Stability of Compounded Ursodiol Suspensions in PCCA Base, SuspendIT™


Xavier University of Louisiana College of Pharmacy, New Orleans, Louisiana

OBJECTIVE

Ursodiol is commercially available as a 300-mg capsule and a 250-mg tablet. However, no compounded suspension of ursodiol in a PCCA base is currently available. The objective of this study was to develop and optimize a compounded suspension of pure drug powder or commercial tablets/capsules would provide an alternative option to meet unique patient needs. The purpose of this study was to determine the biochemical stability of compounded ursodiol suspensions in the PCCA base SuspendIT™. This base is a sugar-free, paraben-free, dye-free, and gluten-free thixotropic vehicle containing a natural sweetener obtained from the roots of a thistle plant. As a result of this, 18 cleanings of any insoluble particles and becomes fluid upon shaking to allow convenient pouring during administration to the patient. The study design included two concentration ranges to provide stability documentation over a bracketed range for eventual use by compounding pharmacies.

METHODS

Development of a Stability-Indicating HPLC assay method for Ursodiol

The HPLC analytical method developed was demonstrated to be stability indicating by subjecting ursodiol samples to accelerated degradation. A forced degradation study was performed to identify degradation products that interfere with the analytical peak for ursodiol. These forced degradation conditions included caustic, acidic, peroxide, light, and ultraviolet light degradation. For the caustic degradation, the ursodiol solution was added to a 10 mL volumetric flask containing 100 mL of 1 M NaOH solution in stock methanol, or approximately 73.9 mg of a test formulation containing 85 mg/mL ursodiol in SuspendIT™. The sample was heated to 60°C for 1 hour. For the acidic degradation, the stock solution or formulation (78.5 mg) was mixed with 0.5 mL of a 1 N HCl solution and stored at room temperature for 1 hour. Similarly, the peroxide degradation was accomplished in an analogous manner by mixing the formulation sample (77.7 mg) stock solution with 483.3 mL of deionized water and 16.7 mL of a 30% hydrogen peroxide solution resulting in a 1% peroxide solution. Forced degradation by ultraviolet (UV) light was achieved by placing 50 mL of stock methanol or stock solution or 76 mg of the formulation sample in a Millipore UV sterilizer for 1 hour.

Preparation of Ursodiol Suspensions in SuspendIT™

Two suspensions, one containing 50 mg/mL, and the other containing 100 mg/mL of ursodiol in SuspendIT™ were prepared by weighing out either 25 grams or 50 grams of ursodiol and mixing it with the suspension to make 50 mL of final suspension. The two suspensions were stored in a refrigerator at 5°C for 1 day, and then refrigerated at room temperature (22°C) for 2 months. The samples were analyzed two times each and refrigerated at room temperature (22°C) for 2 months. The concentration of ursodiol was determined using a Waters 2690 ALC2 detector. A Waters 2487 ALC2 detector was used for the determination of ursodiol concentration.

Analysis of ursodiol suspensions

A stability-indicating HPLC assay method for ursodiol was developed on a High Performance Liquid Chromatography using a Waters 2424 refractive index detector. Since the UV absorbance of ursodiol is quite low, refractive index detection was chosen for the analysis. An isocratic mobile phase was used containing 56% methanol and 42% of acetic acid (0.1%) at a flow rate of 0.8 mL/min. The injection volume was 30 microliters. A Waters X-Bridge™ RP 18 2.1x100mm 5um column was used for the separation. A series of standards ranging from 50 to 1000 mcg/mL were prepared in the mobile phase from a 10 mg/mL stock solution of ursodiol in methanol, prepared fresh for each sampling period. The chromatograms were acquired for the standards and samples, and used to determine the ursodiol peak area. The calibration curve and peak areas were analyzed using analysis of the analyte. The pH of each sample was measured using a pH meter. The pH of each sample was measured using a pH meter. The pH of each sample was measured using a pH meter.

RESULTS

The HPLC method utilized in the study clearly separated any peaks associated with the SuspendIT™ from the analytical peak for ursodiol (Figure 1). The method also displayed good linearity over the observed concentration range (Figure 2). Forced degradation studies revealed that peaks associated with the degradants had much shorter retention times than the ursodiol peak, and showed no interference with its analytical peak (Figure 3).

Ursodiol formed a uniform, easily dispersible suspension in the SuspendIT™ for both the 50 mg/mL and 100 mg/mL drug concentrations. No disruption of the suspension was observed. The pH and viscosity of the samples displayed no significant changes over the test period (Tables 1 and 2). Using a Student’s t-test as a means of determining drug degradation, no degradation of the suspension was observed over the 181 day test period (Tables 3 and 4; Figures 4 and 5). Drug concentrations were equal to, or above 97% of initial values, and no degradation was observed. These results were true for both concentrations and at both temperature conditions studied.

CONCLUSIONS

A robust stability-indicating HPLC assay method for the determination of ursodiol in PCCA Base, SuspendIT™ was developed and validated. This assay was used to determine the chemical stability of the 50 mg/mL and 100 mg/mL concentrations of ursodiol in SuspendIT™ at 5°C and 22°C. Drug concentration did not go below 90% of the label claim (90%±5%) concentration at both concentrations and both temperature conditions studied. Viscosity and pH values did not change significantly. Content uniformity was maintained during the storage at room temperature. This study demonstrates that ursodiol is physically and chemically stable in SuspendIT™ for 181 days at the refrigerator and at room temperature, thus providing a viable, compounded alternative for ursodiol in a liquid dosage form, with an extended beyond-use-date to meet patient needs. The study further provides stability documentation over a bracketed range of 50 – 100 mg/mL of ursodiol, allowing compounding pharmacies more flexibility in customizing their formulations.

ACKNOWLEDGMENTS

This study was sponsored by PCCA, and supported in part by the NIH Grant #1GM080705, DHHS Grant #1DP4HF00500; and the Louisiana Cancer Research Consortium.*

*To whom correspondence should be addressed.