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Stability of Extemporaneously Prepared Rufinamide Oral Suspensions

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Abstract

Background:

Rufinamide is an oral antiepileptic drug indicated for adjunctive therapy in treating generalized seizures associated with Lennox-Gastaut syndrome. Currently, rufinanide is available as 200-mg and 400-mg tablets. A liquid dosage form does not exist at the present time. Lack of a suspension formulation may present an administration problem for many children and adults who are unable to swallow tablets. The availability of a liquid dosage form will provide an easy and accurate way to measure and administer the medication.

Objective:

To determine the stability of both sugar-containing and sugar-free rufinamide suspensions over a 90-day period.

Methods:

A suspension of rufinamide 40 mg/mL was prepared by grinding twelve 400-mg tablets of rufinamide tablets in a glass mortar. Sixty milliliters of Ora-Plus and 60 mL of either Ora-Sweet or Ora-Sweet SF (sugar free) were mixed and added to the powder to make a final volume of 120 mL. Three identical samples of each formulation were prepared and placed in 60-mL amber plastic bottles and were stored at room temperature. A 1-mL sample was withdrawn from each of the 6 bottles with a micropipette immediately after preparation and at 7, 14, 28, 56, and 90 days. After further dilution to an expected concentration of 0.4 mg/mL, the samples were assayed using high-performance liquid chromatography. Stability was defined as the retention of at least 90% of the initial concentration.

Results:

At least 90% of the initial rufinamide concentration remained throughout the 90-day study period in both preparations. There were no detectable changes in color, odor, taste, and pH and no visible microbial growth.

Conclusions:

Extemporaneously compounded suspensions of rufinamide 40 mg/mL in a 1:1 mixture of Ora-Plus and Ora-Sweet or Ora-Sweet SF were stable for at least 90 days when stored in 59-mL amber polypropylene plastic bottles at room temperature.

Disciplines

Pharmacy and Pharmaceutical Sciences

Comments

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Stability of extemporaneously prepared rufinamide oral suspensions

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ABSTRACT

BACKGROUND: Rufinamide is an oral antiepileptic drug indicated for adjunctive therapy in treating generalized seizures associated with Lennox-Gastaut syndrome. Currently, rufinamide is available as 200-mg and 400-mg tablets. A liquid dosage form does not exist at the present time. Lack of a suspension formulation may present an administration problem to many children and adults who are unable to swallow tablets. The availability of a liquid dosage form will provide an easy and accurate way to measure and administer the medication.

OBJECTIVES: To determine the stability of both sugar-containing and sugar-free rufinamide suspensions over a 90-day period.

METHODS: A suspension of rufinamide 40 mg/mL was prepared by grinding twelve 400-mg tablets of rufinamide tablets in a glass mortar. Sixty milliliters of Ora-Plus and 60 mL of either Ora-Sweet or Ora-Sweet SF were mixed and added to the powder to make a final volume of 120 mL. Three identical samples of each formulation were prepared and placed in 2-oz amber plastic bottles and were stored at room temperature. A 1-mL sample was withdrawn from each of the six bottles with a micropipette immediately after preparation and at 7, 14, 28, 56 and 90 days. After further dilution to an expected concentration of 0.4 mg/mL, the samples were assayed using high-performance liquid chromatography. Stability was defined as the retention of at least 90% of the initial concentration.

RESULTS: At least 90% of the initial rufinamide concentration remained throughout the 90-day study period in both preparations. There were no detectable changes in color, odor, taste and pH and no visible microbial growth.

CONCLUSION: Extemporaneously compounded suspensions of rufinamide, 40 mg/mL, in a 1:1 mixture of Ora-Plus and Ora-Sweet or Ora-Sweet SF were stable for at least 90 days when stored in 2-oz amber polypropylene plastic bottles at room temperature.

INTRODUCTION

Lennox-Gastaut syndrome (LGS) is an age-specific disorder characterized by the classic triad of epileptic seizures (i.e. atonic, tonic and atypical absence), slow spike-waves in the waking electroencephalogram (EEG) and fast rhythmic bursts during sleep and moderate-to-severe cognitive dysfunction.[1,2] To date, the optimal therapy for LGS remains uncertain and often includes a combination of various antiepileptic drugs including valproic acid, lamotrigine, topiramate and felbamate.[1] Rufinamide is a new, oral antiepileptic medication indicated for adjunctive therapy in treating generalized seizures associated with LGS in children 4 years and older and adults. Currently, rufinamide is available in a tablet formulation of 200-mg and 400-mg.[3] A liquid dosage form does not exist at the present time. Lack of a suspension formulation may present an administration problem to many children and adults who are unable to swallow tablets. In addition, a weight-based dosage regimen is recommended by the manufacture upon initiation and titration in the pediatric population. The availability of a liquid dosage form will provide an easy and accurate way to measure and administer the medication to an individual patient.

The purpose of this study was to determine the short-term stability of an extemporaneously compounded oral liquid dosage form of rufinamide prepared from commercially available tablets.

METHODS

Suspension Preparation. Twelve 400-mg rufinamide tablets[a] were thoroughly triturated in a glass mortar. Sixty mL of Ora-Plus suspension vehicle[b] was added to the mortar and triturated with the drug powder until a homogeneous suspension was obtained. Sixty mL of Ora-Sweet[c] or Ora-Sweet SF[d] flavoring syrup was then added to the suspension and mixed thoroughly to obtain the final suspension (40mg/mL). A preliminary taste assessment of the two suspensions was performed by two volunteers. No unpleasant taste was reported, and therefore, no additional formulation adjustments were necessary. Details of the compounding procedure are provided in the appendix.

Stability Study. Each of the two suspensions prepared above was divided equally into three samples (~ 40 mL each) and transferred into 2-oz amber polypropylene plastic bottles closed with child resistant caps.[e] All samples were stored at room temperature (23-25°C) and assayed after 0, 7, 14, 28, 56 and 90 days of storage. At each time point, the samples were subjected to visual inspection and reversed phase high-performance liquid chromatography (RP-HPLC) analysis. In addition, pH measurement was performed[f] for all samples on day-0 and day-90. Microbiology testing was not included, because each commercial vehicle already contained effective preservatives. The RP-HPLC data was used to calculate the percentage of the initial drug concentration remaining at each time point. Stability was defined as the retention of at least 90% of the initial concentration.

RP-HPLC Method. Each bottle was shaken thoroughly by hand for approximately 15 seconds immediately before sampling. A 1-mL sample was withdrawn from each bottle and diluted to 100-mL in a volumetric flask with sample diluent consisting of

methanol and water (80:20 v/v). The expected rufinamide concentration after dilution was 0.4 mg/mL. The samples were stirred for one hour and sonicated for one hour. Due to the viscous nature of the suspension vehicle, it was necessary to disperse the suspension in diluent by stirring prior to sonication. Approximately 3 mL of each sample was withdrawn and filtered through a 0.45 µm syringe filter[g] to remove insoluble excipients. The filtered samples were assayed by RP-HPLC.

RP-HPLC analysis was conducted using a Shimadzu model LC-2010A instrument[h] equipped with a C18 column[i] maintained at 40°C and UV detector set at 230 nm. The mobile phase consisted of methanol and water (35:65 v/v) with 1 mL/L trifluoroacetic acid delivered at a flow rate of 0.5 mL/min. It was filtered and degassed on-line before use. For analysis, 10 µL of each sample was injected by the autosampler. The data was collected and processed by the Shimadzu LCSolution software. The retention time of rufinamide was 10.9 minute.

Standards of rufinamide at 0.2, 0.3, 0.4, 0.5, and 0.6 mg/mL were prepared in the same sample diluent (methanol:water 80:20 v/v) for the RP-HPLC method calibration. Because the pure drug substance of rufinamide was not available commercially, the standards were prepared by using the crushed tablet powder from the commercial tablet dosage form.[a] The average weight of the 400-mg strength rufinamide tablets was determined to be 740 mg, and calculations were performed to ensure the proper amount of crushed tablet powder was used to prepare each standard. Once the diluent was added to the crushed tablet powder, the samples were sonicated for 15 minutes followed by 2 hours of stirring to ensure full extraction of the drug substance into the diluent. The samples were filtered through 0.45 µm Nylon syringe filters[g] to remove the insoluble

tablet excipients prior to the RP-HPLC analysis. A calibration curve was produced by linear regression of the peak area of rufinamide against rufinamide concentration. The standard curve was linear ($r^2 = 0.998$) over the working range of concentrations. The between-day and within-day coefficients of variation for the RP-HPLC assay were 0.82% and 0.67%, respectively.

A forced degradation study of rufinamide was conducted under extreme pH and oxidative stress conditions in order to verify the stability indicating ability of the RP-HPLC assay. Four 0.04 mg/mL rufinamide solutions were first prepared by diluting a 0.4 mg/mL rufinamide standard solution (see paragraph above) with sample diluent (methanol: water 80:20 v/v). Sample #1 was adjusted to pH 2 using 1 N hydrochloric acid. Sample #2 was adjusted to pH 12 with 1 N sodium hydroxide. Sample #3 and Sample #4 were each spiked with 3% hydrogen peroxide (final concentration). Samples #1 – 3 were incubated at 60°C for 24 hours. Sample #4 was exposed to direct sunlight for 30 days. RP-HPLC analysis was conducted at the end of each sample treatment. Approximately 4%, 19%, 34%, 95% degradation of rufinamide was observed in Samples# 1, 2, 3, and 4, respectively. No interfering peaks from the degradation products were observed. In Sample #2, an unidentified degradation product peak was noted at 1.3 relative retention time to rufinamide. No major degradation product peaks were observed for Samples #3 & #4 despite the significant amount of loss of parent drug. It was speculated that (a) the oxidation products were polar and co-eluted with the solvent front; (b) the oxidation products did not absorb UV light at 230 nm.

RESULTS AND DISCUSSION

Rufinamide is commercially available as tablet dosage forms in two strengths, 200-mg and 400-mg.[3] Based on composition listed in the labeling,[3] the rufinamide tablets are formulated as conventional immediate release oral tablets containing common excipients and non-functional film coating. Therefore, compounding these tablets into powder or suspension dosage forms is not expected to alter the drug bioavailability or therapeutic effectiveness significantly.

The 40 mg/mL rufinamide suspensions were prepared in this study using 1:1 mixtures of commercially available vehicles, i.e. Ora-Plus with either Ora-Sweet or Ora-Sweet SF (sugar free). The Ora-Plus was intended as the main suspending vehicle; the Ora-Sweet and Ora-Sweet SF syrups provided flavoring and sweetness for taste masking. All vehicles contained effective preservatives to prevent microbial growth.

The RP-HPLC data of the compounded suspensions were summarized in Table 1. Both suspensions remained stable (at least 90% of initial concentration) throughout the 90-day study period. In addition, there was no appreciable change in the pH from the initial mean $\pm$ S.D. in any of the samples made with Ora-Sweet (pH 4.43 $\pm$ 0.08) or in those prepared with Ora-Sweet SF (pH 4.32 $\pm$ 0.07) throughout the study period. There was no visible microbial growth in any samples.

The palatability of the compounded suspensions was also assessed and confirmed to be satisfactory. No additional taste masking agents are necessary.

It is noteworthy that the two strengths of rufinamide tablets share the same excipient composition.[3] The excipients:drug ratio was also identical in the two strengths of tablets based on the average tablet weight determined in this study (370 mg for the 200-mg

strength tablets[j] and 740 mg for the 400-mg strength tablets[a]). Therefore, the 200-mg strength tablets can also be used to compound the same suspensions described in this study following the procedures in the appendix.

CONCLUSION

Extemporaneously compounded suspensions of rufinamide, 40 mg/mL, in a 1:1 mixture of Ora-Plus and Ora-Sweet or Ora-Sweet SF were stable for at least 90 days when stored in 2-oz amber plastic bottles at room temperature.

FOOTNOTES

[a] Rufinamide (Banzel®) 400-mg tablets. Eisai Co., Ltd.; Woodcliff Lake, NJ, lot 004157.

[b] Ora-Plus suspending vehicle. Paddock Laboratories, Minneapolis, MN, lot 8384265.

[c] Ora-Sweet flavored syrup vehicle. Paddock Laboratories, lot 8384261.

[d] Ora-Sweet SF flavored sugar free vehicle. Paddock Laboratories, lot 8374196.

[e] Two-oz amber prescription bottles with child-resistant caps. Apothecary Products, Burnsville, MN.

[f] SevenEasy pH meter. Mettler-Toledo Inc., Columbus, OH.

[g] Syringe filter, Nylon, 0.45 µm, 13-mm. Fisher Scientific, Suwanee, GA.

[h] HPLC 2010A with LCSolutions. Shimadzu Scientific Instruments, Marlborough, MA.

[i] Symmetry C18 column (3.5-µm particle size, 4.6 mm x 150 mm). Waters Corp., Milford, MA.

[j] Rufinamide (Banzel®) 200-mg tablets. Eisai Co., Ltd.; Woodcliff Lake, NJ, lot 004156.

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Appendix – Procedure for compounding rufinamide suspension, 40 mg/mL (120 mL batch):

1. Count out twelve 400-mg rufinamide[a] tablets (or twenty-four 200-mg rufinamide tablets).
2. Crush the tablets from Step 1 in a glass mortar and triturate to a fine powder.
3. Add 60 mL of Ora-Plus[b] to the rufinamide powder from Step 2 via geometric dilution until a smooth suspension is obtained.
4. Add 60 mL of Ora-Sweet[c] or Ora-Sweet SF[d] to the suspension from Step 3 and mix well.
5. Transfer the mixture into a proper amber plastic prescription bottle.
6. Label the bottle "Shake Well Before Use" with an expiration date of 90 days after preparation.

Table 1.

Stability of Rufinamide 40 mg/mL in Two Vehicles at Room Temperature

Suspension[a]	Actual Initial Drug Concentration[a] (mg/mL)	% Initial Concentration Remaining[a]				
		Day 7	Day 14	Day 28	Day 56	Day 90
Rufinamide, Ora-Plus, Ora-Sweet	41 ± 1.7	103 ± 1.4	99 ± 0.0	97 ± 1.4	100 ± 1.4	92 ± 1.4
Rufinamide, Ora-Plus, Ora-Sweet	41 ± 0.0	104 ± 6.5	100 ± 1.4	100 ± 2.9	100 ± 3.8	101 ± 0.0

[a] = Mean ± S.D. for three samples (n=3).