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Stability of levetiracetam oral solution repackaged in oral plastic syringes

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Stability of levetiracetam oral solution repackaged in oral plastic syringes

Abstract

Purpose The long-term stability of levetiracetam solution in oral syringes was investigated in order to define a suitable beyond-use date and demonstrate the feasibility of storing prepared syringes for extended periods as an alternative to commercial levetiracetam unit dose cups.

Methods Levetiracetam oral solution (100 mg/mL) was drawn into 1- and 10-mL amber polypropylene oral syringes. Triplicate samples of the syringe preparations were stored at refrigeration (2–8 °C) or room temperature (20–25 °C) and evaluated at monthly intervals for up to six months. At each time point, the samples were visually inspected and levetiracetam stability was assessed via pH measurement and high-performance liquid chromatography (HPLC). A short-term forced degradation study was conducted to confirm that the HPLC assay method was stability indicating.

Results Over the six-month storage period, there was no significant change in either the visual appearance or pH of any of the levetiracetam samples. The results of serial HPLC assessment indicated that at least 97% of the initial levetiracetam concentration was retained in all samples of 1- and 10-mL oral syringes at both refrigeration and room temperature. Although this study was conducted using a generic product, the stability data obtained may be applied in repackaging decisions regarding other generic formulations of levetiracetam with similar excipient compositions.

Conclusion Commercial levetiracetam 100-mg/mL oral solution was stable for up to six months in amber polypropylene oral syringes stored at both refrigeration and room temperature conditions.

Disciplines

Pharmacy and Pharmaceutical Sciences

Comments

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TITLE

Stability of Levetiracetam Oral Solution Repackaged in Oral Plastic Syringes

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ABSTRACT

Purpose. With the increased use of levetiracetam oral solution in hospitals, there is a need to repackage this solution product in oral plastic syringes to facilitate dispensing and dosing. This study was designed to evaluate the long-term stability of levetiracetam solution in oral syringes with an intention to set a suitable beyond-use date.

Methods. Commercially available levetiracetam oral solution (100 mg/mL) was drawn into 1-mL and 10-mL amber polypropylene oral syringes. The samples were stored at refrigeration (2° – 8°C) or room temperature (20° – 25°C), and they were pulled for evaluation at monthly intervals for up to six months. At each time point, the samples were evaluated by visual inspection, pH measurement, and high performance liquid chromatography (HPLC). A separate forced stability study was conducted to confirm that the HPLC method was stability indicating.

Results. Over the period of six months storage, there was no significant change in visual appearance or pH for any of the levetiracetam stability samples. The HPLC results indicated that levetiracetam retained 97-108% of the initial concentration in 1-mL and 10-mL oral syringes at both refrigeration and room temperature.

Conclusion. Commercial levetiracetam 100 mg/mL oral solution was stable for up to six months in amber polypropylene oral syringes stored at both refrigeration and room temperature conditions.

INTRODUCTION

Levetiracetam is an anticonvulsant used as an adjunctive therapy in the treatment of partial-onset seizures, myoclonic seizures, primary generalized tonic-clonic seizures, and idiopathic generalized epilepsy in both adults and children.¹ An oral solution product of levetiracetam, 100 mg/mL, is available commercially for patients with difficulty swallowing tablets.¹ This solution product has become frequently prescribed in hospitals, which prompts the need to repackage the product into oral plastic syringes to facilitate dispensing and dosing. Unfortunately, there is no published data concerning the stability of the commercial levetiracetam oral solution in commonly used oral plastic syringes.

The purpose of this study is to evaluate the long-term stability of levetiracetam oral solution (100 mg/mL) in oral plastic syringes for up to six months. A commonly used oral amber polypropylene syringe with a matching tip was chosen as the packaging device for the study. The 1-mL and 10-mL syringe volumes were selected to bracket the typical dose range of levetiracetam oral solution.¹ Both refrigeration and room temperature storage conditions were included in this study to provide options and flexibility for the pharmacy.

It is worth mentioning that a few manufacturers market the levetiracetam solution in unit-dose cups. These unit-dose cups provide convenience in dispensing, but the dose volume is not as accurate as the oral syringes. It is common that a significant volume of solution is retained in the cup after oral administration. Accurate dose is always important, especially for the anticonvulsant in this case. In addition, the oral syringes can be used to deliver pediatric doses which are below the lowest volume of the unit-dose cups available. Finally, with the ever changing landscape on drug shortages, institutional pharmacies are frequently called on to create temporary supplies of repackaged medications. With the

accuracy and broad application of the oral syringes, they would provide a satisfactory substitution for the unit-dose cups in case of shortages.

METHODS

Stability Study

Commercially available levetiracetam 100 mg/mL oral solution^a was drawn into 1-mL and 10-mL amber polypropylene oral syringes^b. The syringes tips were capped immediately afterwards. The filled syringes were stored at refrigeration (2° – 8°C) and room temperature conditions (20° – 25°C). Triplicate samples were prepared for each syringe size, storage condition, and time points.

Stability evaluation was performed immediately after preparation and after 1, 2, 3, 4, 5, and 6 months of storage. At every time point, triplicate syringe samples each of 1-mL and 10-mL from both temperature conditions were pulled for evaluation. The entire content of each syringe sample was first expelled into a clear glass vial for visual inspection against a light background for clarity, color, precipitation, and microbial growth. The same sample was then subjected to pH measurement^c. Finally, a 200 µL aliquot from each sample was diluted with purified water in a 100-mL volumetric flask and analyzed by HPLC for chemical stability (three injections for each of the triplicate samples).

High-performance Liquid Chromatography (HPLC)

The HPLC analysis was performed using a Shimadzu model LC-2010A instrument^d. The chromatographic parameters were adapted from a stability indicating assay previously published by Saravanan *et al.*² A YMC C18 column^e was used and maintained at 30°C. The mobile phase consisted of 0.1% aqueous H₃PO₄ and acetonitrile at 85:15 v/v (pH 2.10) with a flow rate of 1.0 mL/min. Each injection volume was 10 µL, and the UV detection was set at 205 nm. Under these conditions, the retention time of levetiracetam was approximately 5.4 minutes as shown in Figure 1a.

Standards of levetiracetam solutions at 0.05, 0.10, 0.15, 0.20, and 0.25 mg/mL were prepared for calibration purpose. This range encompassed the expected concentrations of the diluted stability samples. Because it was cost prohibitive to purchase the pure drug substance of levetiracetam, the standards were prepared by diluting the 100 mg/mL commercial oral solution^a with purified water. The same lot of the levetiracetam oral solution was used as the one for the stability samples. For the practical purpose of this stability study, it was assumed that the drug concentration of this lot of oral solution was at the label claim of 100 mg/mL at the initiation of the study. Aliquots of the standard solutions were frozen for subsequent analysis at each time point in the study. It was also verified that there were no interfering excipients for the HPLC analysis (Figure 1a). A calibration curve was constructed by linear regression of the peak area of levetiracetam against levetiracetam concentration. The curve was found to be linear over the concentration range of the standards with an $r^2 = 0.998$. The standards were injected three times at each stability time point to verify the precision of the method. The intra-day and inter-day coefficients of variation were within 1.11%.

Forced Degradation Study

A short-term forced degradation study of levetiracetam was conducted under extreme pH, light, and oxidative stress conditions. This study was intended to verify the ability of the HPLC assay to separate the potential degradation products from the parent drug. Levetiracetam solutions of 0.2 mg/mL concentration were prepared in 0.5 N HCl, 0.5 N NaOH, and 3% H₂O₂. These samples were incubated at 60°C for up to 72 hours. Three additional samples of 0.2 mg/mL levetiracetam solution in water were prepared and

exposed to 254 nm, 365 nm, and regular sun light for over 72 hours. The UV light at 254 nm and 365 nm was generated by a standard lab hand-held UV lamp^f.

Among these samples, significant degradation was observed in only the two samples of extreme pH conditions. As shown in Figure 1, the degradation products were well separated from the parent molecule by the HPLC method, and no interfering peaks were observed. Therefore, the HPLC method was considered as stability-indicating and suitable for the stability evaluation of levetiracetam oral solution in the repackaged syringes.

RESULTS AND DISCUSSION

USP General Chapter <1136>, previously <681>, provides the guidance on non-commercial repackaging of non-sterile liquid dosage forms into unit-dose containers.³ According to this guidance, the manufacturer's expiration date applies to the original container-closure system and is not intended to apply to the repackaged product. A suitable beyond-use-date (BUD) should be selected based on the nature of the drug, container, and storage condition in addition to the packaging and expiration information in the manufacturer's product labeling.³

Levetiracetam is a relatively simple molecule with only two main functional groups, a 5-membered lactam ring and a terminal amide.¹ Based on the physicochemical properties and the formulation ingredients described in the commercial product package insert,¹ repackaging levetiracetam oral solution in syringes is not expected to significantly alter the physical and chemical stability of the product over the desired 6-month BUD (not exceeding the original manufacturer's expiry date). The solution product also contains paraben preservatives¹ which should prevent microbial growth even after repackaging.

However, due to the high surface area to volume ratio of the syringe sample and the plastic nature of the oral syringes, there are several unique stability concerns. For example, there might be drug loss due to adsorption to the syringe and leachable from the syringe into the drug solution. In comparison to the original HDPE bottle, the thin plastic syringe barrel and weak closures may lead to significant water loss and/or increased exposure to oxygen over long-term storage. With these potential concerns, a stability study was deemed necessary to support the desired 6-month BUD of levetiracetam oral solution in oral syringes. Two syringe volumes, 1-mL and 10-mL, were included to bracket the

typical dose range. The 1-mL syringe represented the worst case scenario for the surface area to volume ratio.

At the initiation of the stability study, the levetiracetam 100 mg/mL oral solution appeared as a clear and colorless liquid. The initial sample pH and concentration values are reported in Tables 1 & 2. Over the six months of storage at refrigeration (2° – 8°C) or room temperature (20° – 25°C), all samples remained clear, colorless, and free of visible precipitation or microbial growth. No significant change in pH was observed for any samples (Table 1). The stability-indicating HPLC analysis also confirmed that all samples retained 97% – 108% of the initial concentration with no new peaks observed (Table 2). Overall, the levetiracetam 100 mg/mL oral solution was found to be stable in amber polypropylene oral syringes.

It is also important to note that the oral solution product was originally developed by UCB (Keppra®) and approved by FDA in 2003.⁴ Currently, the generic product is available via multiple sources,⁴ and most formulations contain similar excipients as the brand name product.⁵ Therefore, the stability data generated in this study should be applicable to other generic products with similar excipient compositions.

FOOTNOTES

- ^a Levetiracetam oral solution, 100 mg/mL. Morton Grove Pharmaceuticals, Inc., Morton Grove, IL, NDC 60432-831-16, lot# 31086A.
- ^b Exacta-Med[®] oral syringes with tips, Baxa Corporation, Englewood, CO.
- ^c SevenEasy pH meter, Mettler-Toledo Inc., Columbus, OH.
- ^d HPLC system, Model 2010A, Shimadzu Scientific Instruments, Marlborough, MA.
- ^e HPLC column, ODS AQ, 5 μ m, 250 x 4.6 mm, YMC America, Inc., Allentown, PA.
- ^f UV Lamp, Spectroline Model ENF-240C, Spectronics Corporation, Westbury, NY.

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Figure 1. HPLC chromatograms of (a) levetiracetam standard solution 0.2 mg/mL in water; (b) levetiracetam solution 0.2 mg/mL in 0.5 N HCl after 48 hours; (c) levetiracetam solution 0.2 mg/mL in 0.5 N NaOH after 24 hours.

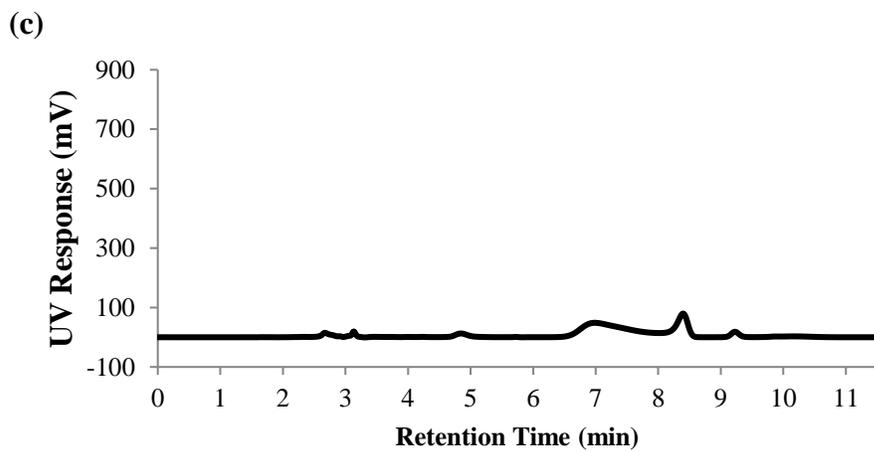
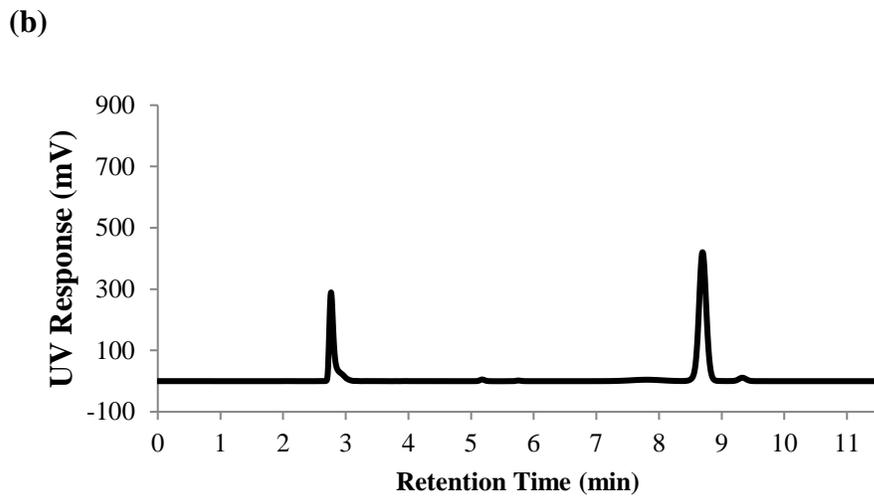
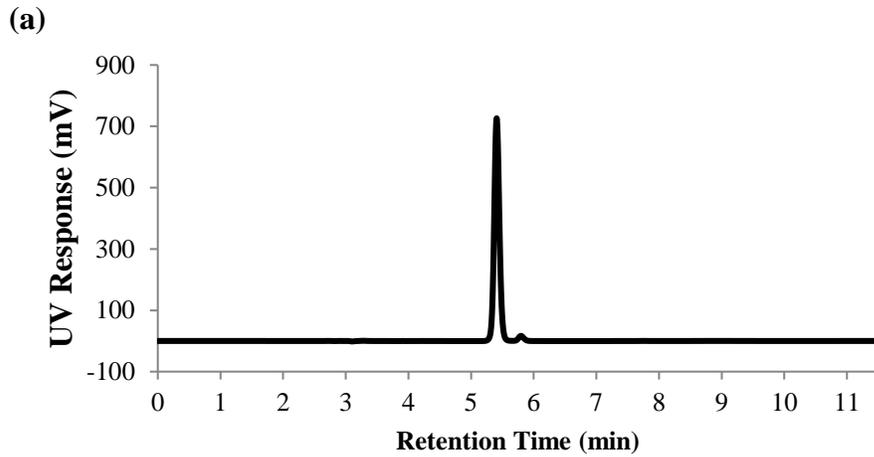


Table 1. pH Stability Results of Levetiracetam 100 mg/mL Oral Solution Repackaged in Plastic Syringes (n = 3)

Storage Temperature and Syringe Size	Initial pH	pH					
		1-month	2-month	3-month	4-month	5-month	6-month
2° – 8°C, 1 mL	5.50 ± 0.00	5.57 ± 0.03	5.61 ± 0.01	5.54 ± 0.01	5.47 ± 0.02	5.49 ± 0.01	5.53 ± 0.02
20° – 25°C, 1 mL		5.57 ± 0.01	5.64 ± 0.02	5.52 ± 0.00	5.46 ± 0.01	5.48 ± 0.00	5.55 ± 0.01
2° – 8°C, 10 mL	5.50 ± 0.00	5.57 ± 0.01	5.57 ± 0.02	5.51 ± 0.01	5.46 ± 0.01	5.51 ± 0.01	5.57 ± 0.01
20° – 25°C, 10 mL		5.55 ± 0.01	5.63 ± 0.02	5.53 ± 0.01	5.45 ± 0.01	5.47 ± 0.00	5.55 ± 0.01

Table 2. HPLC Stability Results of Levetiracetam 100 mg/mL Oral Solution Repackaged in Plastic Syringes (n = 3)

Storage Temperature and Syringe Size	Initial Drug Concentration (mg/mL)	% Remaining					
		1-month	2-month	3-month	4-month	5-month	6-month
2° – 8°C, 1 mL	97.8 ± 0.9	102.7 ± 0.2	102.9 ± 1.0	106.2 ± 2.2	102.8 ± 0.1	103.4 ± 0.5	105.2 ± 0.8
20° – 25°C, 1 mL		103.2 ± 0.4	105.1 ± 0.3	107.8 ± 0.5	105.9 ± 0.7	105.3 ± 0.2	104.3 ± 0.6
2° – 8°C, 10 mL	101.1 ± 1.4	99.1 ± 0.4	101.0 ± 2.9	104.2 ± 1.0	100.6 ± 1.0	101.7 ± 1.5	98.6 ± 1.3
20° – 25°C, 10 mL		99.1 ± 0.9	100.8 ± 0.9	103.0 ± 1.2	102.2 ± 1.1	102.3 ± 1.4	101.0 ± 1.3