T3280 - 2012 AAPS Annual Meeting and Exposition (Chicago)

Establishing a Beyond Use Date for Compounded Norfloxacin Oral Suspension

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Abstract

Purpose: This study was conducted to determine a Beyond Use Date (BUD) for Compounded Norfloxacin Oral Suspension based on storage at ICH conditions for 60 days. USP General Chapter <795> requires a BUD for all compounded pharmaceutical preparations. This date differs from a commercial product expiration date since compounded preparations are intended for immediate use. In the absence of literature data for aqueous oral suspensions, the maximum BUD that can be assigned is 14 days.

Methods: Three batches of Norfloxacin Oral Suspension (20 mg/mL) were compounded by crushing commercial tablets and suspending the ground powder in Vehicle for Oral Solution, NF and Vehicle for Oral Suspension, NF (1:1) and then stored at 5ºC, 25ºC/60%RH, 30ºC/65%RH and 40ºC/75%RH in 2 oz. amber plastic prescription bottles. Samples were analyzed by high-performance liquid chromatography (HPLC) at time zero, 7 days, 14 days, 30 days and 60 days. An HPLC method based on the USP monograph for Norfloxacin was validated and used in this stability study.

Results: Analysis of the Norfloxacin Oral Suspension at each stability timepoint met the proposed USP requirements for Norfloxacin content of 90% - 110% of label claim (20 mg/mL). The average content at time zero was 102% and after 60 days storage decreased to 97.7%, 94.7%, 98.0%, and 97.3% for the 5ºC, 25ºC/60%RH, 30ºC/65%RH and 40ºC/75%RH conditions, respectively. Validation of the HPLC method used in the stability study met requirements for linearity, specificity and accuracy, repeatability, range, and ruggedness.

Conclusion: Based on the results of this study, the assignment of a 60 day BUD for Norfloxacin Oral Suspension (20 mg/mL) compounded in Vehicle for Oral Solution, NF and Vehicle for Oral Suspension, NF (1:1) was supported at all of the ICH storage conditions evaluated.

Introduction

Pharmacy compounding is increasing due to the number of drug shortages and also the introduction of the concept of personalized medicine. Implementation of requirements issued in USP Chapter <795> Pharmaceutical Compounding – Nonsterile Preparations and USP Chapter <797> Pharmaceutical Compounding – Sterile Preparations has resulted in heightened awareness about understanding the stability of compounded preparations. Commercially available products are assigned an expiration date by the manufacturer. A pharmacist must rely on available literature information or conduct costly studies to assign a Beyond Use Date (BUD) for compounded preparations or rely on the default limits established in the USP.

The purpose of this work was to determine the BUD for an oral suspension of norfloxacin prepared from commercially available norfloxacin tablets.

Materials

Norfloxacin 400 mg tablets (Noroxin® lot #s X4100, X4101 and X4102; Merck & Co., Inc., Whitehouse Station, NJ)
Vehicle for Oral Solution, NF (compounded)
Vehicle for Oral Suspension, NF (compounded)

Methods

Compounding

Compounded Norfloxacin Oral Suspension 20 mg/mL was prepared by grinding five (5) norfloxacin tablets, equivalent to 2 g of norfloxacin, in a mortar with a pestle until a fine powder was obtained. A 1:1 blend of Vehicle for Oral Solution, NF and Vehicle for Oral Suspension, NF was prepared and the drug powder was triturated with small portions to obtain a smooth paste. Increasing volumes of the vehicle blend were then added geometrically to obtain a pourable liquid. The contents of the mortar were transferred to a 100 mL volumetric flask, rinsing the mortar several times with additional vehicle blend, then bringing to final volume with additional vehicle blend. The contents were thoroughly mixed, then transferred into 2-oz amber, plastic, child-resistant, oval prescription bottles for stability testing.

HPLC Analytical Method

A high performance liquid chromatography (HPLC) method was developed for measuring norfloxacin content in Compounded Norfloxacin Oral Suspension based on the USP monograph for Norfloxacin. The conditions used for sample analysis were:

- Column: Supelco Discovery® C18, 25cm x 4mm, 5µm
- Column Temperature: 40ºC, +/- 1ºC
- Injection volume: 10 µL
- Flow Rate: 1.0 mL/min
- Detector: UV absorbance at 275 nm
- Pump Program: Isocratic
- Mobile Phase: phosphoric acid (1 in 1000):ACN (85:15)
- Sample Diluent: 0.1% v/v phosphoric acid in water

HPLC Method Validation

The appropriateness of the chromatographic method conditions were evaluated by assessing the following method performance parameters.

- Standard Stress Degradation
- Compounded Preparation Stress Degradation
- Filter Compatibility
- Linearity
- Specificity and Accuracy
- Repeatability
- Range
- Ruggedness

The method met or exceeded all validation criteria. An example chromatogram for the compounded preparation is shown in Figure 1 and the linearity standard curve is provided in Figure 2.

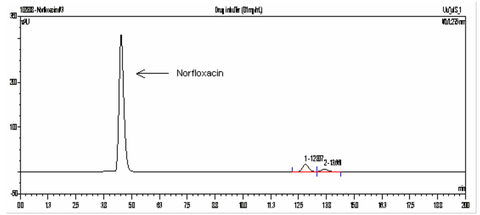

Figure 1 – Example Norfloxacin HPLC Chromatogram

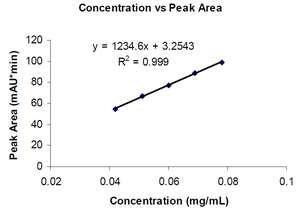

Figure 2 – Linearity Standard Curve

Experimental Design

Chemical Stability

Three batches of Compounded Norfloxacin Oral Suspension (100 mL), each prepared from a different lot of norfloxacin tablets, were packaged in 2-oz amber, plastic, child-resistant, oval prescription bottles and stored according to the stability protocol outlined in Table 1.

ºC / %RH	Release (Time 0)	7 Days	14 Days	30 Days	60 Days
5 / Ambient	X	X	X	X	X
25 / 60		X	X	X	X
30 / 65		X	X	X	X
40 / 75		NA	X	X	X

Table 1 – Storage Conditions and Stability Protocol

Results & Discussion

The stability data are presented in graphical format in Figures 3-6. The 95% confidence interval around the 25ºC/60%RH stability data (Figure 4) indicate a predicted BUD of slightly under 60 days at controlled room temperature. This is determined by where the lower confidence interval curve crosses the lower specification limit of 90% of labeled content. All other conditions evaluated (Figures 3, 5 and 6) predict a BUD greater than 60 days. Based on these data, assignment of a 60 day BUD should be considered. Although the controlled room temperature data were marginal, the exceptional accelerated data provide additional support for this conclusion.

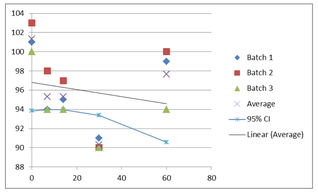

Figure 3 – 5ºC/Ambient Stability Data

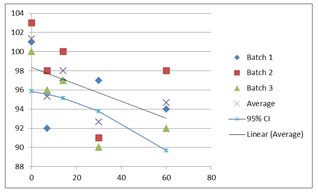

Figure 4 – 25ºC/60%RH Stability Data

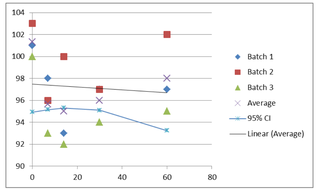

Figure 5 – 30ºC/65%RH Stability Data

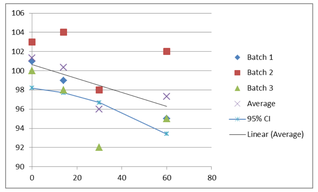

Figure 6 – 40ºC/70%RH Stability Data

Conclusions

Stability studies were conducted using three different batches of Compounded Norfloxacin Oral Suspension with a percent of label claim maintained between 90% and 104% which satisfies the proposed USP criteria (90.0% – 110.0%) for percent of label claim. The stability data support assignment of a 60 day BUD for Compounded Norfloxacin Oral Suspension in a 1:1 blend of Vehicle for Oral Solution, NF and Vehicle for Oral Suspension, NF.

Disclosures

- This work was supported by 2009 Grant Offering for Pharmaceutical Compounding from The United States Pharmacopeial Convention, Inc. (USP).
- Dr. Elder is a member of the 2010-2015 USP Compounding Expert Committee.
  - The information, views and opinions presented here are entirely those of the authors independent work and do not necessarily reflect the views of USP
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