In Vitro Evaluation of Eslicarbazepine Delivery via Enteral Feeding Tubes

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Abstract

Purpose: The feasibility of preparing an eslicarbazepine acetate suspension using Aptiom tablets for administration via enteral feeding tubes was evaluated. **Methods:** Eslicarbazepine acetate suspension (40 mg/mL) was prepared using Aptiom tablets after optimizing the tablet crushing methods and the vehicle composition. A stability-indicating high-performance liquid chromatography (HPLC) method was developed to monitor the eslicarbazepine stability in the prepared suspension. Three enteric feeding tubes of various composition and dimensions were evaluated for the delivery of the suspensions. The suspension was evaluated for the physical and chemical stability for 48 hours. **Results:** The reproducibility and consistency of particle size reduction was found to be best with standard mortar/pestle. The viscosity analysis and physical stability studies showed that ORA-Plus:water (50:50 v/v) was optimal for suspending ability and flowability of suspension through the tubes. The developed HPLC method was found to be stability indicating and suitable for the assay of eslicarbazepine acetate in the prepared suspension. The eslicarbazepine concentrations in separately prepared suspensions were within acceptable range ($\pm 3\%$), indicating accuracy and reproducibility of the procedure. The eslicarbazepine concentrations in suspensions before and after delivery through the enteric feeding tubes were within acceptable range ($\pm 4\%$), indicating absence of any physical/chemical interactions of eslicarbazepine with the tubes and a successful delivery of eslicarbazepine dosage via enteric feeding tubes. The stability study results showed that eslicarbazepine concentration in the suspension remained unchanged when stored at room temperature for 48 hours. **Conclusion:** The study presents a convenient procedure for the preparation of a stable suspension of eslicarbazepine acetate (40 mg/mL) using Aptiom tablets, for administration via enteral feeding tubes.

Keywords

eslicarbazepine acetate, enteric feeding, extemporaneous compounding, suspension

Introduction

Aptiom (eslicarbazepine acetate) is an anticonvulsant drug indicated for an adjunctive treatment of partial-onset seizures.¹ It is a part of the antiepileptic class of medications commonly used in intensive care patients to prevent seizures.¹ Currently, Aptiom is available as 200-, 400-, 600-, and 800-mg immediate-release tablets. These tablets are recommended to be administered orally, may be crushed, and taken with/without food.

In an intensive care setting, there are a growing number of patients who receive food and nutrition via enteral feeding tubes.²⁻⁴ Administration of medication through enteral feeding tubes offers several advantages over the parenteral route.⁵ The common benefits include economy, convenience, compliance, and most importantly lower probability of infections. However, along with the benefits, medication administration through enteric feeding tubes is associated with several challenges.⁶ First, commercially available oral solid drug products, such as Aptiom tablets, cannot be administered directly

via enteral feeding tubes. They need to be formulated into an appropriate liquid form by extemporaneous compounding, which is typically carried out by a pharmacist. Second, a variety of feeding tubes with different diameters, openings, lengths, and polymer compositions are employed in a hospital setting, thus adding to the complexity of drug administration. Furthermore, several studies have reported varying degrees of drug loss when administered via enteric feeding tubes.⁷⁻¹⁵ Clark-Schmidt et al studied the delivery of carbamazepine (an antiepileptic drug) suspension via polyvinyl chloride (PVC) nasogastric (NG) tubes.¹⁶ The authors reported losses (ranging 2%-23.6%) of carbamazepine in an undiluted suspension

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due to physical interaction (adhesion) with the PVC NG tubes. Thus, preparing a compounded liquid formulation from a commercially available oral solid drug product requires a careful formulation strategy and a thorough evaluation of factors that may influence the delivery of drugs via enteric feeding tubes.

Currently, there are no reports in the literature describing the administration of an extemporaneously compounded suspension of eslicarbazepine acetate via enteric feeding tubes. The presented study was aimed at exploring the feasibility of delivering an extemporaneously compounded suspension of eslicarbazepine acetate, prepared using Aptiom tablets, via enteral feeding tubes. The accuracy and short-term chemical stability of eslicarbazepine acetate in the prepared suspension was assessed to optimize the compounding/administration procedures for health care providers.

Materials

Eslicarbazepine acetate powder (pure) and Aptiom tablets (200, 400, 600, and 800 mg) were obtained from Sunovion Pharmaceuticals, Inc (Marlborough, Massachusetts). ORA-Plus was obtained from Perrigo (Minneapolis, Minnesota). Bard NG tube, polyvinyl chloride (PVC, 18 Fr. diameter, 48" length) and Bard NG tube, polyvinyl chloride (PVC, 10 Fr. diameter, 36" length) were obtained from C.R. Bard, Inc (Covington, Georgia). Kangaroo NG tube (polyurethane, 10 Fr. diameter, 36" length) was obtained from Covidien (Mansfield, Massachusetts). All other chemicals used in the study were of analytical grade.

Methods

Preparation of Suspension From Aptiom Tablets (Choice of Tablet Crushing Method and Suspending Medium)

The eslicarbazepine acetate suspensions from Aptiom tablets were prepared, in general, by crushing the tablets and suspending the obtained powder in a predetermined volume of the suspending vehicle. To ensure consistency and convenience in preparing suspensions, commonly used tablet crushing methods, namely, standard mortar-pestle, Pillcrusher Medication Delivery Syringe, and Silent Knight pill crusher, were evaluated for the ease-of-use, efficiency, and consistency of particle size reduction. The tablets were crushed using each of these methods, and the resulting powder was subjected to particle size analysis using laser scattering particle size analyzer (Model: Partica LA950-A2; Horiba Instruments, Inc, Irvine, California). All experiments were performed in triplicate.

The choice and optimization of the vehicle for preparing suspensions of Aptiom tablets was based on a balance of potential suspending ability and flowability through the

enteric feeding tubes. Binary mixtures of ORA-Plus (a commercially available suspending vehicle) and water, in different ratios, were evaluated for viscosity to assess the suitability for preparing eslicarbazepine acetate suspensions. To further confirm the suitability of suspension preparation, several eslicarbazepine acetate suspensions (40 mg/mL) were prepared using different ratios of ORA-Plus:water as a vehicle. These suspensions were analyzed for physical stability and viscosity (Model: DV2T Viscometer; Brookfield Engineering, Inc, Middleborough, Massachusetts) to optimize the choice of vehicle.

For analysis, an aliquot (1.25 mL) was withdrawn from each suspension sample and diluted with a methanol: purified water (50:50 v/v) solution in a 50-mL volumetric flask. The samples were then sonicated for 10 minutes. Using a 3-mL plastic syringe, a sample of each dilution was filtered through a 0.45- μ m nylon syringe filter.

HPLC Assay

A high-performance liquid chromatography (HPLC) method was developed to analyze the eslicarbazepine concentration in the prepared Aptiom suspensions. The analysis was performed using an HPLC system (Model: LC-2010AHT; Shimadzu Scientific Instruments, Marlborough, Massachusetts) equipped with a C18 column (Phenomenex Luna, 150 $\times$ 4.6 mm, 3 μ m, 100 Å). The mobile phase consisted of methanol and water (50:50 v/v) with 0.1% trifluoroacetic acid. The mobile phase flow rate was maintained 0.8 mL/min for a total runtime of 15-minute, and the column oven temperature was maintained at 40°C. The sample injection volume was 3 μ L, and the detection wavelength was set at 230 nm. Under these conditions, the retention time of eslicarbazepine was observed to be about 8.7 minutes.

For calibration purpose, standards of 0.8, 0.9, 1.0, 1.1, and 1.2 mg/mL eslicarbazepine were prepared from pure drug powder in methanol:water (50:50 v/v). This range encompasses 80% to 120% of the nominal concentration of the study samples. A calibration curve was constructed on each day of analysis by plotting the peak area of eslicarbazepine against concentration. The curves were found to be linear over the concentration range of the standards with $R^2 = 0.99$ or better. Each standard was injected 3 times to verify method precision. The intraday and interday coefficients of variation were within 1%.

Forced Degradation Studies

A forced degradation study was conducted to verify the ability of the HPLC method to separate the potential degradation products from the parent drug. Four samples of 0.1 mg/mL eslicarbazepine solution in methanol:water (50:50 v/v) were prepared, and exposed to extreme pH and oxidative stress conditions as shown in Table 1.

Table 1. Forced Degradation Study Parameters.

Sample	Forced degradation treatment
1	Adjusted to pH 2 using 1-N HCl and incubated at 60°C
2	Adjusted to pH 12 using 1-N NaOH and incubated at 60°C
3	Spiked with 3% hydrogen peroxide and incubated at 60°C
4	Spiked with 3% hydrogen peroxide and exposed to direct sunlight (ambient room temperature)

Evaluation of Tube Delivery

Three enteric feeding tubes, that is, PVC/18 Fr/48", PVC/10 Fr/36", and Polyurethane/10 Fr/36", were evaluated for the delivery of the prepared eslicarbazepine acetate suspensions. Eslicarbazepine acetate suspensions were prepared using the above method at 40 mg/mL. Feeding tubes were mounted to a board to mimic the position the tube would be in a patient. An oral syringe was attached to the top of the feeding tube, the suspension (30 mL) was allowed to flow through the tube via gravity, and the samples were collected after passing through the tube for evaluation. Each tube type was tested 3 times using a clean/new tube each time ($n = 3$). Three dilutions were prepared from each sample using the method described above. Dilutions were evaluated using the developed HPLC method, and samples were injected in triplicate for each dilution. Peak area for each sample was compared with a calibration curve developed each day.

Stability of Eslicarbazepine Acetate Suspension

The chemical stability assessment of the optimized suspension was performed at time 0 (immediately after preparation), at 24 h, and at 48 h after preparation. Samples were stored in 2-Oz liquid-dispensing vials at room temperature, and the suspensions were inspected visually for uniformity at each time point. Each sample was analyzed by a stability-indicating HPLC method described above. Three injections were performed for each of the samples.

Results and Discussion

Preparation of Eslicarbazepine Acetate Suspension

The results of particle size analysis of the powders obtained by crushing the tablets using (1) Pillcrusher Medication Delivery Syringe, (2) Silent Knight pill crusher, and (3) standard mortar/pestle are shown in Figure 1 and Table 2. In general, powders obtained after crushing the tablets by either Pillcrusher syringe or the Silent Knight pill crusher exhibited larger mean particle size (~400 μm). The statistical standard deviation (indicating consistency between replicates) was

also found to be higher by these methods. Tablet components formed a thick layer on the inner surface of the syringe. Crushing the tablets using standard mortar/pestle appeared to produce powders with significantly lower mean particle size (~70 μm). The reproducibility and consistency of particle size reduction was also found to be significantly better (SD: ~2.5 μm). Lower particle size is important to formulate a physically stable suspension and avoid rapid sedimentation of particles. Moreover, considering the fact that the suspensions were prepared with an intent to be delivered via enteral feeding tubes (most with narrow lumen diameter), achieving lowest possible particle size was critical. Based on the above observations, standard mortar/pestle was selected as a preferred method for crushing Aptiom tablets to prepare the suspensions.

Binary mixtures of ORA-Plus and water, in different ratios, were evaluated for viscosity to assess the suitability for preparing eslicarbazepine acetate suspensions. Figure 2 shows the viscosity profiles of these binary mixtures as a function of spindle cone speed (shear rate). In general, the viscosity of the mixtures decreased with increasing rate of shear. This is known as "shear-thinning" and is a well-known phenomenon observed with most non-Newtonian liquids. For a given shear rate, the viscosity of the binary mixture decreased in a near-linear manner with increasing ratio of water. This was also expected considering the differences in the native viscosities of ORA-Plus and water. Preliminary experimental trials showed us that liquids with viscosities of 1000 cps or below demonstrated acceptable flow through the enteric tubes. Thus, ORA-Plus:water ratios of 50:50 v/v or lower were initially considered for the preparation of eslicarbazepine acetate suspensions.

The HPLC results confirmed that 40 to 60 mg/mL suspensions could be prepared accurately and reproducibly. Two suspensions (40 or 60 mg/mL) were prepared using ORA-Plus:water (50:50 v/v) as a suspending vehicle and evaluated for viscosity. The results were compared with the viscosity profile of ORA-Plus:water (50:50 v/v; Figure 3). In general, the viscosity of the prepared suspensions was found to be higher compared with the vehicle, significantly at the low shear rates. At any given shear rate, suspension containing 60 mg/mL eslicarbazepine exhibited higher viscosity compared with that containing 40 mg/mL eslicarbazepine. Based on the viscosity profiles, the drug concentration of 40 mg/mL was selected for suspension development and analysis. To further confirm the suitability of suspension preparation, several suspensions (40 mg/mL) were prepared using different ratios of ORA-Plus:water as a vehicle. These suspensions were analyzed for physical stability and viscosity to optimize the choice of vehicle. Figure 4 shows the viscosity profiles of these suspensions as a function of spindle cone speed (shear rate). As observed with blank vehicles (ORA-Plus:water binary mixtures), the viscosity of the mixtures decreased with increasing rate of shear. For a given shear rate, the viscosity of the suspensions decreased in a near-linear manner

Figure 1. Particle size analysis of the powder obtained after crushing the tablets using (a) Pillcrusher syringe, (b) silent knight pill crusher, and (c) standard mortar/pestle.

Table 2. Mean Particle Size of Powders Obtained From Different Tablet Crushing Methods.

Sample	Mean size, μm	SD, μm
Pillcrusher Syringe	389.6	149.5
Silent Knight pill crusher	412.5	81.6
Standard mortar/pestle	68.2	2.4

with increasing ratio of water. Based on these observations, eslicarbazepine acetate suspension (40 mg/mL) prepared using ORA-Plus:water ratio of 50:50 v/v was found to be optimal for delivery through the enteric tubes.

The physical stability of the prepared suspensions was assessed by storing the suspensions in glass vials and visually observing the settling behavior (particle sedimentation)

Figure 2. Viscosity analysis of the binary mixtures containing various ratios of ORA-Plus (O) and water (W).

Figure 3. Viscosity analysis of eslicarbazepine acetate suspension (40 mg/mL and 60 mg/mL) prepared using ORA-Plus:water (O:W) as a suspending vehicle.

at 0, 2, 4, 24, and 48 hours. As shown in Figure 5, suspensions prepared with vehicles containing 50% or more ORA-Plus were observed to be physically stable at the end of 48 hours. No settling behavior was observed in these suspensions. For suspensions prepared with vehicles containing more than 50% water, the extent of particle sedimentation was in proportion to the amount of water. For instance,

suspension prepared with ORA-Plus:water ratio of 30:70 v/v exhibited complete settling with separate solid and liquid phases distinctly visible. Thus, based on the viscosity and physical stability observations, eslicarbazepine acetate suspension (40 mg/mL) prepared using ORA-Plus:water ratio of 50:50 v/v was found to be optimal for delivery through the enteric tubes.

Figure 4. Viscosity analysis of eslicarbazepine acetate suspension (40 mg/mL) in various ratios of ORA-Plus® (O) and water (W).

Forced Degradation Studies

Extreme pH and oxidative stress conditions were used to challenge eslicarbazepine solutions (0.1 mg/mL) in methanol:water (50:50 v/v) to assess the suitability of the developed HPLC method for the analysis of eslicarbazepine acetate suspensions (Table 1). The degradation of eslicarbazepine occurred rapidly at extreme pH conditions. The sample challenged with extreme acidic condition (1-N HCL, pH 2) showed a 49% loss of eslicarbazepine at the end of 48 hours. The sample challenged with extreme alkaline condition (1-N NaOH, pH 12) exhibited a complete loss of eslicarbazepine within 15 min. The degradation products were well separated from the parent drug, and no interference of the parent drug peak with those of the degradation products was observed. Eslicarbazepine was observed to be relatively stable under the 2 oxidative stress conditions. For sample spiked with hydrogen peroxide (3%) and incubated at 60°C, approximately 8% drug loss was observed at the end of 5 days. For the sample spiked with hydrogen peroxide (3%) and exposed to direct sunlight (ambient room temperature), approximately 1.5% loss of eslicarbazepine was observed. Similar to the samples treated with extreme pH conditions, these samples also exhibited a good separation of degradation products, without interference of the parent drug peak with those of the degradation products. Therefore, the developed HPLC method was considered stability indicating and suitable for the proposed stability and enteric tubes delivery study of eslicarbazepine acetate suspension.

Delivery of Optimized Eslicarbazepine Acetate Suspension via Enteric Tubes

To ensure the accuracy and consistency of compounding procedure, 2 sets of 3 eslicarbazepine acetate suspensions were separately prepared and analyzed for eslicarbazepine content

using the developed HPLC method. The results are shown in Table 3. The mean concentration of eslicarbazepine in the prepared suspensions from trials 1 and 2 was found to be 98% and 101% of the nominal concentration, respectively. These results confirmed that the suspension compounding procedure consistently yielded the expected concentration of drug and could be used for tube evaluation.

The prepared eslicarbazepine acetate suspension deliverability and compatibility with enteric feeding tubes, as indicated by eslicarbazepine concentration in the suspensions collected after passing through the tubes, is presented in Table 4. After the suspension traversed the tubes completely, the tubes were visually inspected for the presence of any residual fluid. While some residual volume was observed in each of the 3 tube types, none of the tubes exhibited any signs of blockage. With a 30-mL suspension volume introduced, the volume collected after the suspensions passed through the tube averaged 26 mL. The passage of the suspensions through the tubes was assisted by gravity and took less than 4 minutes for complete delivery. The results showed that there was no reduction of eslicarbazepine concentration with any of the feeding tube types tested. The results demonstrated slightly higher drug concentrations in the collected suspensions after passing through enteric tubes. These observations are expected and can be attributed to pipetting accuracy in preparing dilutions. The concentrations were acceptable based on the potency range of the source products. The concentration of eslicarbazepine in suspension after passing through the tubes was acceptable for all tube types. These observations also indicated the absence of any physical or chemical interaction of the drug with the enteric tubes. To ensure a complete delivery of drug dosage, a water flush could be used to rinse the residual volume of suspension through the tube. After medication administration, tubes are typically flushed with 15 to 30 mL of water.⁴

Figure 5. Physical stability (0-48 hours) of eslicarbazepine acetate suspension (40 mg/mL) in various ratios of ORA-Plus (O) and water (W).

Table 3. Mean Concentration (%) of Eslicarbazepine in the Prepared Suspensions (40 mg/mL).

Trial	Eslicarbazepine concentration, mean (%)			
	Sample 1	Sample 2	Sample 3	Average
1	95.9	98.9	98.7	98 ± 0.02
2	101.7	101.1	99.1	101 ± 0.01

Table 4. Mean Concentration (%) of Eslicarbazepine in the Prepared Suspension (40 g/mL) After Passing Through Enteric Feeding Tubes.

Tube type	Eslicarbazepine concentration, mean (%)			
	Sample 1	Sample 2	Sample 3	Average
PVC, 18 Fr, 48"	101.5	103.6	102.6	102.6 ± 1.1
PVC, 10 Fr, 36"	101.7	104.3	100.8	102.3 ± 1.8
Polyurethane, 10 Fr, 36"	102.5	103.3	103.9	103.2 ± 0.7

Table 5. Mean Concentration (%) of Eslicarbazepine in the Prepared Suspension (40 mg/mL) Following 24- and 48-Hour Storage at Room Temperature.

Time	Eslicarbazepine concentration, mean (%)			
	Sample 1	Sample 2	Sample 3	Average
0 h	104.0	102.0	104.0	103.3 ± 1.2
24 h	103.0	97.0	104.0	101.3 ± 3.8
48 h	103.0	102.0	105.0	103.3 ± 1.5

Stability of Optimized Eslicarbazepine Acetate Suspension

The prepared eslicarbazepine acetate suspension was subjected to a 48-hour stability study at room temperature. The suspensions were analyzed for eslicarbazepine concentrations at time 0 (initial concentration), at 24 hours, and at 48 hours. As shown in Table 5, the mean eslicarbazepine concentrations in the prepared suspensions ranged between 101% and 104%. The storage did not appear to have an influence on the chemical stability of the suspensions. Visual inspection revealed that the suspension remained uniform for the duration of storage, with no observed settling behavior. While carbamazepine has been reported to adhere to certain types of delivery tubes, these results indicate that eslicarbazepine suspension (eslicarbazepine acetate suspension, 40 mg/mL) prepared using ORA-Plus:water (50:50 v/v) as suspending vehicle does not interact physically or chemically to the plastic tubing, thus making it suitable for delivery through PVC/18 Fr/48", PVC/10 Fr/36", and Polyurethane/10 Fr/36" tubes.¹⁶ A general guideline procedure to be used by the health care professionals for the preparation of a stable eslicarbazepine acetate suspension using Aptiom tablets is shown in Appendix.

Conclusions

A 40 mg/mL suspension of eslicarbazepine acetate in ORA-Plus:water (50:50 v/v) was identified as suitable for administration through enteral feeding tubes. The concentration of eslicarbazepine after passing through the selected enteric feeding tubes was found to be within acceptable range ($\pm 10\%$) of the label claim. The eslicarbazepine acetate suspension in ORA-Plus:water (50:50 v/v) was found to be the easiest to prepare, and stable at room temperature for 48 hours without compromising the integrity of the suspension. The study presents the feasibility of preparing an extemporaneous suspension of eslicarbazepine for delivery via enteric feeding tubes, using Aptiom tablets.

Appendix

General guideline procedure for the preparation of a stable eslicarbazepine acetate suspension using Aptiom tablets:

- Prepare 30-mL suspending vehicle, that is, ORA-Plus and purified water (50:50 v/v).
- Crush the desired dose (1200 mg) of Aptiom tablets in a mortar and pestle.
- Add 10 mL of vehicle, that is, ORA-Plus:water (50:50 v/v), to a mortar and triturate until there are no visible clumps.
- Pour the mixture into a dispensing container/vial.
- Rinse the mortar and pestle with a small amount of vehicle (5-10 mL) and add to the dispensing container/vial.
- Make up the volume of the suspension in the dispensing cup by adding the remaining quantity of the vehicle.
- To administer, pour suspension into oral syringe attached to the top of feeding tube and allow it to flow through via gravity.
- After administration of the suspension, flush the tubing with 15- to 30-mL purified water.

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