Physicochemical and Microbiological Stability of Compounded Amitriptyline Hydrochloride Oral Liquid Dosage Forms in PCCA Base, SuspendIt™

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OBJECTIVE

Amitriptyline HCl is commercially available as 10-mg, 25-mg, 50-mg, 75-mg, 100-mg and 150-mg tablets. No commercial liquid dosage form of amitriptyline hydrochloride currently exists. An extemporaneously compounded suspension from 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 physicochemical and microbiological stability of extemporaneously compounded amitriptyline hydrochloride 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 monk fruit. It thickens upon standing to minimize settling of any insoluble drug particles and becomes fluid upon shaking to allow convenient pouring during administration to the patient. The study design included two concentrations to provide stability documentation over a bracketed range for eventual use by compounding pharmacists.

A robust stability-indicating HPLC assay for the determination of the chemical stability of amitriptyline hydrochloride in SuspendIt™ was developed and validated. Suspensions of amitriptyline hydrochloride were prepared in SuspendIt™ at 1 mg/mL and 5 mg/mL concentrations, selected to represent a range within which the drug is commonly dosed. Samples were stored in plastic amber prescription bottles at two temperature conditions (5^{0}C and 25^{0}C) and assayed over an extended period of time. Physical data such as pH, viscosity, and appearance were also noted. Samples were also tested for microbiological stability. The goal was to provide a viable, compounded alternative for amitriptyline hydrochloride in a thixotropic liquid dosage form, with an extended beyond-use-date to meet patient needs.

METHODS

Development of a stability-indicating HPLC assay method for Amitriptyline Hydrochloride

The HPLC analytical method developed was demonstrated to be stability indicating by subjecting amitriptyline hydrochloride samples to accelerated degradation. A forced degradation study was performed to determine if any degradants interfered with the analytical peak for amitriptyline hydrochloride. These forced degradations included caustic, acidic, peroxide, and ultraviolet light degradation.

For the caustic degradation, 0.5 mL of 5N NaOH was added to a 10-mL volumetric flask containing either 200 µL of 1-mg/mL stock solution of amitriptyline hydrochloride in mobile phase, or approximately 40 mg of a test formulation containing 5 mg/mL amitriptyline hydrochloride in PCCA SuspendIt. The sample was heated to 60°C for 1 hour. For the acidic degradation, the stock solution or formulation was mixed with 0.5 mL of a 1N HCl solution and stored at room temperature for 1 hour. The peroxide degradation was accomplished in an analogous manner by mixing the sample or stock solution with 483.3 µL of deionized water and 16.7 µL of a 30% hydrogen peroxide solution, resulting in a 1% peroxide solution. Forced degradation by UV light was achieved by placing either 5-mg/mL stock solution, or a small amount of the 5-mg/mL formulation in 10-mL volumetric flasks in a Millipore UV sterilizer (Catalog No. XX6370000, Billerica, Massachusetts) for 1 hour.

Preparation of Amitriptyline Hydrochloride Suspensions in SuspendIt™

Two suspensions, one containing 1 mg/mL, and the other containing 5 mg/mL of amitriptyline hydrochloride in SuspendIt™ were prepared by first weighing out either 1.0 gram or 5.0 grams of amitriptyline hydrochloride respectively, and placing the powder in a mortar. The powder was levigated to a smooth paste using a small amount of SuspendIt™ base. Additional SuspendIt™ was added to the mortar and the contents transferred into a 1000 mL volumetric flask using a rubber spatula. For both drug concentrations, six 4-oz. amber plastic prescription bottles were filled with 80 mL of the prepared suspension, and six bottles were filled with 60 mL of the suspension, retaining the remainder for initial (zero day) analysis. The specific gravity was determined to be 1.0 for both the 1-mg/mL, and the 5-mg/mL batches. The bottles containing 80 mL of suspension were sealed, wrapped in parafilm, divided into two groups of three bottles each, and stored either at room temperature (25°C) in a desiccator, or under refrigerated conditions (5°C). The temperature at each storage location was monitored throughout the study. Samples from each temperature and concentration were analyzed and characterized initially on day zero, and subsequently after 7, 14, 28, 49, 63, 91, 119 and 185 days of storage. The bottles containing 60 mL of the suspension were tested for microbiological stability.

Analysis and Characterization of Amitriptyline Hydrochloride Suspensions

Samples of amitriptyline hydrochloride in SuspendIt™ were analyzed on a Waters chromatographic system (Waters Corporation, Milford, Massachusetts) using a 717 autosampler, a 600-quaternary pump, and a 996-photodiode array detector set at 238 nm for the detection of the amitriptyline hydrochloride. An isocratic mobile phase containing 70% v/v of a 50 mM potassium phosphate solution adjusted to pH 3.0 using phosphoric acid and 30% v/v acetonitrile was used at a flow rate of 1.0 mL/min. The injection volume was 10.0 microliters. An Xbridge C18 2.1 X 100-mm 5-µm particle size column was used for the separation. A series of standards ranging from 5 µg/mL to 40 µg/mL were prepared in mobile phase from a 0.5-mg/mL stock solution of amitriptyline hydrochloride in mobile phase prepared fresh for each sampling period. Chromatograms were acquired for the standards and samples. A least squares analysis was performed on the calibration curve using the peak areas from the amitriptyline hydrochloride peaks at 238 nm, and the sample concentrations were determined. Using the initial specific gravity measurements of the formulations, the weight/weight measurements were converted to weight/volume units. The suspensions were also analyzed for pH, appearance and intrinsic viscosity. The pH of each sample was measured on a VWR Scientific pH meter using an Ag/AgCl combination electrode, calibrated prior to analysis. The viscosity was determined using a Brookfield DV-III Ultra programmable cone/plate rheometer fitted with a cpe-40 spindle.

RESULTS

The HPLC method utilized in the study clearly separated any peaks associated with the SuspendIt™ from the analytical peak for the amitriptyline hydrochloride (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 amitriptyline hydrochloride peak and showed no interference with its analytical peak (Figure 3).

Amitriptyline hydrochloride formed a translucent suspension in PCCA SuspendIt at both concentrations, with the 5-mg/mL concentration showing a slightly higher opacity. The pH of the samples displayed no significant changes over the test period (Table 1). The decrease in viscosity (Table 2) could be due to an interaction between the dissolved amitriptyline hydrochloride salt and the SuspendIt. Given that amitriptyline hydrochloride is soluble in water, uniformity of drug concentration is independent of viscosity. Using a ±10% criterion as a means of determining drug degradation, no significant degradation of the amitriptyline hydrochloride was found over the 185-day test period (Tables 3, 4; Figures 4, 5). Drug concentrations were above 99% of initial values, and no degradation was observed for both concentrations, and at both temperature conditions studied.

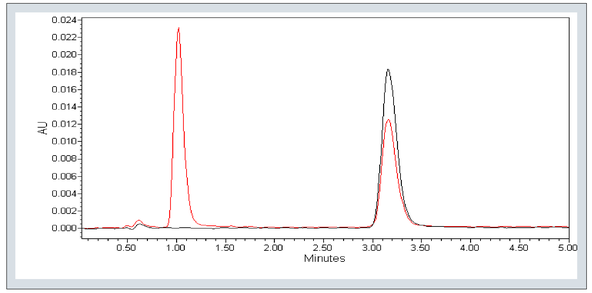

Figure 1. Sample chromatographic run of Amitriptyline Hydrochloride standard (black) and Amitriptyline Hydrochloride in PCCA SuspendIt (red) using an analysis wavelength of 238 nm.

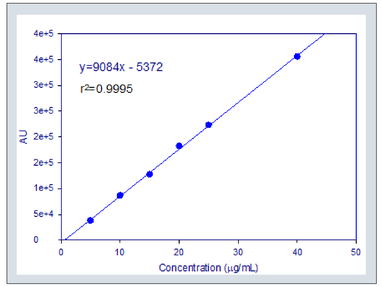

Figure 2. Calibration curve for high-performance liquid chromatographic analysis of Amitriptyline Hydrochloride (range: 5 µg/mL to 40 µg/mL).

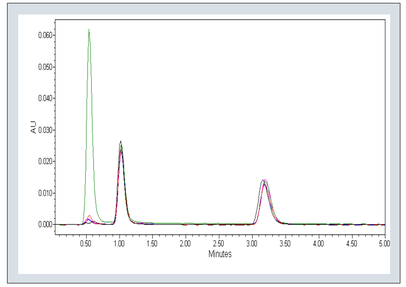

Figure 3. Chromatographic runs of Amitriptyline Hydrochloride in PCCA SuspendIt; standard (black), with caustic degradation (blue), acidic degradation (red), oxidative degradation (green), and ultraviolet light degradation (violet).

Table 1. Measurements of pH of of Amitriptyline Hydrochloride in PCCA SuspendIt™

Time	1 mg/mL		5 mg/mL	
	5°C	25°C	5°C	25°C
Day 0	5.16 ± 0.01	5.16 ± 0.01	5.16 ± 0.01	5.16 ± 0.01
Day 7	5.17 ± 0.02	5.17 ± 0.02	5.08 ± 0.02	5.08 ± 0.02
Day 14	5.12 ± 0.02	5.15 ± 0.02	5.08 ± 0.02	5.16 ± 0.08
Day 28	5.13 ± 0.01	5.13 ± 0.03	5.08 ± 0.01	5.09 ± 0.02
Day 49	5.15 ± 0.01	5.16 ± 0.03	5.09 ± 0.01	5.07 ± 0.01
Day 63	5.13 ± 0.01	5.14 ± 0.03	5.11 ± 0.01	5.10 ± 0.01
Day 91	5.16 ± 0.02	5.18 ± 0.02	5.11 ± 0.01	5.12 ± 0.02
Day 119	5.17 ± 0.01	5.16 ± 0.02	5.12 ± 0.03	5.14 ± 0.01
Day 185	5.13 ± 0.01	5.17 ± 0.06	5.07 ± 0.02	5.09 ± 0.02

Table 2. Viscosity (cP) measurements of Amitriptyline Hydrochloride in PCCA SuspendIt™

Time	1 mg/mL		5 mg/mL	
	5°C	25°C	5°C	25°C
Day 0	60.1 ± 0.9	60.1 ± 0.9	11.0 ± 0.3	11.0 ± 0.3
Day 7	35.6 ± 1.3	37.5 ± 0.4	9.3 ± 0.7	9.3 ± 0.5
Day 14	36.7 ± 2.7	38.7 ± 0.9	7.7 ± 0.4	8.0 ± 0.3
Day 28	36.7 ± 1.4	38.9 ± 2.9	7.5 ± 0.4	7.8 ± 0.6
Day 49	35.7 ± 0.3	38.1 ± 1.8	8.4 ± 0.8	8.2 ± 0.7
Day 63	37.4 ± 0.1	41.5 ± 3.0	7.1 ± 0.5	7.1 ± 0.2
Day 91	35.5 ± 1.5	42.8 ± 4.6	7.1 ± 0.7	6.9 ± 1.1
Day 119	33.3 ± 2.0	45.5 ± 6.8	6.8 ± 0.4	5.6 ± 0.9
Day 185	35.8 ± 0.9	47.3 ± 1.9	5.3 ± 0.3	5.4 ± 0.8

Table 3. Amitriptyline Hydrochloride Concentration (mg/mL) in PCCA SuspendIt™

Time	1 mg/mL		5 mg/mL	
	5°C	25°C	5°C	25°C
Day 0	1.01 ± 0.01	1.01 ± 0.01	4.99 ± 0.15	4.99 ± 0.15
Day 7	1.04 ± 0.06	1.02 ± 0.01	5.04 ± 0.09	5.09 ± 0.02
Day 14	1.04 ± 0.01	1.01 ± 0.02	5.04 ± 0.03	4.98 ± 0.08
Day 28	1.02 ± 0.02	1.02 ± 0.01	5.05 ± 0.07	5.13 ± 0.03
Day 49	1.02 ± 0.01	1.02 ± 0.02	5.04 ± 0.16	5.06 ± 0.05
Day 63	1.05 ± 0.01	1.02 ± 0.00	5.03 ± 0.01	5.07 ± 0.01
Day 91	1.03 ± 0.00	1.02 ± 0.03	5.11 ± 0.13	5.08 ± 0.06
Day 119	1.02 ± 0.01	1.01 ± 0.02	5.06 ± 0.04	5.05 ± 0.04
Day 185	1.04 ± 0.02	1.03 ± 0.02	5.06 ± 0.04	5.09 ± 0.15

Table 4. Percent of Amitriptyline Hydrochloride in PCCA SuspendIt™ relative to Day Zero sample

Time	1 mg/mL		5 mg/mL	
	5°C	25°C	5°C	25°C
Day 0	100.0 ± 1.5	100.0 ± 1.5	100.0 ± 4.3	100.0 ± 4.3
Day 7	103.1 ± 6.0	101.0 ± 1.7	100.9 ± 3.5	101.9 ± 3.1
Day 14	102.8 ± 1.2	100.0 ± 2.0	101.1 ± 3.1	99.8 ± 3.4
Day 28	101.4 ± 2.1	101.0 ± 1.4	101.3 ± 3.3	102.8 ± 3.2
Day 49	100.6 ± 1.3	100.9 ± 2.1	101.0 ± 4.4	101.5 ± 3.2
Day 63	104.0 ± 1.4	100.8 ± 1.2	100.9 ± 3.0	101.7 ± 3.1
Day 91	102.1 ± 1.1	100.9 ± 2.7	102.4 ± 4.0	101.9 ± 3.3
Day 119	101.2 ± 1.6	99.8 ± 2.5	101.4 ± 3.1	101.3 ± 3.2
Day 185	102.4 ± 2.1	101.3 ± 2.3	101.5 ± 3.2	101.9 ± 4.3

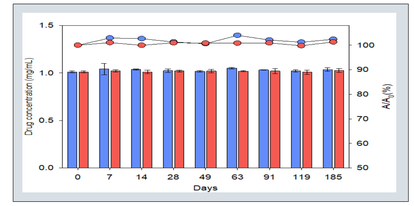

Figure 4. Change in drug concentration over 185 days on left axis for the 1-mg/mL samples of Amitriptyline Hydrochloride in PCCA SuspendIt stored at 5°C (blue) and 25°C (red); and relative change in percent on right axis as compared to initial concentration [A/Ao = drug content at time t (A) over initial drug content (Ao) x100] .

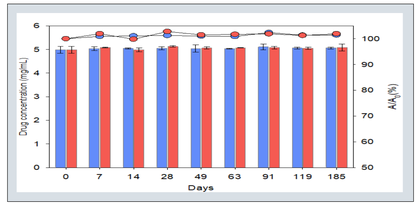

Figure 5. Change in drug concentration over 185 days on left axis for the 5-mg/mL samples of Amitriptyline Hydrochloride in PCCA SuspendIt stored at 5°C (blue) and 25°C (red); and relative change in percent on right axis as compared to initial concentration [A/Ao = drug content at time t (A) over initial drug content (Ao) x100].

CONCLUSIONS

A robust stability-indicating HPLC assay method for the determination of amitriptyline hydrochloride in PCCA SuspendIt was developed, validated, and used to determine the chemical stability of the 1-mg/mL and 5-mg/mL concentrations of amitriptyline hydrochloride in PCCA SuspendIt at 5^{0}C and 25^{0}C. Drug concentration did not go below 99.8% of the label claim (initial drug concentration) at both concentrations and both temperature conditions studied. The pH values did not change significantly. The viscosity of the suspensions was sufficient to allow easy re-dispersal of the drug particles upon shaking. Content uniformity was maintained, and no caking was observed. The preservative system in PCCA SuspendIt successfully protected the suspensions from growth of challenge microorganisms per the *USP* Chapter <51> AME Test. This study demonstrates that amitriptyline hydrochloride is physically, chemically, and microbiologically stable in PCCA SuspendIt for 185 days in the refrigerator and at room temperature, thus providing a viable, compounded alternative for amitriptyline hydrochloride in a liquid dosage form, with an extended BUD to meet patient needs.

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