyrSpend SF Cherry Flavored. The suspension was stored in a low-actinic plastic bottle at a concentration of 30 mcg/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 66 days.

MATERIALS AND METHODS

Chemical Reagents

Ursodiol raw powder was purchased from Medisca (Lot 71533; Plattsburgh, New York). SyrSpend SF Cherry Flavored was received from Fagron US—formerly Gallipot (Lot 0909185J12; St. Paul, Minnesota). High-performance liquid chromatographic (HPLC)-grade acetonitrile (Lot CZ076; Burdick and Jackson, Kalamazoo, Michigan), acetic acid (Lot 092617; Fisher Scientific, Pittsburgh, Pennsylvania), and HPLC-grade methanol (Lot C1007236; Pharmco-Aaper, Butler, Wisconsin) were used in this study. HPLC-grade water was supplied by filtering deionized water from a Millipore Elix through a Millipore Simplicity (Billerica, Massachusetts).

Equipment and Chromatographic Conditions

A Varian Prostar (Palo Alto, California) HPLC equipped with a tertiary gradient solvent delivery system, a photodiode array detector (PDA), an evaporative light scattering detector (ELSD), and an 84-vial programmable autosampler with a 100-mcL sample loop and 250-mcL syringe was used. The Varian HPLC used Galaxie chromatography software. The mobile phase for the HPLC method was water, acetonitrile, and methanol (300:350:350). The mobile phase's pH was adjusted to 4.00 with acetic acid and was delivered at 1.4 mL/min. Chromatographic separation was achieved using a 150 × 4.6 mm Phenomenex (Torrence, California) Gemini C18 column with 5 mcm particle packing. The ELSD nebulizer was set to 35°C, the evaporator to 60°C, and the gas flow to 1.8 SLM. A water:acetonitrile:methanol (30:35:35) diluent was used for standard curve preparations from 20 mcg/mL to 100 mcg/mL and assay preparations to 60 mcg/mL. The assay was monitored following a 100 mcL injection.

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

Due to the mode of detection, the ELSD is not a stability-indicating detector; therefore, a PDA was used to analyze the forced-degradation samples. Ursodiol samples were stressed and assayed at 214 nm to determine the specificity of the HPLC method to any possible degradation product produced during storage of an oral suspension. Ursodiol was diluted to 5.36 mg/mL in solutions of acid (0.1M HCl), base (0.1M NaOH), 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 ursodiol to each individual degradation pathway. Any extraneous peaks found in the chromatogram were labeled and checked for separation from the ursodiol peak. Purity calculations were performed in Galaxie on the ursodiol peak using the controlled unstressed standard as a reference.

Preparation of Ursodiol Suspension Samples

The ursodiol suspension was prepared by adding 3.32 g of ursodiol to a 4-oz low actinic cylindrical prescription bottle. Four 25-mL aliquots of SyrSpend SF Cherry Flavored were added to the bottle and stirred vigorously following each addition. Another 10 mL of SyrSpend SF Cherry Flavored was added to bring the volume to 110 mL and stirred until a homogeneous preparation was achieved. The contents were stored at *USP*-controlled refrigerated temperature (2°C to 8°C) for the stability study.

STABILITY STUDY

The sample of ursodiol suspended in SyrSpend SF Cherry Flavored at a concentration of 30 mcg/mL was submitted for stability. The sample was packaged in 4-oz low-actinic plastic prescription bottles, and stored at *USP* controlled 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), 1 day (T=1), 8 days (T=8), 11 days (T=11), 15 days (T=15), 30 days (T=30), and 66 days (T=66). The evaluation parameter was percent recovery assay. The stability of ursodiol 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 1 mL of suspension with a volumetric pipette to 30 mL of HPLC-grade water and 70 mL of 50/50 mixture of methanol/acetonitrile in a 100-mL volumetric flask. One milliliter of that stock was pipetted using a volumetric pipet into a 5-mL volumetric flask and brought to volume using a water:acetonitrile:methanol (30:35:35) diluent. The average and standard deviation of all replicate injections at each time point was used to calculate the percent recovery.

RESULTS

The stability of ursodiol in SyrSpend SF Cherry Flavored is shown in Table 1. The result of 29.04 mg/mL at T=0 was set as the initial concentration for the study, and all subsequent time points were compared to this value. The Figure that accompanies this article shows the data in terms of concentration and also shows that the concentration of the suspension remained within the specification (90%<[ursodiol]<110%) throughout the duration of the study.

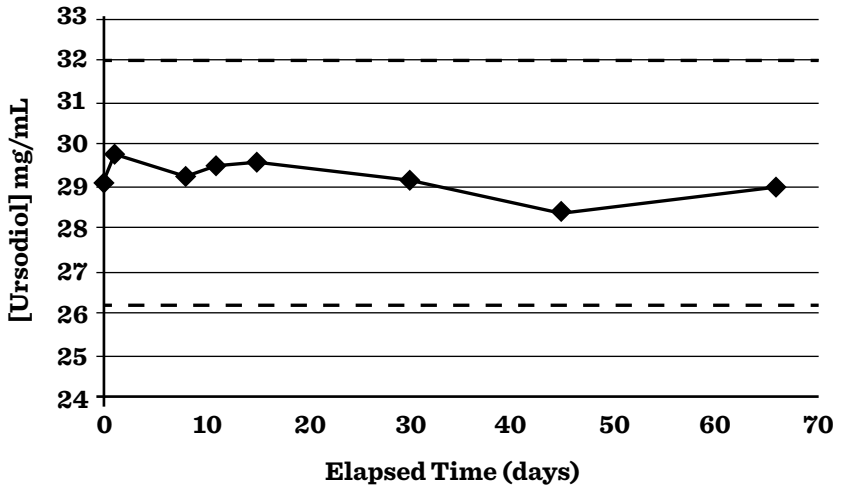
TABLE 1. Stability of Ursodiol in SyrSpend SF Refrigerated (2°C to 8°C) for 66 Days.

ELAPSED TIME	% RECOVERY
T=0	100.00
T=1	102.53 ± 0.89
T=8	100.72 ± 1.57
T=11	101.53 ± 2.22
T=15	101.57 ± 1.71
T=30	100.15 ± 0.72
T=45	97.69 ± 1.97
T=66	99.73 ± 1.36

DISCUSSION

The HPLC method was shown to be stability indicating by forcibly degrading ursodiol and separating the degradant peaks from that of the main analyte. Ursodiol was stable to heat; however, acid, oxidizer,

FIGURE. Plot of ursodiol concentration in SyrSpend SF Cherry Flavored suspension.



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

TABLE 2. Summary of the Validation Parameters for the High-performance Liquid Chromatographic Method Used in the Stability Study of Ursodiol in SyrSpend SF.

VALIDATION PARAMETER	RESULTS
Peak tailing	1.32
Theoretical plates	6443.6
Range	2.65 to 105.84 mcg/mL R2 = 0.9999
Extraction precision (SyrSpend SF Cherry Flavored) *n*=6	% Relative standard deviation = 4.78
Accuracy (mcg/mL)	% Target = 101.09

and light created slight degradation. Base created significant degradation. The degradants present were all completely separated from the analyte with acceptable resolution. Additionally, the validation parameters listed in Table 2 show that all system suitability results met acceptable criteria.

Ursodiol *United States Pharmacopeia* Raw Powder (Medisca) in SyrSpend SF Cherry Flavored Suspension

The initial potency of the Ursodiol USP Raw Powder in SyrSpend SF Cherry Flavored Suspension was 29.04 mg/mL, which is shown in the Figure that accompanies this article. This concentration was 96.8% of the compounding target of 30 mg/mL. The T=0 result was set as the baseline for all other time points tested. The assay results varied between 28.37 mg/mL (T=45) and 29.50 mg/mL (T=15). All sample preparations at each time point were within specification, with a high % relative standard deviation of 2.22% (T=11). Every replicate chromatogram for every time point was clear of the degradant peaks and had the same chromatographic profile.

CONCLUSION

Ursodiol was stable in SyrSpend SF Cherry Flavored for 66 days when stored under refrigerated (2°C to 8°C) conditions and compounded from the raw powder. The samples were still within specifications at day 66. However, no general trend was observed during the course of the study; therefore, the beyond-use date is concluded to be 66 days.

The findings of this study show that SyrSpend SF Cherry Flavored is an acceptable oral syrup and suspending vehicle for preparing individual compounded ursodiol 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. ACTIGALL (ursodiol) capsule [product information] Corona, CA: Watson Pharma, Inc. [NIH Website.] March 2009. Available at: http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=aeb6c8c8-4dec-4574-8f26-b6b701b04b25. Accessed February 28, 2012.

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