Stability *of* Gabapentin *in* SyrSpend SF

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ABSTRACT

Gabapentin is used with other medications to control and prevent seizures. It is also used to treat neuropathic pain following surgery due to shingles. Gabapentin comes in many different forms, including capsules, tablets, and oral solutions. Some patients, however, cannot use oral solutions containing alcohol or sorbitol. The objective of this study was to determine the stability of gabapentin in SyrSpend SF, a suspending agent that does not contain either sorbitol or alcohol. The studied samples were compounded into a 50-mg/mL suspension and stored in low actinic bottles at room temperature and refrigerated conditions. Samples were assayed at each time point out to 90 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 data collected, the beyond-use date of this product is at least 90 days when refrigerated or stored at room temperature and protected from light. Based on the final potency data at day 90, the beyond-use date may be longer, but 90 days was the limit of this study.

INTRODUCTION

Gabapentin is a GABA analogue anticonvulsant originally used to treat epilepsy, and is now also used to relieve neuropathic pain and hot flashes. Gabapentin is available as commercially-prepared capsules, tablets, and oral solutions. Gabapentin acts in epileptic patients with specific seizure disorders to decrease abnormal excitement in the brain. Gabapentin is also used as an adjunctive analgesic in herpetic neuralgia (PHN) and diabetic neuropathy. The extended-release form is used to treat restless legs syndrome (RLS).[1]

Gabapentin is a white to off-white crystalline solid. It is freely soluble in water and in both basic and acidic aqueous solutions. SyrSpend SF ([Fagron US-formerly Gallipot], St. Paul, Minnesota) is a sugar- and sorbitol-free suspending agent which could serve as an alternative for formulating gabapentin oral suspensions extemporaneously.

The objective of this study was to examine the stability of gabapentin prepared in an oral suspension using SyrSpend SF. Two suspensions were compounded with gabapentin raw powder in the SyrSpend SF suspension to a final concentration of approximately 50 mg/mL. The compounded suspensions were stored in low actinic prescription bottles under two different storage conditions: *United States Pharmacopeia (USP)* refrigerated (2°C to 8°C) storage, and *USP* room temperature (18°C to 26°C) storage. Stability was assessed by percent recovery studies performed at varying time points over 90 days.

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MATERIALS AND METHODS

Chemical Reagents

Gabapentin USP raw powder was purchased from Medisca (Lot 77375/E; Plattsburg, New York). High-performance liquid chromatographic (HPLC)-grade acetonitrile (Lot DE551; Burdick & Jackson, Kalamazoo, Michigan), and HPLC-grade methanol (Lot K22E17; J.T. Baker, Center Valley, Pennsylvania) were used in this study. HPLC-grade water was obtained by filtering deionized water from a Millipore Elix through a Millipore Simplicity (Billerica, Massachusetts).

Equipment and Chromatographic Conditions

Two different types of HPLC's 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-vial programmable autosampler with a peltier tray, 200-mcL sample loop, and a 250-mL 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 (PDA), and an 84-vial programmable autosampler with a 100-mcL sample loop and a 250-mcL syringe. The Perkin Elmer HPLC was operated and data was collected using Perkin Elmer Totalchrom chromatography software, while the Varian HPLC used Galaxie chromatography software. The mobile phase for the HPLC method was HPLC-grade water, methanol, and acetonitrile (950 mL: 30 mL: 20 mL). The mobile phase was delivered at 1.5 mL/min. Chromatographic separation was achieved using a 150 × 4.6 mm Phenomenex (Torrence, California) Gemini C18 column with 5-mcm particle packing. The mobile phase was used as solvent in diluting the standard and assay preparations to 250 mcg/mL. The assay was monitored at 210 nm following a 100-mcL injection.

Validation of Forced-Degradation Studies to Determine Stability Indicating Characteristics of the High-performance Liquid Chromatographic Method

Gabapentin samples were stressed and assayed to determine the specificity of the HPLC method to any possible degradation product produced during storage of an oral suspension. Gabapentin was diluted to 250 mcg/mL in a solution of acid (0.1M HCl), base (0.1 M NaOH) and, 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 gabapentin to each individual degradation pathway. Any extraneous peaks found in the chromatogram were labeled and the resolution (*USP*) was determined between the degradant and the gabapentin. A resolution of 1.5 was considered full separation. Purity calculations were performed in Galaxie on the Gabapentin peak using the controlled unstressed standard as a reference.

Preparation of Gabapentin Suspension Samples

Gabapentin suspension was prepared by adding 5 grams of gabapentin powder into a 100-mL low actinic volumetric flask. Added to the flask while stirring with a stir bar was 100 mL of SyrSpend SF. This procedure was repeated to obtain two suspensions. One suspension was stored at *USP* controlled refrigerated temperature and the other at *USP* controlled room temperature for the duration of the stability study.

Stability Study

The gabapentin samples suspended in SyrSpend SF at a concentration of 50 mg/mL was submitted for stability. One sample was packaged in a low actinic flask and stored at *USP* controlled refrigerated temperature (2°C to 8°C) using a laboratory refrigerator with digitally-controlled temperature from Forma Scientific (Edison, New Jersey). The other sample was packaged in low actinic flasks and stored at *USP* controlled room temperature condition (18°C to 26°C). Time points for the study were initial (T=0), 7 days (T=7), 14 days (T=14), 31 days (T=31), 46 days (T=46), 61 days (T=61), and 90 days (T=90). The evaluation parameter was percent recovery assay. The stability of gabapentin in suspension was defined by the percent recovery with respect to T=0 using the validated HPLC method. The sample stock was prepared by adding 1 mL of suspension with a volumetric pipette to 250 mL with water. The average and standard deviation of all replicate injections at each time point was used to calculate the percent recovery.

RESULTS

The stability of gabapentin room temperature in SyrSpend SF is shown in Table 1. The stability of gabapentin refrigerated in SyrSpend SF is shown in Table 2. The result of 48.555 mg/mL for the refrigerated and 49.100 mg/mL for the room temperature was set as the initial concentration for the study, and all subsequent time points were compared to this value. Figures 1 and 2 show the data in terms of concentration of the suspension remained within the specification (90%<[gabapentin]<110%) throughout the duration of the study.

DISCUSSION

The HPLC method was shown to be stability indicating by forcibly degrading gabapentin and separating the degradant peaks from that of the main analyte. Gabapentin was stable to acid, base, light, and heat. Slight degradation was seen with oxidation. Additionally, validation parameters listed in Table 3 show that all system suitability results met acceptance criteria.

Gallipot SyrSpend Gabapentin Suspension

The initial potencies of the gabapentin suspensions were 49.1 mg/mL and 48.555 mg/mL for the preparations stored at room temperature and in a refrigerator, respectively, as shown in Figures 1 and 2. These concentrations were 98.2% (room temperature) and 97.11% (refrigerated) of the 50-mg/mL target concentration. The T=0 result was set as the baseline for all

TABLE 1. Stability of Gabapentin in SyrSpend SF at Room Temperature (18°C to 26°C) for 90 Days.

ELAPSED TIME	% RECOVERY
T=0	100 +/- 1.253
T=14	104.96 +/- 0.845
T=31	107.15 +/- 0.3304
T=46	103.65 +/- 1.429
T=67	109.45 +/- 1.16
T=98	104.32 +/- 0.891

TABLE 2. Stability of Gabapentin in SyrSpend SF Refrigerated (2°C to 8°C) for 90 Days.

ELAPSED TIME	% RECOVERY
T=0	100 +/- 1.633
T=14	101.49 +/- 1.501
T=31	105.46 +/- 0.4137
T=46	101.84 +/- 1.516
T=61	108.27 +/- 1.479
T=125	104.63 +/- 0.56

TABLE 3. Summary of the Validation Parameters for the High-performance Liquid Chromatographic Method Used in the Stability Study of Gabapentin in SyrSpend SF.

VALIDATION PARAMETER	RESULTS	
Peak Tailing	1.059	%RSD = 0.22
Theoretical Plates	6558.528	
Linear range (210 nm)	2 to 600 mcg/mL	R2 = 1.00
Extraction Precision *n*=6	%RSD = 1.25	
Accuracy (20, 100, 300 mcg/mL)	%Target = 100.62%, 100.26%, 100.08%	
Specificity (resolution from main degradant peak)	Res (*USP*) = 4.36	

other time points. The assay results varied between 48.56 mg/mL (T=0) and 52.57 mg/mL (T=61) for the refrigerated, and between 49.1 mg/mL (T=0) and 53.74 mg/mL (T=67) for the preparation stored at room temperature. All sample preparations at each time point were within specifications and all %RSDs were below 2.0%. Each replicate for every time point was clear of any degradant peaks and had the same chromatographic profile.

CONCLUSION

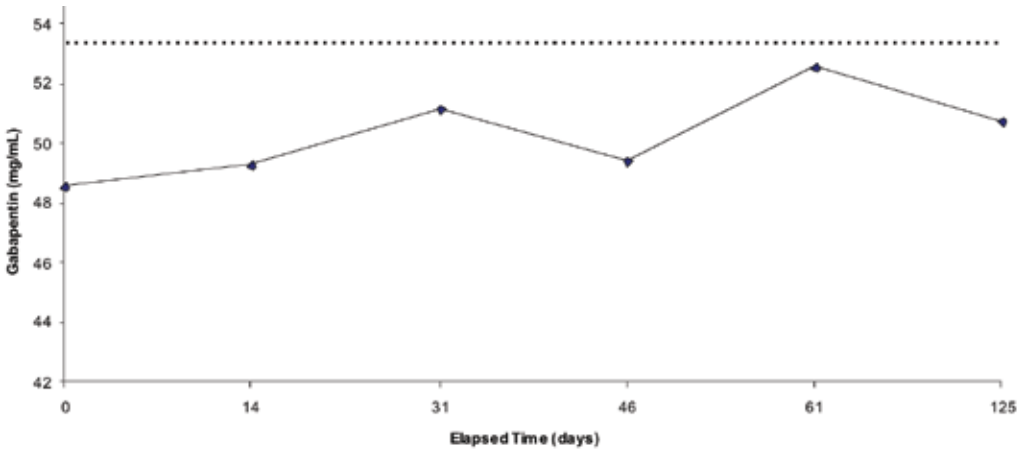
Gabapentin was stable in SyrSpend for 98 days when stored under room temperature (18°C to 26°C) conditions. Gabapentin was stable for 125 days when stored under refrigerated (2°C to 8°C) conditions. Concentrations of both storage conditions trended upward during the course of the study. This trend was used to determine the beyond-use date as 120 days for refrigerated and 90 days for room temperature storage.

The findings of this study show that SyrSpend is an acceptable suspending vehicle for preparing individually-compounded gabapentin formulations. This formulation is acceptable as an alcohol- and sorbitol-free suspension. The formulations would be a viable alternative to commercially available capsules when that dose form is inappropriate.

REFERENCES

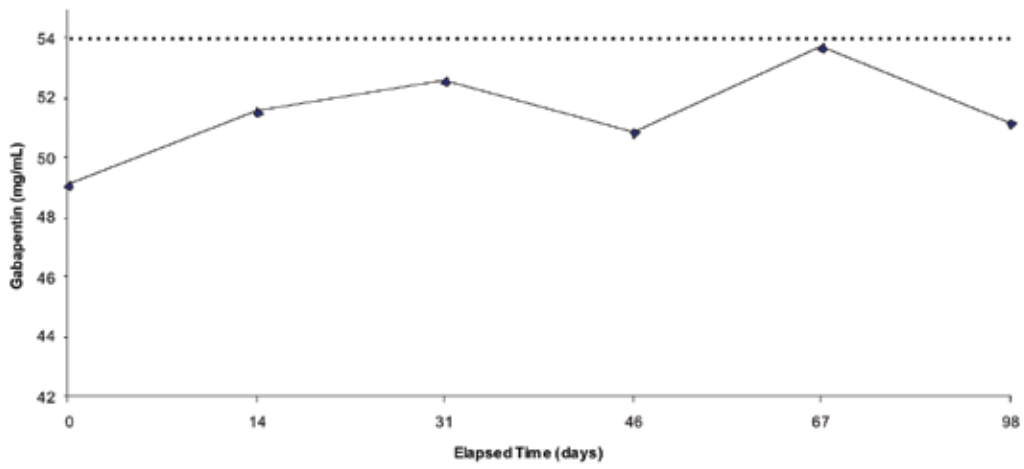
1. U.S. National Library of Medicine. *Gabapentin.* [U.S. National Library of Medicine Website.] July 15, 2011. Available at: www.ncbi.nlm.nih.gov/pubmedhealth/PMH0000940. Accessed March 6, 2012.

FIGURE 1. Plot of refrigerated gabapentin concentration in SyrSpend SF.



(Dashed lines represent upper and lower limits of gabapentin specification.)

FIGURE 2. Plot of room temperature gabapentin concentration in SyrSpend SF.



(Dashed lines represent upper and lower limits of gabapentin specification.)

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