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Compounded Apixaban Suspensions for Enteral Feeding Tubes

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Abstract

Objective: There is limited information on compounded apixaban formulations for administration via enteral feeding tubes. This study was designed to identify a suitable apixaban suspension formulation that is easy to prepare in a pharmacy setting, is compatible with commonly used feeding tubes, and has a beyond-use date of seven days.

Methods: Apixaban suspensions were prepared from commercially available 5 mg Eliquis® tablets. Several vehicles and compounding methods were screened for ease of preparation, dosage accuracy, and tube compatibility. Two tubing types, polyurethane and polyvinyl chloride (PVC), with varying lengths and diameters, were included in the study. They were mounted on a peg board during evaluation to mimic the patient body position. A seven-day stability study of the selected formulation was also conducted.

Results: Vehicles containing 40-60% Ora-Plus® in water all exhibited satisfactory flowability through the tubes. The mortar/pestle compounding method was found to produce more accurate and consistent apixaban suspensions than the pill crusher or crushing syringe method. The selected formulation, 0.25 mg/mL apixaban in 50:50 Ora-Plus®:water, was compatible with both tubing types, retaining > 98% drug in post-tube samples. The stability study also confirmed that this formulation was stable physically and chemically over seven days of storage at room temperature.

Conclusions: A suitable apixaban suspension formulation was identified for administration via enteral feeding tubes. The formulation consisted of 0.25 mg/mL apixaban in 50:50 Ora-Plus®:water. The stability study results supported a beyond-use date of seven days at room temperature.

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Compounded apixaban suspensions for enteral feeding tubes

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Running Head: apixaban suspensions for enteral feeding

ABSTRACT

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Conclusions: A suitable apixaban suspension formulation was identified for administration via enteral feeding tubes. The formulation consisted of 0.25 mg/mL apixaban in 50:50 Ora-Plus®:water. The stability study results supported a beyond-use date of seven days at room temperature.

INTRODUCTION

Apixaban is an oral, selective, reversible factor Xa inhibitor approved for thromboprophylaxis of post-operative hip and knee surgery, stroke prevention in patients with non-valvular atrial fibrillation, and treatment of deep vein thrombosis and pulmonary embolism.[1] It is available commercially as 2.5 and 5 mg oral tablets (Eliquis®) and is administered either as whole, or crushed tablets, with or without food.[1] To date, no oral liquid or i.v. formulation is available in the United States. The use of apixaban is increasing due to various factors, including ease of administration (compared to warfarin), evidence-based renal dosing, and no need of routine lab monitoring. It is expected to further popularize once the reversal agent is approved by the FDA.

Medication administration via enteral feeding tubes may be necessary for patients who are unable to take medication by mouth. Such patients may include individuals in nursing homes or in intensive care units.[2] Proper drug administration via enteral tubes is important. Incorrect medication administration may result in clogged tubing, increased adverse events, and decreased medication efficacy.[3] However, data is scarce on drug preparation and compatibility with various enteral feeding tubes. This is a particular concern for low strength medications (e.g. apixaban) which may suffer significant percentage drug loss due to sorption to enteral feeding tubes.[3,4] One study reported that the bioavailability of an apixaban suspension administered via nasogastric tube was comparable to that of a tablet taken orally.[5,6] However, the study was limited to only one type of tubing, and the suspension was prepared in water or D5W with no suspending agents. The beyond-use date (BUD) was only 4 hours, which presents scheduling and dispensing challenges for central pharmacies in healthcare facilities.

Historically, there is evidence-based data demonstrating the importance of continued anticoagulant use within certain patient populations. Discontinuing anticoagulation therapy or providing insufficient therapy increases the risk of thromboembolisms.[7] Hence, there is a need for an apixaban suspension formulation which is compatible with commonly used enteral feeding tubes and has a BUD of greater than 4 hours. The goal of this study is to identify a suitable apixaban suspension formulation which is easy to prepare in a pharmacy setting, is compatible with commonly used enteral feeding tubes, and has a BUD of seven days.

METHODS

Preparation of Apixaban Suspensions

Suspension vehicles were prepared by mixing Ora-Plus® with purified water at 40:60, 50:50, and 60:40 ratios. Various 20 mL apixaban suspensions of 0.25 mg/mL concentration were prepared from 5 mg strength Eliquis® tablets. Three different methods were employed to crush the tablet and prepare the suspension, and the devices are shown in Figure 1. These methods were compared for ease of preparation and dosage accuracy (potency analysis by HPLC). In the first method, a set of mortar/pestle was used to crush the tablet to a fine powder. About 10 mL vehicle was added to the powder and thoroughly mixed to form a suspension. The suspension was transferred to a pre-calibrated flask followed by mortar/pestle wash. Sufficient vehicle was finally added to the 20-mL mark. In the second method, a Silent Knight Pill Crusher® was used to crush the tablet in a disposable plastic pouch. The powder was then transferred in a pre-calibrated flask, and the vehicle was added to the 20-mL mark. The flask was shaken vigorously to produce a uniform suspension. In the third method, a Welcon® Pill Crushing Enteral Irrigation Syringe was used to crush the tablet directly in the syringe. Once the tablet was ground to a

powder, ~ 10 mL vehicle was drawn up with an additional 10 mL of air. The syringe was capped and shaken vigorously to produce a uniform suspension. The cap was then removed, and the air was pushed out. About 10 mL additional vehicle was drawn up to a final volume of 20 mL. For simplicity, these three preparation methods are referred as mortar/pestle, pill crusher, and crushing syringe in the remaining text.

Tube Flowability and Compatibility

Two types of nasogastric (NG) feeding tubes were used in this study to represent the commonly used tube materials and to bracket the typical tube diameter range for adults. The tubes used in the study were Kangaroo® 10 French (3.3 mm), 36 inch polyurethane tube and Bard® 18 French (5.9 mm), 48 inch polyvinyl chloride (PVC) tube. For flowability and compatibility evaluation, each tube was mounted on a peg board as shown in Figure 2 to simulate the patient position and to maintain method consistency throughout the study.

The suspension vehicles were first screened for tube flowability. Twenty milliliters of each vehicle were poured into an AMSure® Enteral Feeding/Irrigation Syringe which was connected to the tube. The vehicle was allowed to flow through the tube via gravity. The tube was flushed with 60 mL water and 60 mL air between runs. All evaluations were done in triplicates for each vehicle and each tube type.

Selected apixaban suspensions were administered through each type of tube for flowability and compatibility evaluation (n=3 with fresh tubes). The suspension was poured into an AMSure® Enteral Feeding/Irrigation Syringe which was connected to the tube. The suspension was allowed to flow through the tube via gravity. The tube was then flushed with 60 mL of air. The post-tube suspension was collected in a 50 mL centrifuge tube for subsequent analysis by HPLC.

Stability Study

A seven-day stability study of the lead apixaban suspension formulation was conducted. Twenty milliliters of 0.25 mg/mL apixaban suspension was prepared in Ora-Plus®:water 50:50 using the mortar/pestle method described above. The suspension was stored in an amber polypropylene bottle at room temperature and analyzed on day-0, 1, 3, and 7 by HPLC.

High Performance Liquid Chromatography (HPLC)

An HPLC method was developed for apixaban to measure the drug concentration in the suspensions and to monitor the drug stability. The Shimadzu LC-2010A HT system was fitted with a C18 column maintained at 40°C and a UV detector set at 254 nm. The mobile phase consisted of methanol:water (46:54 v/v) with 0.1% trifluoroacetic acid, and the flow rate was 0.8 mL/min. The data was collected and processed by the Shimadzu LCSolution software. The retention time for apixaban was 8.3 minutes.

For the analysis of apixaban suspensions, 1-mL aliquot was withdrawn from each sample and diluted to 10 mL in a volumetric flask with the sample diluent of methanol:water 50:50 v/v. The samples were shaken thoroughly and sonicated for 10 minutes. The samples were then filtered through 0.2-μm syringe filters and analyzed by HPLC. The expected drug concentration was 0.025 mg/mL.

Standards of apixaban at 0.020, 0.023, 0.025, 0.028, 0.030 mg/mL were prepared in the sample diluent (methanol:water 50:50 v/v) for HPLC method calibration. This range was selected to cover the 80 - 120% range of the expected drug concentration. The pure powder of apixaban was not commercially available at the time of the study, and therefore the standards were prepared using the crushed tablet powder from the 5 mg strength tablets with the

assumption of 100% label claim. The average weight of the 5 mg strength tablet was determined to be 207 mg, so the percent strength of the crushed tablet powder was calculated to be 2.42%. In other words, 100 mg crushed tablet powder contained 2.42 mg apixaban. 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 shaken thoroughly and sonicated for 10 minutes. The samples were filtered through 0.2-µm syringe filters and analyzed by HPLC. A calibration curve was produced by linear regression of the peak area of apixaban against apixaban concentration. The standard curve was found to be linear ($r^2 = 0.9908$) over the concentration ranges of interest.

A forced degradation study of apixaban was performed under extreme conditions to verify that the HPLC method was capable of separating the potential degradation products from the original drug. Four 0.5 mg/mL apixaban solutions were prepared in the sample diluent (methanol:water 50:50 v/v). Sample 1 was adjusted to a pH of 2 using 1 M hydrochloric acid. Sample 2 was adjusted to a pH of 12 using 1 M sodium hydroxide. Samples 3 and 4 were each spiked with hydrogen peroxide at 3% final concentration. Samples 1-3 were incubated at 60°C for 7 days. Sample 4 was exposed to direct sunlight for 7 days. Approximately 10%, 14%, and 17% degradation of apixaban was observed in Samples 1, 3, and 4, respectively. As shown in Figure 3, the degradation product peaks were well separated from the original drug peak. Therefore, the HPLC method was considered to be stability-indicating and suitable for the stability study of the apixaban suspension.

RESULTS

Vehicle and Compounding Method Screening

Based on visual observations, vehicles of Ora-Plus® and water mixtures, at 40:60, 50:50, and 60:40 ratios, flowed through the 10 and 18 French tubes at slightly varying speeds, with little to no residual volume. Due to its simplicity and ease of preparation, the 50:50 Ora-Plus®:water mixture was selected as the vehicle to prepare apixaban suspensions.

Three compounding methods were evaluated for the preparation of apixaban suspensions. All three methods were found to be easy to perform by the study investigators. The dosage accuracy and variability data of the resulting suspensions were summarized in Table 1. While all suspensions were within the typical acceptance range of 90%-110% of label claim, the mortar/pestle approach produced the most accurate and consistent suspensions. The pill crusher method appeared to suffer some material loss during the compounding process, and the crushing syringe method exhibited significant variability among the suspension samples prepared. Based on this set of data, the mortar/pestle method was selected for further evaluation.

Suspension Flowability and Compatibility with Tubes

The 0.25 mg/mL apixaban suspension prepared by the mortar/pestle method was evaluated for flowability and compatibility with the polyurethane (10 French, 36″) and PVC (18 French, 48″) tubes. The suspensions flowed through both types of tubes with no significant residual volume. The drug concentration in pre- and post-tube suspension samples was analyzed by HPLC. As shown in Table 2, more than 98% drug was retained in the post-tube suspension samples, suggesting minimal apixaban sorption to polyurethane or PVC tube materials.

Stability Study

A seven-day stability study was conducted on the lead apixaban suspension formulation at room temperature. The formulation consisted of 0.25 mg/mL apixaban suspension in 50:50 Ora-Plus®:water and was prepared by the mortar/pestle method. The HPLC analysis data were summarized in Table 3, and the stability sample retained more than 95% of initial drug concentration over seven days of storage. No significant degradation products were observed in the HPLC chromatograms.

DISCUSSION

It is a common practice in pharmaceutical compounding to preparing drug suspensions using commercially available tablets. However, for administration via enteral feeding tube, the viscosity and the particle size of the suspension need to be carefully assessed to avoid potential tube blockage. In addition, the long feeding tubes present significant surface area for potential drug sorption. It is important to collect post-tube samples and verify the drug concentration.

Ora-Plus® is a commonly used suspension vehicle which is typically mixed with other sweetened and flavored vehicles for oral suspensions. Since taste is not a concern for dosing via enteral feeding tube, this study evaluated Ora-Plus® and water mixtures as potential vehicles for apixaban suspension. All three Ora-Plus® and water mixtures exhibited satisfactory flowability through the 10 French and 18 French tubes. For simplicity, the 50:50 mixture was recommended as the vehicle. When prepared by the traditional mortar/pestle method, the 0.25 mg/mL apixaban suspension in the 50:50 mixture vehicle exhibited satisfactory flowability and compatibility with the two commonly used types of enteral feeding tubes. The stability study also confirmed that

this suspension formulation was stable physically and chemically for up to seven days at room temperature.

The authors would like to point out two limitations of this study. First, the pill crusher and crushing syringe are convenient options for suspension preparations at patient bedside. This study confirmed that these methods can be used to prepare apixaban suspensions of acceptable dosage accuracy. However, the tube flowability was not evaluated due to limited time and resource. It is possible that these two methods may produce larger powder particles than the mortar/pestle method, which may cause blockage in narrow tubes. Secondly, this study only evaluated polyurethane and PVC enteral feeding tube materials. Silicone represents another commonly used tube material. However, the authors were unsuccessful at sourcing the silicone enteral feeding tubes during this study.

CONCLUSIONS

A suitable apixaban suspension for enteral feeding tube administration was identified as 0.25 mg/mL apixaban in 50:50 Ora-Plus®:water. This suspension was prepared from the 5 mg strength oral tablets using the traditional mortar/pestle. The apixaban suspension formulation exhibited satisfactory flowability via 10 and 18 French enteral feeding tubes with minimal sorption to the polyurethane and PVC tube materials. The beyond-use date of this apixaban suspension was established for up to seven days at room temperature.

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Table 1. Dosage accuracy and variability of apixaban suspensions prepared from three methods (n = 3 for each method).

Method	Concentration (mg/mL)	% Label Claim
Mortar/Pestle	0.247 ± 0.005	98.8 ± 2.0%
Pill Crusher	0.235 ± 0.007	94.0 ± 2.8%
Crushing Syringe	0.245 ± 0.017	98.0 ± 6.8%

Table 2. Compatibility of 0.25 mg/mL apixaban suspension with enteral feeding tubes by HPLC analysis (n = 3 for each tube type).

Tube	Sample	Concentration (mg/mL)	% Retained
Polyurethane 10 French, 36 inch	Pre-tube	0.244 ± 0.005	--
	Post-tube	0.240 ± 0.005	98.4%
PVC 18 French, 48 inch	Pre-tube	0.242 ± 0.002	--
	Post-tube	0.240 ± 0.003	99.4%

Table 3. Stability of 0.25 mg/mL apixaban suspension at room temperature by HPLC analysis (n = 3 for each time point).

Day	Concentration (mg/mL)	% Initial Concentration Remaining
0	0.252 ± 0.002	--
1	0.240 ± 0.005	95.0 ± 2.0%
3	0.250 ± 0.002	99.2 ± 0.8%
7	0.241 ± 0.003	95.6 ± 1.2%

Figure 1. Compounding devices used in the three methods to prepare apixaban suspensions from the 5 mg Eliquis tablets. Left to right: mortar/pestle, Silent Knight Pill Crusher®, and Welcon® Pill Crushing Enteral Irrigation Syringe. These methods are abbreviated as mortar/pestle, pill crusher, and crushing syringe throughout the text.

Figure 2. Nasogastric feeding tube mounted on a peg board for suspension flowability and compatibility evaluation.

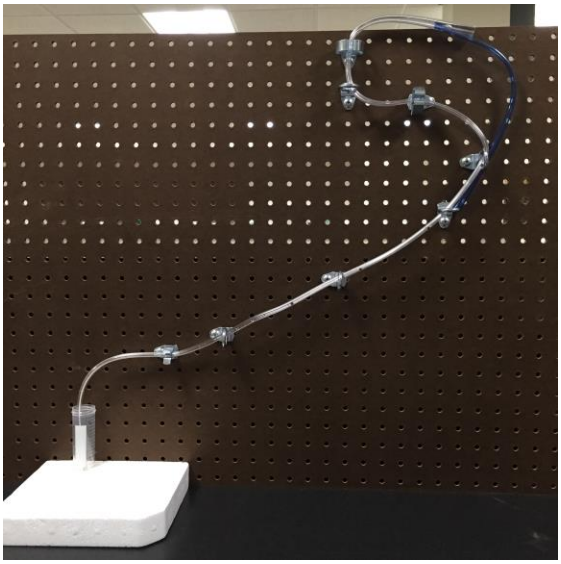
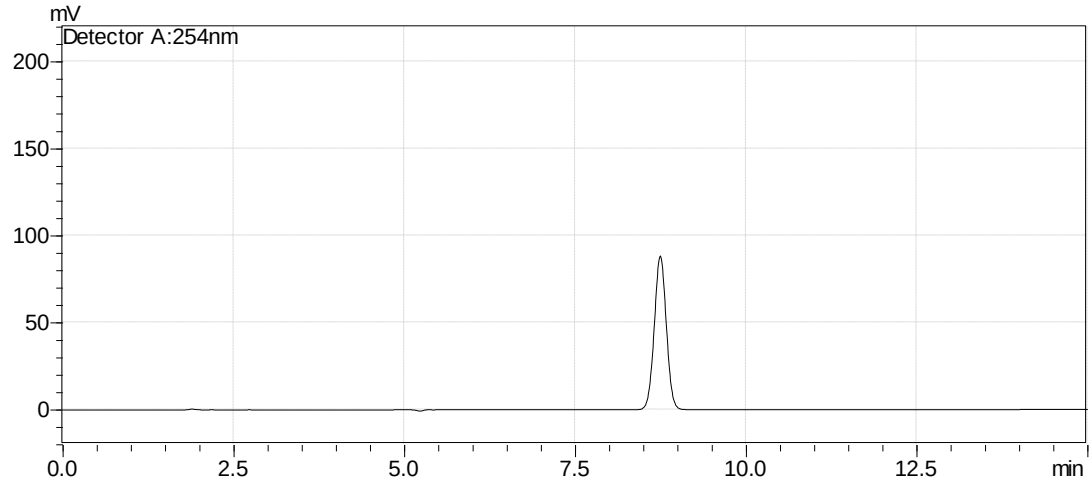
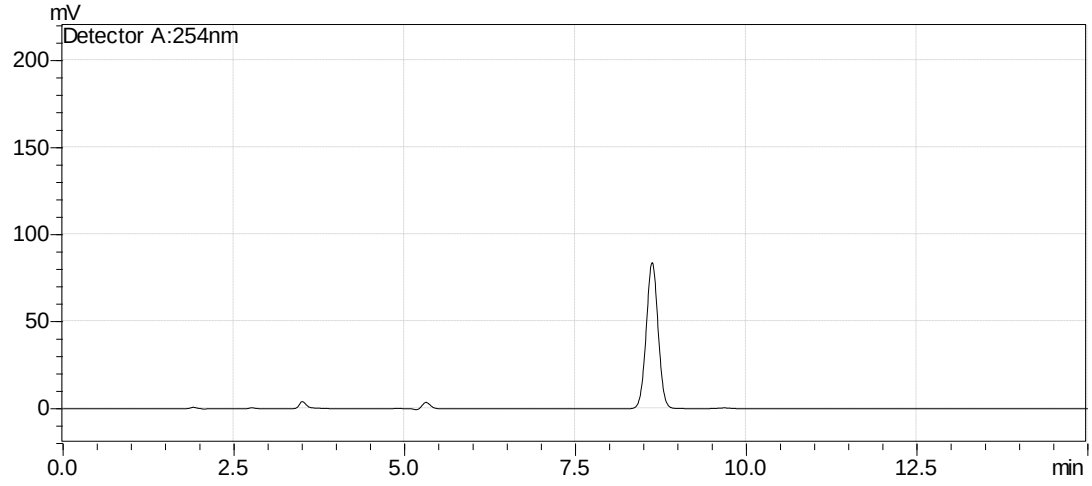


Figure 3. Representative HPLC chromatograms of the forced stability study of apixaban: (a) control at time 0; (b) pH 2 sample at 60°C for 7 days; (c) 3% H_2O_2 sample at 60°C for 7 days; (d) 3% H_2O_2 sample with direct sunlight exposure for 7 days. Note: the major peak at ~2 min in chromatograms (c) and (d) was mainly due to H_2O_2.

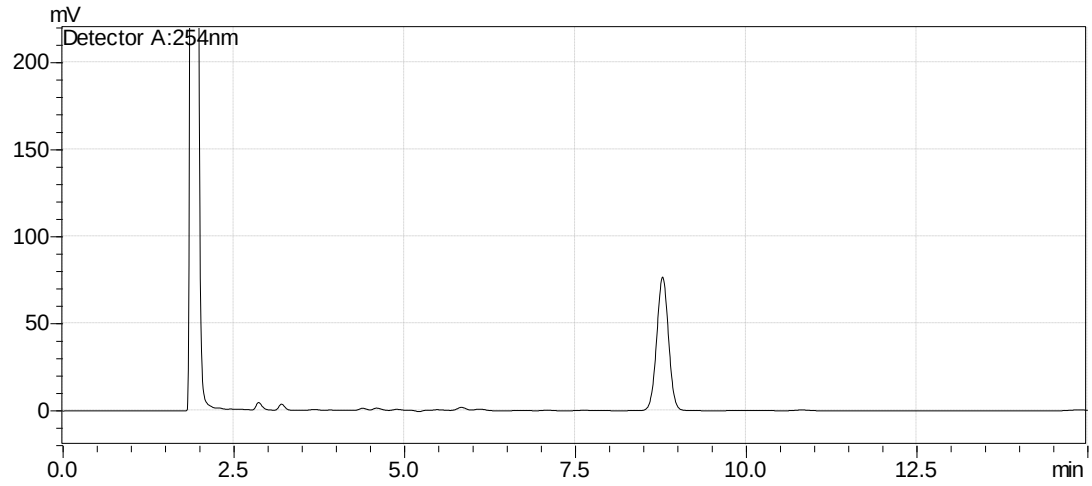
(a)



(b)



(c)


mV
Detector A:254nm
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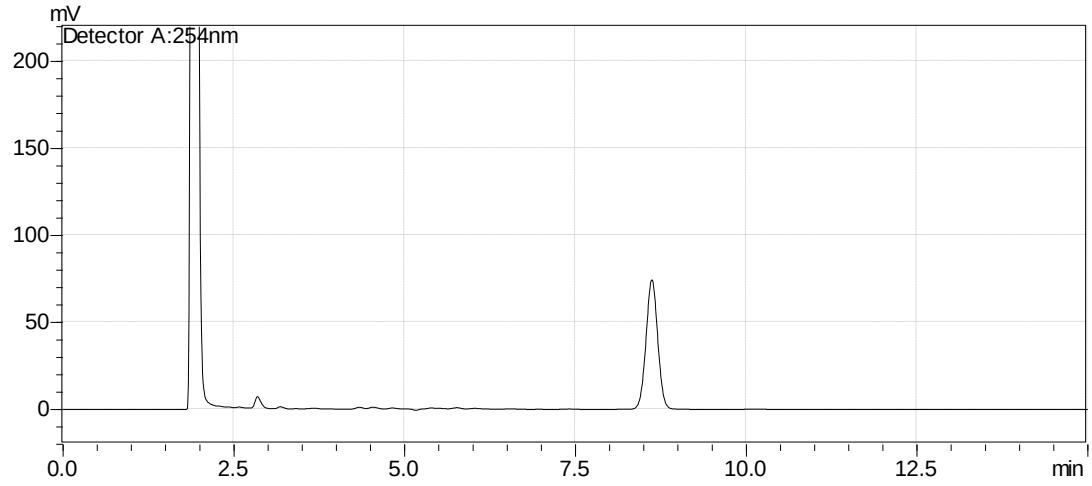
100
50
0
0.0
2.5
5.0
7.5
10.0
12.5
min

(d)


mV
Detector A:254nm
200
150
100
50
0
0.0
2.5
5.0
7.5
10.0
12.5
min