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Abstract

Eslicarbazepine acetate is an anticonvulsant drug with a recent U.S. Food and Drug Administration approval for expanded use in children and adolescents. Currently, eslicarbazepine acetate is only available in the U.S. as 200-mg to 800-mg strength tablets (Aptiom), which are not easy to administer for pediatric patients. This study was initiated to develop an oral suspension formulation for extemporaneous compounding by pharmacists and to generate stability data for storage recommendations. Nine suspension formulations of eslicarbazepine acetate were prepared from Aptiom tablets and commercially available liquid vehicles using the standard mortar/pestle method. The vehicles varied mainly in their solvents, viscosities, and sweeteners. The formulations were evaluated for ease of preparation, physical properties, and initial potency. Two lead formulations were selected for a two-month stability study at room temperature or under refrigeration (2°C to 8°C). The stability samples were withdrawn at pre-determined time points and analyzed by visual inspection, pH measurement, and a stability-indicating high-performance liquid chromatographic assay. The majority of the 9 formulations were found to be easy to prepare and administer at a concentration of 40-mg/mL eslicarbazepine acetate. Particle settling was observed in several formulations over time, but they were re-suspended satisfactorily upon shaking. Two suspensions in 50:50 v/v mixtures of Ora-Sweet or Ora-Sweet SF with Ora-Plus were selected as the lead formulations for the two-month stability study. At the initiation of the study, all samples appeared as white and smooth suspensions with pH ranging from 4.39 to 4.46. The high-performance liquid chromatographic results confirmed that the initial samples contained 100.4% to 102.2% of the label claim strength. Over two months of storage at room temperature or refrigeration, there were no significant changes in visual appearance, re-suspendability, pH, or potency for any samples. No new degradation peaks were observed in any highperformance liquid chromatograms. Based on the study results, two eslicarbazepine acetate suspensions are recommended for extemporaneous compounding from Aptiom tablets. The formulations consist of 40 mg/mL eslicarbazepine acetate in 50:50 v/v Ora-Sweet:Ora-Plus or Ora-Sweet SF:Ora-Plus. Once prepared, these suspensions can be stored at room temperature or under refrigeration for up to two months.

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Formulation and Stability Study of Eslicarbazepine Acetate Oral Suspensions for Extemporaneous Compounding



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INTRODUCTION

Eslicarbazepine acetate (ESL) is an anti-convulsant drug indicated for the treatment of partial-onset seizures.¹ Recently, ESL has received U.S. Food and Drug Administration (FDA) approval for expanded use in children and adolescents 4 to 17 years of age.²

Currently, ESL is only available as 200-mg to 800-mg strength tablets in the U.S. under the brand name of Aptiom. With the presence of excipients, the total weight of each Aptiom tablet ranges from 235 mg to 933 mg (Unofficial laboratory data generated by the investigators using one lot of Aptiom tablets for each strength [$n=10$]). Swallowing these large size tablets presents significant challenges to many pediatric patients, and elderly patients with dysphagia.^{3,4} An alternative solution to overcome this barrier is to prepare liquid suspensions from the tablet dosage forms. The bioequivalence has been established for ESL between the tablet and suspension dosage forms at the 800-mg dose level in healthy volunteers.⁵ Another recent publication also confirmed that the oral bioavailability of ESL was similar between the crushed tablets (taken with applesauce) and intact tablets.⁶

ABSTRACT

Eslicarbazepine acetate is an anticonvulsant drug with a recent U.S. Food and Drug Administration approval for expanded use in children and adolescents. Currently, eslicarbazepine acetate is only available in the U.S. as 200-mg to 800-mg strength tablets (Aptiom), which are not easy to administer for pediatric patients. This study was initiated to develop an oral suspension formulation for extemporaneous compounding by pharmacists and to generate stability data for storage recommendations. Nine suspension formulations of eslicarbazepine acetate were prepared from Aptiom tablets and commercially available liquid vehicles using the standard mortar/pestle method. The vehicles varied mainly in their solvents, viscosities, and sweeteners. The formulations were evaluated for ease of preparation, physical properties, and initial potency. Two lead formulations were selected for a two-month stability study at room temperature or under refrigeration (2°C to 8°C). The stability samples were withdrawn at pre-determined time points and analyzed by visual inspection, pH measurement, and a stability-indicating high-performance liquid chromatographic assay. The majority of the 9 formulations were found to be easy to prepare and administer at a concentration of 40-mg/mL eslicarbazepine acetate. Particle settling was observed in several formulations over time, but they were re-suspended satisfactorily upon shaking. Two suspensions in 50:50 v/v mixtures of Ora-Sweet or Ora-Sweet SF with Ora-Plus were selected as the lead formulations for the two-month stability study. At the initiation of the study, all samples appeared as white and smooth suspensions with pH ranging from 4.39 to 4.46. The high-performance liquid chromatographic results confirmed that the initial samples contained 100.4% to 102.2% of the label claim strength. Over two months of storage at room temperature or refrigeration, there were no significant changes in visual appearance, re-suspendability, pH, or potency for any samples. No new degradation peaks were observed in any high-performance liquid chromatograms. Based on the study results, two eslicarbazepine acetate suspensions are recommended for extemporaneous compounding from Aptiom tablets. The formulations consist of 40 mg/mL eslicarbazepine acetate in 50:50 v/v Ora-Sweet:Ora-Plus or Ora-Sweet SF:Ora-Plus. Once prepared, these suspensions can be stored at room temperature or under refrigeration for up to two months.

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All retail and hospital pharmacists are trained in extemporaneous compounding and can prepare suspensions from immediate-release tablets, such as Aptiom tablets. A variety of oral suspension vehicles are available commercially to facilitate the preparation of oral suspensions, and they

include both sugar-based (SB) and sugar-free (SF) grades. Due to the relatively high dose of ESL, formulation screening should be carried out to optimize the palatability and physical properties of the suspension formulations. The first objective of this study was to identify two oral suspension

formulations (SB and SF) which are easy to prepare by pharmacists, easy to dose, palatable, and exhibit satisfactory physical properties.

For nonsterile dosage forms prepared by extemporaneous compounding, the storage conditions and beyond-use dates (BUD) are specified in the *United States Pharmacopeia*.⁷ Without any stability data, compounded suspensions in aqueous vehicles have to be stored under refrigeration with a BUD of only 14 days. The ESL molecule has an ester functional group which is prone to hydrolysis catalyzed by extreme pH and heat. However, given the low-water solubility of this drug,¹ the rate of hydrolysis is expected to be slow for a suspension formulation, especially when buffered properly by the vehicle. The second objective of this study was to conduct a stability evaluation on the selected oral suspensions with a goal to extend the BUD for up to two months at both room temperature (RT) and under refrigeration. This will provide flexibility for the pharmacies to plan the compounding activities and manage the inventory.

METHODS

MATERIALS

The pure active pharmaceutical ingredient (API) powder of ESL (Lot 1040155) and 600-mg Aptiom tablets (Lot PNKN; EXP June 2018) were provided by Sunovion Pharmaceuticals Inc. (Marlborough, Massachusetts). The suspension vehicles were purchased from multiple vendors as listed in Table 1.

INITIAL SCREENING

Prototype suspension formulations of 40-mg/mL ESL were prepared at a 30-mL batch size for initial screening. The following procedures were used to prepare each formulation. A 2-oz glass bottle was pre-calibrated with 30 mL of purified water. Two 600-mg Aptiom tablets were crushed and thoroughly triturated in a 4-oz glass mortar. About 10 mL of vehicle

RECOMMENDED FORMULA AND COMPOUNDING PROCEDURES FOR A 30-ML BATCH OF A 40-MG/ML ESLICARBAZEPINE ACETATE ORAL SUSPENSION

INGREDIENT	AMOUNT
Aptiom Tablet, 600 mg ^a	2 tablets
Suspension Vehicle ^b	qs 30 mL

^aOther strengths of Aptiom tablets may be used, and the number of tablets should be re-calculated accordingly to provide the same total amount of eslicarbazepine acetate.

^bThe suspension vehicle is a mixture of 50:50 v/v Ora-Sweet:Ora-Plus or Ora-Sweet SF:Ora-Plus (from Perrigo Pharmaceuticals). Include at least 20% overage to account for loss during transfer. For example, prepare at least 36 mL premix for the 30-mL batch of the suspension.

- Calculate the required quantity of each ingredient for the total amount to be prepared.
- Prepare the suspension vehicle by mixing 18 mL of Ora-Sweet (or Ora-Sweet SF) and 18 mL of Ora Plus. *Note: This includes 20% overage to account for loss during transfer.*
- Pre-calibrate a 2-oz amber plastic prescription bottle with purified water for 30 mL.
- Place the two Aptiom tablets in a 4-oz glass mortar.
- Crush the tablets and triturate thoroughly to a fine powder.
- Add 10 mL of suspension vehicle to the mortar in ~2-mL increments and triturate until a smooth suspension is obtained.
- Pour the mixture into the pre-calibrated bottle.
- Rinse the mortar and pestle with 5 mL of suspension vehicle and transfer into the bottle. *Note: Repeat this step once.*
- Add a sufficient quantity of the suspension vehicle directly into the bottle to the pre-calibrated mark.
- Cap the bottle and shake thoroughly to disperse the suspension.
- Store the suspension at room temperature or under refrigeration for up to 2 months. Shake well before using.

TABLE 1. SOURCE INFORMATION OF SUSPENSION VEHICLES.

VEHICLES	VENDOR	CATALOG NUMBER	NDC NUMBER	LOT NUMBER AND EXPIRATION DATE
Ora-Sweet	Perrigo	--	0574-0304-16	7260310, 6/30/2020
Ora-Sweet SF	Perrigo	--	0574-0302-16	5211709, 5/2019
Ora-Plus	Perrigo	--	0574-0303-16	7219887, 5/31/2019
Oral Mix	Medisca	--	38779-2512-8	137502/A, 10/2019
Oral Mix SF	Medisca	--	38779-2600-8	137485/A, 08/2018
SyrSpend SF	Fagron	805359	51552-1123-5	16A05-U06-028553, 1/5/2019
UniSpend anhydrous, sweetened	Fagron	906909	51552-1544-05	17K01-U05-040766 11/01/2019
UniSpend anhydrous, unsweetened	Fagron	806910	51552-1545-05	17K01-U08-040741 11/01/2019

NDC = National Drug Code; SF = sugar free

was added to the mortar in ~1-mL increments with trituration until a smooth suspension was obtained. The suspension was carefully poured into the pre-calibrated bottle, followed by two mortar rinses of 5 mL of vehicle each. Finally, a sufficient amount of vehicle was added directly into the bottle to the pre-calibrated mark. Each bottle was shaken thoroughly to disperse the suspension. The ease of pre-

TABLE 2. PALATABILITY EVALUATION RUBRIC.

TASTE	SCALE OF 1 TO 5 (LEAST TO MOST INTENSE; 5 = MOST)				
	Bitter	1	2	3	4
Sweet	1	2	3	4	5
Sour	1	2	3	4	5
Salty	1	2	3	4	5
Oily	1	2	3	4	5
Metallic	1	2	3	4	5
ODOR	SCALE OF 1 TO 5 (LEAST TO MOST INTENSE BAD ODOR; 5 = MOST)				
	1	2	3	4	5
TEXTURE	SCALE OF 1 TO 5 (LEAST TO MOST GRITTY; 5 = MOST)				
	1	2	3	4	5
IRRITATION	SCALE OF 1 TO 5 (LEAST TO MOST IRRITATING/ AVERSIVE; 5 = MOST)				
	1	2	3	4	5
AFTERTASTE (up to 10 minutes after rinse)	SCALE OF 1 TO 5 (LEAST TO MOST AVERSIVE AFTERTASTE; 5 = MOST)				
	1	2	3	4	5

**TABLE 3. PROTOTYPE ORAL SUSPENSIONS OF 40 MG/ML
ESLICARBAZEPINE ACETATE.**

FORMULATION NUMBER	VEHICLE	SUGAR-BASED OR SUGAR-FREE
118-1	Ora-Sweet	Sugar-based
118-2	Ora-Sweet SF	Sugar-free
118-3	50:50 v/v Ora-Sweet: Ora-Plus	Sugar-based
118-4	50:50 v/v Ora-Sweet SF: Ora-Plus	Sugar-free
118-5	Oral Mix	Sugar-based
118-6	Oral Mix SF	Sugar-free
118-7	SyrSpend SF	Sugar-free
118-8	UniSpend anhydrous sweetened	Sugar-based
118-9	UniSpend anhydrous unsweetened	Sugar-free

paration and initial observations were recorded immediately. The suspensions were then evaluated for ease of dosing, palatability, and physical properties.

The ease of dosing was first evaluated using the graduated oral syringes (Catalog 2111; Total Pharmacy Supply, Inc., Arlington, Texas). It was observed that some suspensions were difficult to expel from the syringes. Therefore, the oral dosing spoons (Catalog 2102; Total Pharmacy Supply, Inc.) were added to the evaluation. Palatability of the suspensions was evaluated by the two study investigators using the rubric listed in Table 2. A teaspoonful dose (5 mL) of each suspension was swished around in the mouth for 10 seconds and spat out. The mouth was rinsed with a sufficient amount of warm water, and the palatability results were recorded immediately. A minimum of a 2-hour-wait period was maintained before the next sample. Evaluation of the physical properties of the suspensions included particle settling, re-suspendability, and foaming. One set of the suspensions were inspected and re-suspended daily for 4 days. A second set of the suspensions were left undisturbed on a laboratory bench for 8 weeks, and camera images were taken daily during the first week and weekly afterwards. Re-suspendability of these suspensions was evaluated at the end of the 8-week period.

TWO-MONTH STABILITY STUDY

Two lead formulations of 40-mg/mL ESL in 50:50 v/v Ora-Sweet:Ora-Plus or Ora-Sweet SF:Ora-Plus, were selected for the two-month stability study. Batches of 120-mL suspensions were prepared using the following method:

Method of Preparation of 120-mL Suspension Batches

1. Calculated the required quantity of each ingredient for the total amount to be prepared.
2. Pre-calibrated a 4-oz amber prescription bottle with 120 mL of purified water.
3. Crushed and thoroughly triturated eight 600-mg Aptiom tablets in an 8-oz glass mortar.
4. Added about 40 mL of the vehicle to the mortar in ~10-mL increments with trituration until a smooth suspension was obtained.
5. Poured the suspension carefully into the pre-calibrated bottle followed by three mortar rinses of 20 mL of the vehicle each.
6. Added a sufficient amount of vehicle directly into the bottle, to the pre-calibrated mark.
7. Shook the bottle thoroughly to disperse the suspension.
8. Transferred and packaged aliquots of the suspensions, 30 mL each, in 2-oz amber prescription bottles for the stability study.
9. Stored the bottles at RT or under refrigeration (2°C to 8°C).

Three replicates were included for each formulation. At 0, 1-week, 2-week, 4-week, 6-week, and 9-week time points, the bottles were shaken for re-suspension, and samples were withdrawn for visual

TABLE 4. PROTOTYPE SUSPENSION FORMULATIONS AND INITIAL SCREENING RESULTS.

FORMULATION NUMBER	EASE OF PREPARATION	EASE OF DOSING	ACCEPTABLE PALATABILITY	PARTICLE SETTLING (AFTER 4 DAYS)	RE-SUSPENDABILITY
118-1	Yes	Yes	Yes	No	Yes
118-2	Yes	Yes	Yes	Yes	Yes
118-3	Yes	Yes	Yes	No	Yes
118-4	Yes	Yes	Yes	No	Yes
118-5	Yes	Yes	Yes	No	Yes
118-6	Yes	Yes	Yes	No	Yes
118-7	No	Yes	Yes	No	Yes
118-8	Yes	No ^a	Yes	Yes	Yes
118-9	Yes	No ^a	No	Yes	Yes

^aIt was easy to withdraw the suspension into the syringe, but it was very difficult to expel the suspension for dosing. There were no issues with dosing spoons.

TABLE 5. THE pH RESULTS OF THE TWO-MONTH STABILITY STUDY (n=3).

SAMPLE	STORAGE	pH					
		TIME 0	1 WEEK	2 WEEKS	4 WEEKS	6 WEEKS	9 WEEKS
40-mg/mL ESL suspension in 50:50 v/v Ora-Sweet:Ora-Plus	2°C to 8°C	4.45 ± 0.01	4.46 ± 0.01	4.48 ± 0.02	4.46 ± 0.02	4.51 ± 0.02	4.49 ± 0.02
	RT	4.46 ± 0.01	4.46 ± 0.01	4.48 ± 0.03	4.45 ± 0.01	4.51 ± 0.01	4.48 ± 0.01
40-mg/mL ESL suspension in 50:50 v/v Ora-Sweet SF:Ora-Plus	2°C to 8°C	4.39 ± 0.01	4.42 ± 0.01	4.43 ± 0.01	4.42 ± 0.01	4.44 ± 0.01	4.42 ± 0.01
	RT	4.40 ± 0.01	4.44 ± 0.02	4.42 ± 0.01	4.43 ± 0.01	4.43 ± 0.01	4.42 ± 0.02

ESL = eslicarbazepine acetate; RT = room temperature

TABLE 6. HIGH-PERFORMANCE LIQUID CHROMATOGRAPHIC RESULTS OF THE TWO-MONTH STABILITY STUDY (n = 3).

SAMPLE	STORAGE	% LABEL CLAIM					
		TIME 0	1 WEEK	2 WEEKS	4 WEEKS	6 WEEKS	9 WEEKS
40-mg/mL ESL suspension in 50:50 v/v Ora-Sweet:Ora-Plus	2°C to 8°C	101.8 ± 1.4	102.1 ± 0.4	100.9 ± 0.1	102.7 ± 0.2	101.5 ± 0.4	102.3 ± 0.2
	RT	102.2 ± 1.4	101.2 ± 0.3	102.5 ± 1.5	103.3 ± 1.1	102.4 ± 0.8	103.4 ± 0.6
40-mg/mL ESL suspension in 50:50 v/v Ora-Sweet SF:Ora-Plus	2°C to 8°C	100.4 ± 0.3	100.8 ± 1.3	101.5 ± 2.1	101.3 ± 0.6	100.9 ± 0.9	101.0 ± 0.3
	RT	101.9 ± 3.4	99.6 ± 0.3	101.3 ± 0.5	102.1 ± 0.7	102.0 ± 0.9	101.8 ± 0.5

ESL = eslicarbazepine acetate; RT = room temperature

inspection, pH measurement, and high-performance liquid chromatographic (HPLC) analysis.

For the HPLC analysis, a 1.25-mL aliquot from each stability sample was transferred into a 50-mL volumetric flask and diluted to the line with 50:50 v/v methanol:water. The expected drug concentration was 1 mg/mL. The flasks were sonicated for 10 minutes and

allowed to cool to RT. About 1 mL of sample from each flask was filtered through a 0.45- μ m polytetrafluoroethylene membrane into an autosampler vial for the HPLC analysis (see below for details). Please note that it was not possible to transfer the desired 1.25-mL volume accurately by the routine pipetting technique for viscous suspensions. Instead, the samples were transferred with weight monitoring. To be more specific, each volumetric flask was tared on a balance, and the sample was added slowly to the flask using a pipet until the target weight was reached. The target weight values were 1.44 g and 1.28 g for the Ora-Sweet/Ora-

Plus and Ora-Sweet SF/Ora-Plus samples, based on the measured density values of 1.155 g/mL and 1.023 g/mL, respectively.

HIGH-PERFORMANCE LIQUID CHROMATOGRAPHIC ANALYSIS

A stability-indicating HPLC method was previously developed and implemented in the investigators' laboratory for ESL suspensions intended for enteral feeding tubes.⁸ The method was verified to be suitable for

FIGURE 1A. PHYSICAL APPEARANCE OF ESLICARBAZEPINE ACETATE SUSPENSION FORMULATIONS AFTER 0 TO 5 DAYS.



the analysis of the current oral suspension formulations. Briefly, the analysis was performed using a Shimadzu HPLC system (Model LC-2010AHT) equipped with a Phenomenex C18 column (Luna, 150 × 4.6 mm, 3 μ, and 100 Å). The mobile phase consisted of a methanol and water mixture (50:50 v/v) with 0.1% trifluoroacetic acid. The mobile phase flow rate was set at 0.8 mL/minute, and the column oven was set at 40°C. The sample injection volume was 3 μL, and the detection wavelength was set at 230 nm. Under these conditions, the retention time of ESL was observed to be about 8.9 minutes.

For calibration purposes, standard solutions of 0.8 mg/mL, 0.9 mg/mL, 1.0 mg/mL, 1.1 mg/mL, and 1.2 mg/mL ESL were prepared from pure drug powder in 50:50 v/v methanol:water. This range encompasses 80% to 120% of the expected drug concentration in the diluted stability samples for HPLC analysis. A calibration curve was constructed on each day of the analysis by plotting the peak area of ESL against concentration. The curves were found to be linear over the concentration range of the standards with $R^2 = 0.994$ or better. The middle standard was also injected three times throughout the analysis on each day to assess the method precision. The intra-day and inter-day coefficients of variation were within 0.6%.

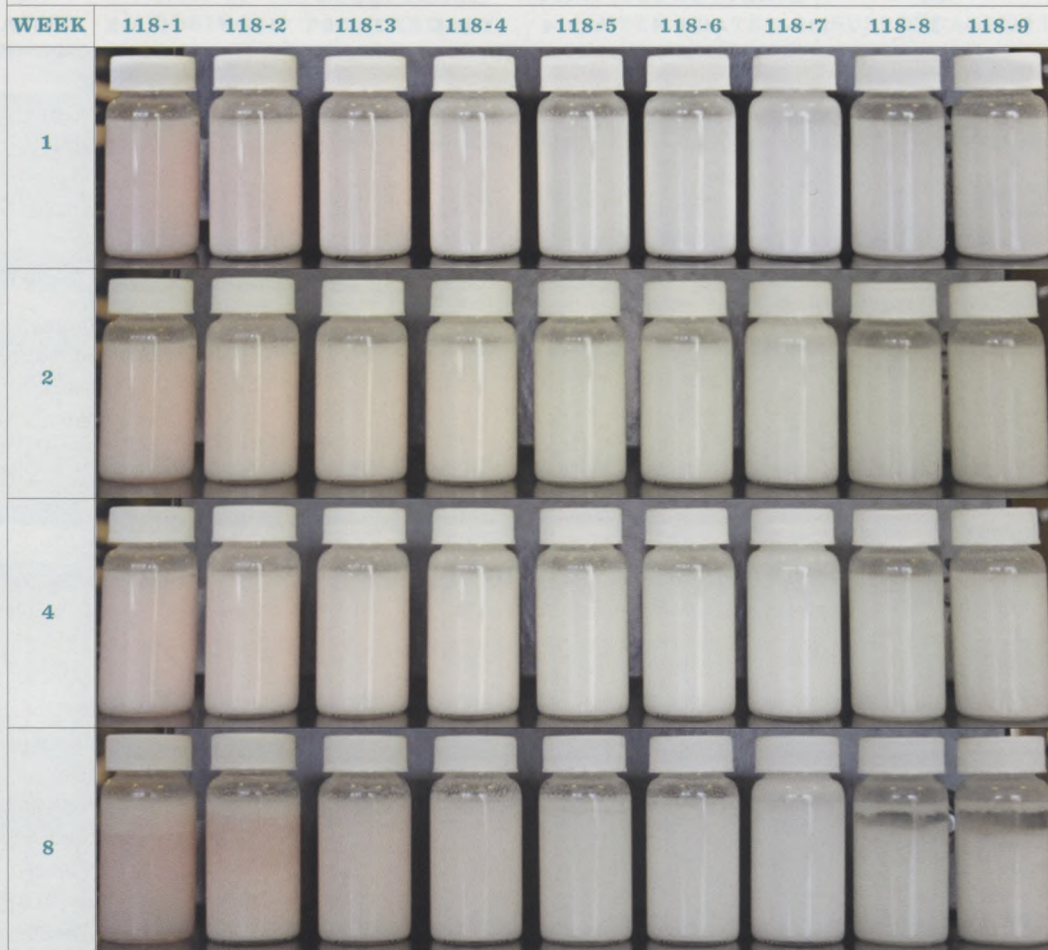
RESULTS AND DISCUSSION

INITIAL SCREENING

Nine prototype suspension formulations (118-1 to 118-9) were prepared in commercially available liquid vehicles as listed in Table 3. Both sugar-based (SB) and sugar-free (SF) systems were included. The first seven vehicle systems are commonly used by pharmacists. The last two are relatively new anhydrous (lipid-based) vehicles, which can potentially minimize the hydrolytic degradation of drug molecules, such as ESL. The 40-mg/mL drug concentration was chosen so as to provide a dose of 200-mg ESL in a convenient 5-mL volume (equivalent to a 1-teaspoonful measurement in the U.S.).

The initial screening data are summarized in Table 4. All nine formulations except 118-7 were relatively easy to prepare from the 600-mg strength Aptiom tablets. The vehicle used in formulation 118-7, SyrSpend SF, has a high intrinsic viscosity, which led to a very thick drug suspension and significant drug loss during transfer steps. The anhydrous (lipid-based) formulations, 118-8 and 118-9, exhibited a lower viscosity than all other formulations (aqueous based) and were easier to transfer from mortar to prescription bottles. In terms of ease of dosing, all suspensions, except formulations 118-8 and 118-9, were compatible with oral syringes and dosing spoons. The palatability was also found to be acceptable for most formulations with an average score of ≤ 3 (out a scale of 5) for each evaluation category. Formulation 118-9 was scored 3.5 for its oily

FIGURE 1B. PHYSICAL APPEARANCE OF ESLICARBAZEPINE ACETATE SUSPENSION FORMULATIONS AFTER 1 WEEK, 2 WEEKS, 4 WEEKS, AND 8 WEEKS.



taste and thus considered unacceptable. After 4 days of storage at RT, some particle settling was observed in formulations 118-2, 118-8, and 118-9. The settling was not unexpected, since the 118-2 contains no suspending agents, and the two anhydrous vehicles have a low intrinsic viscosity. Nevertheless, all formulations exhibited satisfactory re-suspendability upon shaking, with no foaming issues.

A second set of the suspension formulations were used to monitor the particle settling behavior over an extended period of 8 weeks at RT without any physical disturbances. The camera images from day 0 to 5 days are shown in Figure 1A, and the ones from 1 week to 8 weeks are shown in Figure 1B. All suspensions retained their structure on days 0, 1, and 2. On Day-3, suspensions 118-8 and 118-9 exhibited signs of particle settling along with the formation of a layer of clear vehicle at the top surface. Suspensions 118-1 and 118-2 also showed initial signs of settling behavior,

although a clear separation of vehicle and the particles was not observed. The settling behavior of these four suspensions progressed over the following days and weeks. Suspensions 118-5 and 118-6 started to settle at the end of Week-1 and progressed over the following weeks. Suspension 118-5 appeared to settle at a faster rate compared to 118-6. Suspensions 118-3 and 118-4 began settling during Week-2 and progressed over the following weeks. Similar to the observations above, suspension 118-3 appeared to settle at a greater rate compared to 118-4. Suspension 118-7 appeared to be most stable against settling among all of the formulations evaluated. This formulation retained its structure throughout the testing period. The settling behavior of prepared suspension formulations appeared to be a function

of the intrinsic viscosity of the vehicles. Similar to previous observations, all formulations were re-suspended satisfactorily upon shaking after 8 weeks of storage at RT.

Based on the initial screening data, formulations 118-3 and 118-4 were selected as the leads for additional evaluation. Formulation 118-3 contained 50:50 v/v Ora-Sweet:Ora-Plus (sugar based), and formulation 118-4 contained 50:50 v/v Ora-Sweet SF:Ora-Plus (sugar free). They provided the optimal balance of all the desired attributes for compounded oral suspensions. HPLC analysis was then performed on the freshly prepared samples of these two formulations. The ESL concentration was confirmed to match the expected value, and there were no interfering peaks from the excipients used in the Aptiom tablets or the suspension vehicles.

TWO-MONTH STABILITY STUDY OF THE LEAD FORMULATIONS

A two-month stability study was conducted on the two lead suspension formulations stored at both RT and under refrigeration (2°C to 8°C) with three replicates for each condition. At the initiation of the study, all samples appeared as white and smooth suspensions. The pH readings of the samples ranged from 4.39 to 4.46 (Table 5), which were consistent with the pH range (4.0 to 4.5) of the buffered source vehicles.⁹ The HPLC results (Table 6) confirmed that the initial samples contained 100.4% to 102.2% of the label claim strength of 40 mg/mL.

Over two months of storage, all stability samples exhibited good re-suspendability. There were no significant changes in visual appearance, pH (Table 5), or strength (Table 6) for any samples. The HPLC chromatograms were also carefully examined for potential degradation, and no new peaks were observed. The data suggest that the two lead suspension formulations are stable physically and chemically at RT or under refrigeration for up to two months.

It is worth mentioning that the source vehicles in the two lead formulations contained an effective preservative system that consisted of parabens and potassium sorbate.⁹ Therefore, the ESL formulations are not expected to have issues of microbial growth over the two-month storage period.

Based on the excipient information in the package insert¹ and tablet weight data (Unofficial laboratory data generated by the investigators using one lot of Aptiom tablets for each strength [$n=10$]), all strength of Aptiom tablets are assumed to be prepared from the same stock granulation or blend. In other words, all strengths contain the same weight ratio of drug to excipients. Therefore, even though the study was conducted using the 600-mg strength tablets, all recommendations and findings from this study should be applicable when other strengths of Aptiom tablets are used to prepare the oral suspensions.

CONCLUSION

This study investigated oral suspension formulations of ESL prepared by extemporaneous compounding. Two formulations

were selected from the initial screening work based on ease of preparation, ease of dosing, palatability, and physical properties. The formulations consisted of 40 mg/mL of eslicarbazepine acetate in 50:50 v/v Ora-Sweet:Ora-Plus (sugar-based) or Ora-Sweet SF:Ora-Plus (sugar-free). Both formulations exhibited satisfactory physical and chemical stability over the two months of storage period at RT or under refrigeration (2°C to 8°C). The vehicles also contained preservatives to prevent potential microbial growth. The recommended formula and compounding procedure for a 30-mL preparation is conveniently provided on page 434.

REFERENCES

1. Aptiom® (eslicarbazepine acetate) tablet package insert. Available at: www.aptiom.com/. Accessed October 4, 2017.
2. U.S. Department of Health and Human Services. U.S. Food and Drug Administration. Approval letter for NDA 022416 Suppl-9 submission, issued Sep 13, 2017. [FDA Website.] Available at www.accessdata.fda.gov/scripts/cder/daf/index.cfm. Accessed October 4, 2017.
3. Breitzkreutz J, Boos J. Paediatric and geriatric drug delivery. *Expert Opin Drug Deliv* 2007; 4(1): 37–45.
4. Hanning SM, Lopez FL, Wong IC et al. Patient centric formulations for paediatrics and geriatrics: Similarities and differences. *Int J Pharm* 2016; 512(2): 355–359.
5. Fontes-Ribeiro C, Nunes T, Falcão A et al. Eslicarbazepine acetate (BIA 2-093): Relative bioavailability and bioequivalence of 50 mg/mL oral suspension and 200 mg and 800 mg tablet formulations. *Drugs R D* 2005; 6(5): 253–260.
6. Sunkaraneni S, Kharidia J, Schutz R et al. A pharmacokinetic study comparing eslicarbazepine acetate administered orally as a crushed or intact tablet in healthy volunteers. *Clin Pharmacol Drug Dev* 2016; 5(4): 278–284.
7. United States Pharmacopeial Convention, Inc. *United States Pharmacopeia–National Formulary*. Rockville, MD: US Pharmacopeial Convention, Inc.; Current Edition.
8. Reindel K, Zhao F, Hughes S et al. *In vitro* evaluation of eslicarbazepine delivery via enteral feeding tubes. *Hosp Pharm* 2017; 52(11): 752–760.
9. Product Data Sheets for Ora-Blend, Ora-Blend SF, Ora-Sweet, Ora-Sweet SF, and Ora-Plus. [Perrigo Website.] Available at: www.perrigo.com/business/education.aspx. Accessed June 4, 2018.

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