T3385 - 2013 AAPS Annual Meeting and Exposition (San Antonio)

Establishing a Beyond Use Date for Compounded Marbofloxacin Oral Suspension

Marsha P. Pribadi, Karen J. Jones, M.S., Edmund J. Elder, Jr., Ph.D., R.Ph.

Zeeh Pharmaceutical Experiment Station, School of Pharmacy, University of Wisconsin – Madison

Abstract

Purpose: USP General Chapter <795> requires a Beyond Use Date (BUD) for all compounded pharmaceutical preparations. In the absence of literature data, the maximum BUD that can be assigned for an aqueous oral suspension is 14 days. This study was conducted to determine a BUD for Compounded Marbofloxacin Oral Suspension (MOS) in three conventional suspension vehicles stored at ICH conditions up to 3 months.

Methods: MOS was compounded by crushing tablets and suspending the ground powder in: 1:1 mixture of Ora-Sweet/Ora-Plus (OS/OP), Syrup NF, and OraBlend. Formulations were stored at 5C, 25C/60%RH, 30C/65%RH and 40C/75%RH in 2 oz amber plastic prescription bottles. Samples were analyzed by HPLC at time zero, 1 week, 1 month, 2 months and 3 months. An HPLC method was developed based on review of the literature and passed requirements for linearity, reproducibility, and accuracy.

Results: Analysis of the MOS at each stability timepoint was compared to the proposed USP specification for Marbofloxacin content of 90% - 110% of label claim (20 mg/mL). The Syrup and OraBlend formulations showed low and/or highly variable results for all timepoints (92.6% +/- 6.8% and 90.0% +/- 0.8%, at time zero respectively). The average content in OS/OP at time zero was 97.3%. This formulation met the proposed specifications through 2 months storage at 25/60, 30/65 and 40/75 conditions (95.5%, 95.1%, and 91.1%, respectively), but did not meet specifications when stored at 5C (110.7% LC at 2 months). Regression analysis was conducted on the data and a 95% confidence interval was calculated. The BUD for MOS was 12 weeks at the 25/60 storage condition. This was supported by accelerated conditions where the BUD was 19 weeks at 30/65 and 14 weeks at 40/75 storage conditions, but the BUD at 5C was only 7 weeks.

Conclusion: Based on the results of this study, the assignment of a 60 day BUD for MOS compounded in OS/OP was supported when stored at controlled room temperature. The compounded preparation should not be refrigerated. Further evaluation of Marbofloxacin Oral Suspension in other compounding vehicles is needed due to the inconclusive results obtained for Syrup and OraBlend.

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 <795> Pharmaceutical Compounding – Nonsterile Preparations and USP <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 oral suspensions of marbofloxacin prepared from commercially available marbofloxacin tablets for veterinary use.

Materials

Marbofloxacin 100 mg tablets (Zeniquin® lot # PF08085, Pfizer Animal Health)
OraBlend (lot # 1356750, Paddock Labs)
OraPlus (lot # 1417226, Paddock Labs)
OraSweet (lot # 1346657, Paddock Labs)
Syrup, NF (compounded)

Methods

Compounding

Marbofloxacin Oral Suspension 20 mg/mL was compounded in three vehicles for stability comparison: OraBlend, OraSweet/OraPlus 1:1, or Syrup NF. Each suspension was compounded by grinding twenty (20) marbofloxacin tablets (equivalent to 2 g marbofloxacin) in a mortar with a pestle into a coarse powder. Film coating was separated by passing the ground material through a 10 mesh screen. The screened powder was returned to the mortar and further ground into a fine powder, wetted with a few drops of glycerin NF, then triturated with small portions of vehicle to obtain a smooth paste. Increasing volumes of the vehicle were 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, then bringing to final volume with vehicle. 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 marbofloxacin content in Marbofloxacin Oral Suspension based on the USP monograph for Marbofloxacin. The conditions used for sample analysis were:

- Column: Supelco Discovery® C18, 5µm, 250 x 4.6mm
- Column Temperature: 40ºC, +/- 1ºC
- Injection volume: 10 µL
- Flow Rate: 1.0 mL/min
- Pump Program: Isocratic
- Detector: UV absorbance at 300 nm
- Mobile Phase: ACN / 0.1% H_3PO_4 (10:90)
- Sample Diluent: 0.02M, pH 7.0 phosphate buffer

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 HPLC method met all validation criteria. An example chromatogram is shown in Figure 1 and the linearity standard curve is provided in Figure 2.

Figure 1 – Example Marbofloxacin HPLC Chromatogram

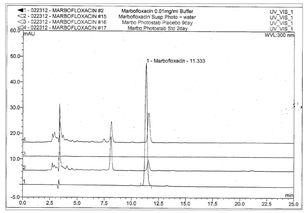
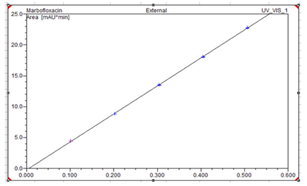


Figure 2 – Linearity Standard Curve



Experimental Design

Chemical Stability

Marbofloxacin Oral Suspension compounded in each vehicle, was packaged in 2-oz amber, plastic, child-resistant, oval prescription bottles and stored according to the stability protocol outlined in Table 1.

Table 1 – Storage Conditions and Stability Protocol

ºC / %RH	Release (Time 0)	7 days	30 days	60 days	90 days
5 / ambient	X	X	X	X	X
25 / 60		X	X	X	X
30 / 65		X	X	X	X
40 / 75			X	X	X

Figure 3 – 25ºC/60%RH Stability Data in OraSweet/OraPlus 1:1

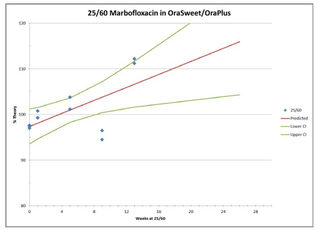


Figure 4 – 30ºC/65%RH Stability Data in OraSweet/OraPlus 1:1

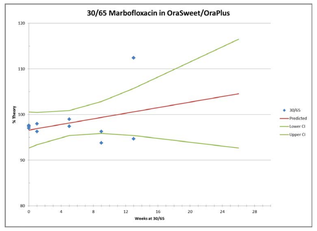


Figure 5 – 25ºC/60%RH Stability Data in OraBlend

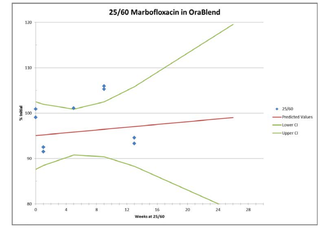
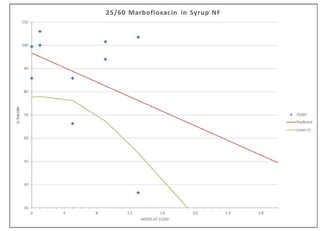


Figure 6 – 25ºC/60%RH Stability Data in Syrup NF



Results & Discussion

The stability data are presented in graphical format in Figures 3-6. Regression analysis was conducted on the data and a 95% confidence interval (CI) was calculated. The 95% CI around the stability data indicate a predicted BUD where the lower or upper CI curve crosses the specification limit of 90% or 110% of labeled content (20 mg/mL), respectively.

Based on this 90 day stability study, only the OraSweet/OraPlus formulation provided support for the assignment of a BUD beyond the default 14 days specified in USP <795> for aqueous preparations. The 25/60 data (Figure 3) indicate a BUD of ~11.5 weeks and the 30/65 data (Figure 4) predict a BUD of ~18.5 weeks. Based on this data a 60 day BUD is recommended for Marbofloxacin Oral Suspension compounded in OraSweet/OraPlus and stored at controlled room temperature.

The OraBlend formulation (Figure 5) showed highly variable assay results at all conditions tested. The Syrup NF formulation (Figure 6) showed highly scattered assay results. The variability may be due to the limited volume of suspension prepared; however, neither of these vehicles would currently be recommended for compounding Marbofloxacin Oral Suspension. All formulations had a notable increase in grittiness as they aged, especially when stored at 5°C.

Conclusions

Stability studies were conducted on three different formulation vehicles for Compounded Marbofloxacin Oral Suspension. The stability data support assignment of a 60 day BUD for Compounded Marbofloxacin Oral Suspension in a 1:1 blend of OraSweet and OraPlus when stored at controlled room temperature. The suspension should not be refrigerated.

Disclosure

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.
- Information presented should not be construed as an official explanation or interpretation of USP Standards.