Physicochemical Stability of Compounded Naltrexone Hydrochloride Solutions in PCCA Base, SuspendIt

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Introduction

Oral liquid preparations are well suited for special populations that may experience difficulty in swallowing solid dosage forms, such as tablets and capsules. In addition, liquid dosage forms offer the benefit of flexibility by providing convenient and accurate dosing options that can be customized for pediatric and geriatric patients. However, palatable liquid dosage forms of various drugs are often not commercially available, or they may be in short supply. In such situations, the compounding pharmacist is uniquely qualified to meet patient needs by

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Abstract

Naltrexone hydrochloride is an orally active narcotic antagonist used to facilitate rapid transition from methadone maintenance. The dosing schedule of naltrexone hydrochloride in detoxification protocols needs to be flexible to permit precise, customized dose titration for individual patients. This flexibility is readily achieved using an oral liquid dosage form. However, no commercial liquid dosage form of naltrexone hydrochloride currently exists. Naltrexone hydrochloride is commercially available as a scored, film-coated, 50-mg tablet. An extemporaneously compounded suspension from pure drug powder or commercial tablets would provide a convenient option to meet unique patient needs. The purpose of this study was to determine the physicochemical stability of extemporaneously compounded naltrexone hydrochloride solutions in 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. The study design included two naltrexone hydrochloride concentrations to provide stability documentation over a bracketed concentration range for eventual use by compounding pharmacists. A robust stability-indicating HPLC assay for the determination of the chemical stability of naltrexone hydrochloride in SuspendIt was developed and validated. Solutions of naltrexone hydrochloride were prepared in SuspendIt at 0.5-mg/mL and 5.0-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°C and 25°C). Samples were assayed initially, and at the following time points: 7 days, 14 days, 29 days, 44 days, 61 days, 90 days, 120 days, and 180 days. Physical data such as pH, viscosity, and appearance were also noted. All measurements were obtained in triplicate. A stable extemporaneous preparation is defined as one that retains at least 90% of the initial drug concentration throughout the sampling period. The study showed that naltrexone hydrochloride concentrations did not go below 94% of the label claim (initial drug concentration) at both temperatures studied. Viscosity and pH values also did not change significantly. This study demonstrates that naltrexone hydrochloride is physically and chemically stable in SuspendIt for 180 days in the refrigerator and at room temperature, thus providing a viable, compounded alternative for naltrexone hydrochloride in a liquid dosage form, with an extended beyond-use date to meet patient needs.

extemporaneously compounding oral liquids using pure drug powder or tablets/capsules. Aqueous vehicles are frequently used to prepare compounded oral liquids, raising the possibility of chemical drug degradation. In addition, the pure drug powder and the tablet/capsule excipients are often insoluble in water; therefore, the resulting preparation will be a suspension, instead of a solution. It is the responsibility of the compounding pharmacist to prepare a suspension that is physically and chemically stable throughout its period of use. Physical stability is achieved by formulating a homogeneous suspension that does not cake upon standing, and re-disperses easily upon shaking. The pharmacist must also obtain validated chemical stability information in order to assign accurate beyond-use dates to compounded preparations.

One of the methods to treat narcotic addiction is the Methadone Maintenance Treatment (MMT).[1,2] Patients wishing to overcome their addiction face withdrawal symptoms lasting several weeks, often leading to relapse. Rapid withdrawal with an orally active narcotic antagonist, combined with aggressive treatment of the symptoms, has been demonstrated to be effective in the treatment of opioid dependence.[3,4] Naltrexone hydrochloride (HCl) is one such orally active narcotic antagonist used to precipitate withdrawal and prevent relapse by facilitating rapid transition from methadone maintenance.[5,6]

The detoxification protocol requires low initial naltrexone doses of about 1 mg, followed by subsequent titration depending on patient tolerance levels.[7,8] After 4 days on increasing naltrexone HCl doses, supplemented with adjuvant drug therapy to treat withdrawal symptoms, patients are generally able to initiate naltrexone maintenance up to daily doses of 50 mg.[9] The dosing schedule of naltrexone HCl in such detoxification protocols needs to be flexible to permit precise, customized dose titration for individual patients. This flexibility is readily achieved using an oral liquid dosage form. However, no commercial liquid dosage form of naltrexone HCl currently exists. Naltrexone HCl is commercially available as a scored, film-coated, 50-mg tablet. An extemporaneously compounded suspension from pure drug powder or commercial tablets would provide a convenient option to meet unique patient needs.

Naltrexone HCl is soluble in water, having a solubility of about 100 mg/mL.[10] The degradation of naltrexone HCl has been previously investigated in a sweetened, flavored vehicle consisting of sorbitol solution, ascorbic acid, and distilled water, and has been reported to be stable for periods up to 90 days at 4°C and 25°C.[11] A more recent study investigated the chemical stability of naltrexone HCl injection, concluding that the injection was stable for 42 days when stored in clear glass vials at room temperature and protected from light.[12] These studies provide useful information regarding short-term drug stability in certain select vehicles. No documentation regarding long-term naltrexone HCl stability in the newer thixotropic vehicles is available. Therefore, stability studies of naltrexone stability in contemporary vehicles, such as the PCCA Base, SuspendIt (hereinafter referred to as SuspendIt), are required to establish accurate beyond-use dates up to six months.

The purpose of the current study was to determine the physicochemical stability of naltrexone HCl in a new suspending agent, SuspendIt. Professional Compounding Centers of America (PCCA), Houston, Texas, has developed this unique, hypoallergenic, oral suspending vehicle with special thixotropic properties for use by compounding pharmacists. This innovative vehicle 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. SuspendIt utilizes a natural patented thixotropic agent which is ideal for the compounding of oral liquids. It has been found to form uniform suspensions with a wide variety of active pharmaceutical ingredients.[13]

Method

The current study was conducted to develop and validate a stability-indicating high-performance liquid chromatographic (HPLC) assay for naltrexone HCl in SuspendIt, and to evaluate the chemical and physical stability of the extemporaneous preparations for a 6-month period. The study design included two naltrexone HCl concentrations to provide stability documentation over a bracketed concentration range for eventual use by compounding pharmacists. Solutions of naltrexone HCl were prepared in SuspendIt at 0.5-mg/mL and 5-mg/mL concentrations, to represent a range in which the drug is commonly dosed. Samples were stored in plastic, amber prescription bottles at two temperature conditions (5°C and 25°C). Samples were assayed initially and at pre-determined time intervals over a 6-month period. Physical data such as pH, viscosity, and appearance were also noted. All measurements were obtained in triplicate. A stable extemporaneous preparation is defined as one that retains at least 90% of the initial drug concentration throughout the sampling period. The goal was to provide a viable, compounded alternative for naltrexone HCl in a thixotropic liquid dosage form, with an extended beyond-use date to meet patient needs.

Reagents

Naltrexone (Lot C181242), steviol glycosides 95% (Lot C175764), and SuspendIt (Lot 7287302) were generously provided by PCCA. The HPLC-grade acetonitrile (Lot 17J231484) was purchased from VWR Chemicals (Radnor, Pennsylvania). The reagent-grade ammonium acetate (Lot 077K0724), reagent grade acetic acid (Lot 95H3689), sodium hydroxide (Lot 935523), hydrochloric acid (Lot 119H3484), and hydrogen peroxide (Lot MKBF1744V) were purchased from Sigma Aldrich Corporation (St. Louis, Missouri). Deionized water (18.2 MΩ) was prepared in-house using the ELGA Pure Lab Classic system (ELGA LLC, Woodridge, Illinois).

SAMPLE PREPARATION

Two solutions, one containing 0.5 mg/mL and the other containing 5 mg/mL of naltrexone HCl in SuspendIt were prepared by first weighing out either 0.250 grams or 2.50 grams of naltrexone HCl, respectively, and placing the powder in a mortar. In addition, 2.5 grams of steviol glycosides 95% was added to the 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 500-mL volumetric flask using a rubber spatula. This process was repeated three times to facilitate complete removal and transfer of the liquid from the mortar to the flask. The volumetric flask was filled to the mark with additional SuspendIt, vortexed on a vortex mixer, and sonicated in an ultrasonic bath for 5 minutes to remove any air bubbles. The volumetric flask was again filled to the mark with SuspendIt and placed on a magnetic stirrer.

For both drug concentrations, six 4-oz. plastic, amber prescription bottles were filled with 80 mL of the prepared solution, retaining 20 mL for initial, zero-day analysis. The bottles were sealed, divided into two groups of three bottles each, and stored 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 days, 14 days, 29 days, 44 days, 61 days, 90 days, 120 days, and 180 days of storage.

SAMPLING PROCEDURE

On each of the 8 sampling days of (e.g., 7, 14, 29, 44, 61, 90, 120, 180), the bottles were removed from storage and uniformly shaken. An approximate volume of 8 mL was removed from each bottle for analysis prior to the bottles being returned to storage. For each of the six bottles of the 0.5-mg/mL naltrexone samples, three 5-mL volumetric flasks were tared and approximately 500 µL of the suspensions were pipetted and weighed to the nearest 0.1 mg. The volumetric flasks were brought up to volume with a 50/50 mixture of acetonitrile and pH 5.5 ammonium acetate buffer, giving a target sample concentration of 50 µg/mL. The six 5-mg/mL naltrexone samples were treated in a similar manner, using 10-mL tared volumetric flasks and pipetting 100 µL of the suspensions, weighed to the nearest 0.1 mg, to similarly achieve a target concentration of 50 µg/mL. The samples were pipetted into 1.5-mL HPLC sampling vials, being careful not to transfer any globular gelled SuspendIt. Transfer of the gelled SuspendIt was found to clog the HPLC system. The samples were analyzed by HPLC using a method adapted from the literature by Jafari-Nodoushan[14], and the Waters Columns Application Notebook[15].

HIGH-PERFORMANCE LIQUID CHROMATOGRAPHIC ANALYSIS

All samples were analyzed on a Waters HPLC system (Waters Corporation, Milford, Massachusetts) consisting of a 717 autosampler, 600E pump, and a Waters PDA detector. An isocratic mobile phase containing 82% 100 mM Ammonium Acetate (pH 5.0) and 18% acetonitrile was used at a flow rate of 0.8 mL/min. The injection volume was 10 microliters. A Waters X-Bridge RP18 2.1×100 mm 5-µm column was used for the separation. A series of standards ranging from 5 µg/mL to 100 µg/mL were prepared in the mobile phase from a 1.0-mg/mL stock solution of naltrexone HCl in mobile phase prepared fresh for each sampling period. The chromatograms were acquired for the standards and samples, and using the peak areas from the naltrexone HCl peaks at 280 nm, a least squares analysis was performed on the calibration curve, and the sample concentrations were determined.

PH AND VISCOSITY MEASUREMENTS

The suspensions were also analyzed for pH, appearance, and intrinsic viscosity. The pH of each sample was measured on a VWR Scientific pH meter (VWR) using an Ag/AgCl combination electrode calibrated prior to analysis. Measurements were taken in auto mode with each sample ran in triplicate. The viscosity was determined using a Brookfield DV-III Ultra programmable cone/plate rheometer (Brookfield Engineering Laboratories Inc., Middleboro, Mississippi) fitted with a cpe-40 spindle. After the instrument was leveled and aligned, approximately 1 mL of sample was placed in the viscometer for measurement. Using the Rheocalc program, a viscosity protocol was selected to determine the average viscosity over a 15-second measurement period at a fixed spindle speed of 16 rpm, with each measurement being performed in triplicate after a 3-minute rest period between measurements. For the determination of the thixotropic index, a similar protocol was followed to determine the viscosity at two spindle speeds of 4 rpm and 40 rpm, with a 30-second measurement period and a 3-minute wait time between triplicate measurements.

FORCED DEGRADATION STUDY

The analytical method was demonstrated to be stability indicating by subjecting naltrexone HCl samples to accelerated degradation. A forced degradation study was performed to determine if any degradants interfered with the analytical peak of naltrexone HCl. These forced degradations included caustic, acidic, peroxide, and ultraviolet (UV) light degradation. For the caustic degradation, 0.5 mL of 5N NaOH was added to a 10-mL volumetric flask containing either 100 µL of a 5-mg/mL stock solution of naltrexone HCl in mobile phase, or approximately 100 mg of a test formulation containing 5 mg/mL of naltrexone HCl in SuspendIt. The sample was heated to 60°C for 1 hour, followed by the neutralization of both the standard and sample with 2.5 mL of a 1N HCl solution. The flasks were then brought up to volume with mobile phase. 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 acidic solution was then neutralized with 0.1 mL of the 5N NaOH solution and filled to volume with mobile phase. Similarly, 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 a 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. The samples were placed on the blue sample plate of the sterilizer, exposing them to the upper two UV tubes only. This meant that they were exposed to approximately 0.63 mW/cm^2.[16] In all cases, the volumetric flasks were filled to the mark with mobile phase prior to analysis.

Results and Discussion

Naltrexone HCl formed a clear, uniform solution in the SuspendIt at both the 0.5-mg/mL and 5-mg/mL drug concentrations. No discoloration of the samples was observed, and there was no other observable difference in the physical nature of the solutions. The pH and viscosity of the samples displayed no significant changes over the test period (**TABLES 1 AND 2**). The pH measurements were consistent (5.04 to 5.12), averaging 5.08 for all the samples. Viscosity measurements showed minor variability, ranging from an average of 56.3 cP (5°C) to 58.0 cP (25°C) for both naltrexone concentrations. Minor variations of viscosity can be attributed to the thixotropic nature of the SuspendIt vehicle. Viscosities at 25°C for both concentrations were slightly higher than the viscosities at 5°C. This could be because the thixotropic properties of the vehicle allow it to regain more of the original viscosity at room temperature, compared to being refrigerated. The rapid cooling in the refrigerator may hinder the ability of the vehicle to return completely to its original viscosity. The thixotropic indices (viscosity ratio) comparing viscosity at low to high shear show a consistent pattern (**TABLE 3**), with values consistently above 1. The high shear attained at 40 rpm produced a consistently thinner, more pourable product compared to the viscosity at the low shear of 4 rpm. Viscosity measurements at subsequent time points indicated that removal of shear restored the original, thicker consistency.

The HPLC method utilized in the study clearly separated any peak associated with the SuspendIt from the analytical peak of the naltrexone HCl (**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 naltrexone peak and showed no interference with its analytical peak (**FIGURES 3** and **4**). The most significant degradation was observed following the caustic treatment, revealing a degradant at 3.8 minutes; as well as the peroxide treatment which revealed two rather large products at the beginning of the run and no remaining sample peak (**FIGURE 4**).

Using a ±10% criterion as a means of determining drug degradation, no significant degradation of the naltrexone HCl was found over the 180-day test period (**TABLES 4** and **5; FIGURES 5** and **6**). Drug concentrations were equal to, or above, 94% of initial values, and no degradation was observed. This result was true for both concentrations, and at both temperature conditions studied.

Conclusions

A robust stability-indicating HPLC assay method for the determination of naltrexone HCl in SuspendIt was developed and validated. This assay was used to determine the chemical stability of the 0.5-mg/mL and 5.0-mg/mL concentrations of naltrexone HCl in SuspendIt at 5°C and 25°C. Drug concentration did not go below 90% of the label claim (initial drug concentration) at both concentrations and both temperature conditions studied. Viscosity and pH values also did not change significantly. Content uniformity was maintained due to the thixotropic nature of the vehicle. This study demonstrates that naltrexone HCl is physically and chemically stable in SuspendIt for 180 days in the refrigerator and at room temperature, thus providing a viable, compounded alternative for naltrexone in a liquid dosage form, with an extended beyond-use date to meet patient needs. The study further provides stability documentation over

TABLE 1.

MEASUREMENTS OF pH OF NALTREXONE HYDROCHLORIDE IN SUSPENDIT.

TIME	0.5 MG/ML		5.0 MG/ML	
	5°C	25°C	5°C	25°C
Day 0	5.10 ± 0.02	5.10 ± 0.02	5.07 ± 0.01	5.07 ± 0.01
Day 7	5.11 ± 0.03	5.07 ± 0.02	5.07 ± 0.01	5.08 ± 0.02
Day 14	5.10 ± 0.01	5.11 ± 0.01	5.08 ± 0.01	5.08 ± 0.01
Day 29	5.10 ± 0.01	5.11 ± 0.01	5.08 ± 0.01	5.08 ± 0.01
Day 44	5.10 ± 0.01	5.11 ± 0.01	5.08 ± 0.01	5.08 ± 0.01
Day 61	5.10 ± 0.01	5.11 ± 0.01	5.08 ± 0.01	5.08 ± 0.01
Day 90	5.07 ± 0.01	5.07 ± 0.01	5.04 ± 0.01	5.05 ± 0.01
Day 120	5.12 ± 0.01	5.12 ± 0.01	5.09 ± 0.01	5.09 ± 0.01
Day 180	5.09 ± 0.01	5.11 ± 0.01	5.07 ± 0.01	5.08 ± 0.01

TABLE 2.

VISCOSITY (cP) MEASUREMENTS OF NALTREXONE HYDROCHLORIDE IN SUSPENDIT.

TIME	0.5 MG/ML		5.0 MG/ML	
	5°C	25°C	5°C	25°C
Day 0	56.5 ± 1.5	56.5 ± 1.5	55.1 ± 3.0	55.1 ± 3.0
Day 7	59.6 ± 1.9	57.5 ± 0.9	58.4 ± 3.8	57.6 ± 1.5
Day 14	56.3 ± 1.4	56.0 ± 2.1	55.7 ± 2.4	55.2 ± 3.2
Day 29	55.5 ± 11.7	55.0 ± 0.8	56.9 ± 3.3	54.4 ± 1.3
Day 44	52.8 ± 1.4	53.5 ± 2.4	56.7 ± 6.9	52.7 ± 2.6
Day 61	59.0 ± 0.7	60.1 ± 2.1	60.0 ± 2.0	60.6 ± 0.3
Day 90	52.7 ± 1.8	58.4 ± 4.0	57.8 ± 10.2	63.0 ± 5.5
Day 120	58.1 ± 5.8	54.2 ± 0.8	51.2 ± 0.8	59.1 ± 7.7
Day 180	53.2 ± 2.3	64.6 ± 3.0	57.5 ± 6.2	70.6 ± 3.8

TABLE 3.

THIXOTROPIC INDICES OF NALTREXONE HYDROCHLORIDE IN SUSPENDIT.

TIME	0.5 MG/ML		5.0 MG/ML	
	5°C	25°C	5°C	25°C
Day 0	3.65 ± 0.21	3.65 ± 0.21	3.54 ± 0.07	3.54 ± 0.07
Day 7	3.54 ± 0.12	3.49 ± 0.12	3.88 ± 0.41	3.36 ± 0.15
Day 14	3.57 ± 0.25	3.61 ± 0.13	3.30 ± 0.05	3.62 ± 0.27
Day 29	3.67 ± 0.27	3.55 ± 0.10	3.64 ± 0.11	3.44 ± 0.08
Day 44	3.24 ± 0.01	3.70 ± 0.27	3.48 ± 0.44	3.50 ± 0.20
Day 61	3.81 ± 0.26	3.91 ± 0.08	4.01 ± 0.10	3.95 ± 0.05
Day 90	3.88 ± 0.26	3.74 ± 0.08	3.83 ± 0.44	4.18 ± 0.11
Day 120	3.71 ± 0.37	3.62 ± 0.36	3.50 ± 0.56	3.89 ± 0.60
Day 180	3.50 ± 0.12	4.06 ± 0.19	4.40 ± 0.55	4.52 ± 0.07

a bracketed naltrexone HCl concentration range of 0.5 mg/mL to 5.0 mg/mL, allowing compounding pharmacists more flexibility in customizing their formulations.

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FIGURE 1.

OVERLAY OF CHROMATOGRAPHIC RUNS OF NALTREXONE HYDROCHLORIDE.

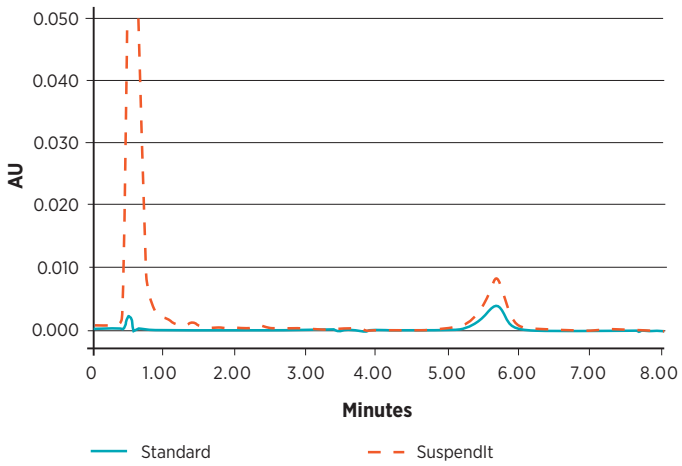

FIGURE 2.

CALIBRATION CURVE FOR HIGH-PERFORMANCE LIQUID CHROMATOGRAPHY ANALYSIS OF NALTREXONE HYDROCHLORIDE (5 µG/ML TO 100 µG/ML RANGE).

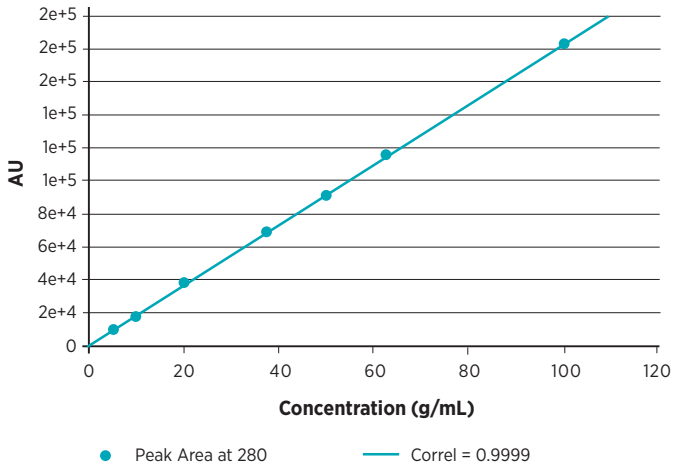

FIGURE 3.

CHROMATOGRAPHIC RUNS OF NALTREXONE HYDROCHLORIDE.

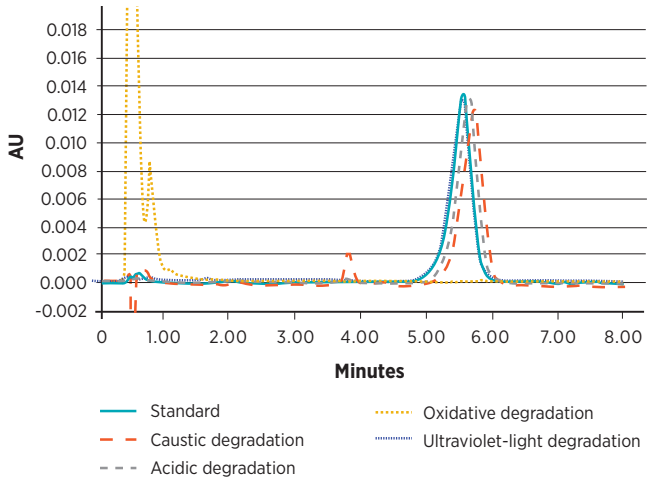

FIGURE 4.

CHROMATOGRAPHIC RUNS OF NALTREXONE HYDROCHLORIDE IN SUSPENDIT.

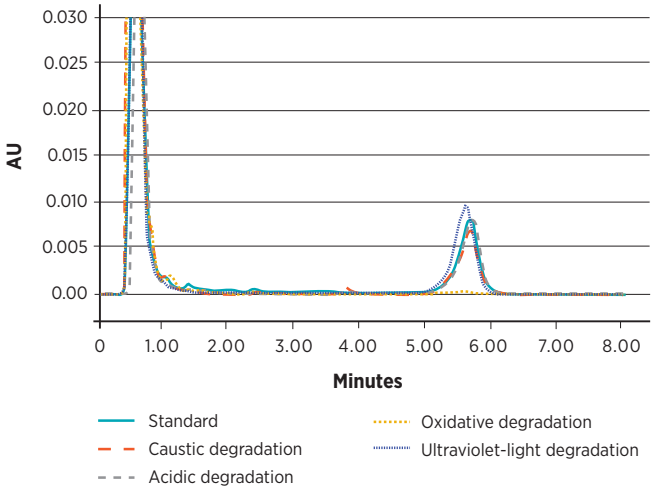

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TABLE 4.

NALTREXONE HYDROCHLORIDE CONCENTRATION (MG/ML) IN SUSPENDIT.

TIME	0.5 MG/ML		5.0 MG/ML	
	5°C	25°C	5°C	25°C
Day 0	0.501 ± 0.002	0.501 ± 0.002	4.93 ± 0.05	4.93 ± 0.05
Day 7	0.507 ± 0.005	0.499 ± 0.002	5.01 ± 0.09	4.93 ± 0.05
Day 14	0.510 ± 0.010	0.503 ± 0.008	4.93 ± 0.05	4.96 ± 0.06
Day 29	0.503 ± 0.003	0.495 ± 0.012	5.03 ± 0.01	4.97 ± 0.05
Day 44	0.510 ± 0.006	0.505 ± 0.011	5.15 ± 0.06	5.13 ± 0.08
Day 61	0.479 ± 0.008	0.482 ± 0.002	4.85 ± 0.07	4.88 ± 0.02
Day 90	0.497 ± 0.010	0.488 ± 0.004	5.01 ± 0.07	4.87 ± 0.02
Day 120	0.499 ± 0.001	0.482 ± 0.010	4.88 ± 0.04	4.99 ± 0.10
Day 180	0.474 ± 0.010	0.484 ± 0.024	4.71 ± 0.04	4.91 ± 0.17

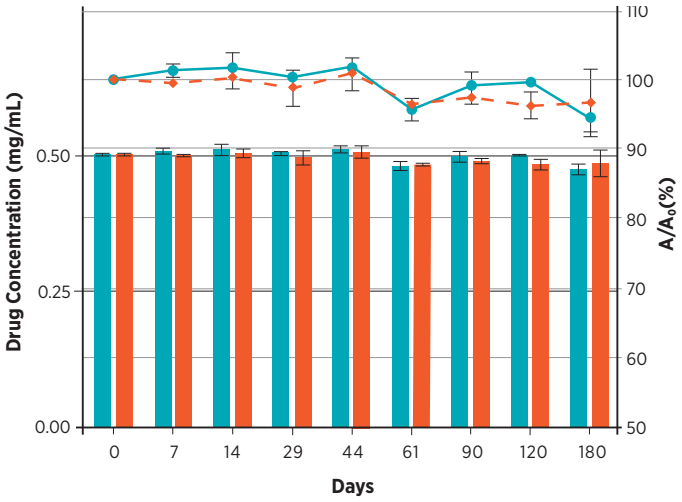
TABLE 5.

PERCENT OF NALTREXONE HYDROCHLORIDE IN SUSPENDIT RELATIVE TO DAY ZERO SAMPLE.

TIME	0.5 MG/ML		5.0 MG/ML	
	5°C	25°C	5°C	25°C
Day 0	100.0 ± 0.64	100.0 ± 0.64	100.0 ± 1.48	100.0 ± 1.48
Day 7	101.2 ± 1.14	99.6 ± 0.60	101.6 ± 2.07	100.0 ± 1.41
Day 14	101.8 ± 2.14	100.4 ± 1.63	100.0 ± 1.48	100.6 ± 1.58
Day 29	100.4 ± 0.77	98.8 ± 2.51	102.1 ± 1.09	100.8 ± 1.47
Day 44	101.8 ± 1.36	100.8 ± 2.34	104.5 ± 1.64	104.1 ± 1.93
Day 61	95.6 ± 1.59	96.2 ± 0.59	98.4 ± 1.68	98.9 ± 1.15
Day 90	99.2 ± 2.01	97.4 ± 0.90	101.6 ± 1.76	98.8 ± 1.15
Day 120	99.6 ± 0.46	96.2 ± 1.97	99.1 ± 1.37	101.2 ± 2.33
Day 180	94.6 ± 2.02	96.6 ± 4.91	95.5 ± 1.35	99.6 ± 3.63

FIGURE 5.

CHANGE IN DRUG CONCENTRATION OVER 180 DAYS.

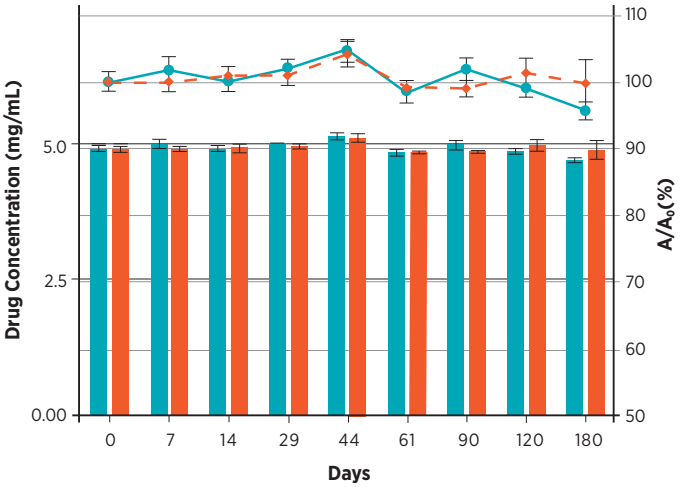


On left axis for the 0.5 mg/mL samples of naltrexone hydrochloride in SuspendIt stored at 5°C

Stored at 25°C, Relative change in percent on right axis as compared to initial concentration [At/Ao = drug content at time t (At) over initial drug content (Ao) ×100].

FIGURE 6.

CHANGE IN DRUG CONCENTRATION OVER 180 DAYS.



On left axis for the 5.0-mg/mL samples of naltrexone hydrochloride in SuspendIt stored at 5°C

Stored at 25°C, Relative change in percent on right axis as compared to initial concentration [At/Ao = drug content at time t (At) over initial drug content (Ao) ×100].

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