# Stability of Amoxicillin 50 mg/mL Suspension in Oral Mix/Oral Syrup or Ora-Sweet/Ora-Plus in Plastic Oral Syringes and Plastic Amber Bottles at 4°C and 25°C

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## INTRODUCTION

Amoxicillin suspension is one of the most commonly used antibiotics, especially in pediatric patients to treat a variety of different bacterial infections. There are typically multiple different manufacturers of this product generally ensuring a good market supply in Canada.

In the fall of 2022, there was a sudden backorder of all brands of amoxicillin suspension which necessitated the use of other antibiotics with possibly broader spectrum than required with the potential for creating increased antibiotic resistance.

The commercial availability of amoxicillin capsules was minimally affected, however no stability information was found in the literature regarding preparing or the stability of extemporaneous compounded suspension formulations.

## OBJECTIVES

To evaluate the stability of an extemporaneously prepared amoxicillin suspension in Medisca Oral Mix/Oral Syrup (MOMOS) and Perrigo Ora-Sweet/Ora-Plus (POSOP) stored in amber polyethylene terephthalate (PET) bottles at 4°C and 25°C for 18 days and polypropylene syringes at 4°C and 25°C for 18 days

The concentration of amoxicillin was evaluated during storage at each temperature using a validated, stability indicating, liquid chromatographic method using UV detection.

**Table 1. Percent Remaining of the Initial Amoxicillin Concentration when stored in Refrigerator (4°C) and at Room Temperature (25°C).**

| Study Arm → / Study Tests and Results ↓ | MOMOS PET 4°C | POSOP PET 4°C | MOMOS PET 25°C | POSOP PET 25°C | MOMOS Oral Syringe 4°C | POSOP Oral Syringe 4°C | MOMOS Oral Syringe 25°C | POSOP Oral Syringe 25°C |
|---|---|---|---|---|---|---|---|---|
| Nominal Initial Concentration (mg/mL) | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 |
| Study Day 0 (% of Day 0 ± CV) | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 |
| Study Day 2 (% of Day 0 ± CV) | 99.6 ± 3.9 | 102.5 ± 1.5 | 98.6 ± 2.3 | 99.3 ± 2.1 | 97.3 ± 1.0 | 97.7 ± 3.1 | 97.0 ± 1.4 | 105.4 ± 0.9 |
| Study Day 5 (% of Day 0 ± CV) | 102.1 ± 4.0 | 101.8 ± 1.9 | 102.4 ± 1.7 | 101.6 ± 3.8 | 104.1 ± 0.8 | 104.0 ± 1.3 | 98.1 ± 0.3 | 103.4 ± 1.0 |
| Study Day 7 (% of Day 0 ± CV) | 103.0 ± 3.6 | 99.2 ± 2.7 | 101.7 ± 2.3 | 100.3 ± 4.6 | 103.4 ± 0.1 | 104.9 ± 0.8 | 92.8 ± 0.7 | 99.5 ± 1.4 |
| Study Day 9 (% of Day 0 ± CV) | 104.5 ± 2.7 | 102.2 ± 3.1 | 99.8 ± 5.3 | 101.3 ± 2.8 | 104.3 ± 0.5 | 103.6 ± 0.5 | 93.9 ± 0.6 | 104.9 ± 0.5 |
| Study Day 11 (% of Day 0 ± CV) | 103.1 ± 3.3 | 102.1 ± 4.0 | 100.4 ± 5.4 | 100.7 ± 4.3 | 107.4 ± 0.2 | 106.3 ± 0.8 | 98.1 ± 2.1 | 97.3 ± 1.0 |
| Study Day 14 (% of Day 0 ± CV) | 96.3 ± 2.4 | 104.1 ± 2.4 | 101.0 ± 2.0 | 102.6 ± 3.1 | 103.7 ± 0.6 | 106.1 ± 0.7 | 93.0 ± 1.3 | 98.0 ± 3.1 |
| Study Day 18 (% of Day 0 ± CV) | 97.7 ± 4.1 | 103.2 ± 3.0 | 97.4 ± 4.2 | 95.1 ± 1.8 | 99.9 ± 0.7 | 103.7 ± 0.7 | 98.2 ± 0.7 | 94.3 ± 1.0 |
| Slope (Degradation Rate %/day) | -0.158 | 0.163 | -0.080 | -0.122 | 0.168 | 0.337 | -0.134 | -0.451 |
| Fastest Slope 95 % CI | -0.600 | -0.044 | -0.335 | -0.475 | -0.336 | -0.025 | -0.571 | -0.919 |
| Slowest Slope 95 % CI | 0.283 | 0.370 | 0.175 | 0.232 | 0.672 | 0.700 | 0.302 | 0.017 |
| Shortest time to 90 % of day 0 concentration at 95% CI (Days) | **16.7** | **227.6** | **29.8** | **21.0** | **29.7** | **392.7** | **17.5** | **10.9** |

## METHODS

**Liquid Chromatographic Method**

The liquid chromatographic system consisted of 95% 0.05M potassium phosphate monobasic with 5 % Methanol which was pumped through 150mm x 4.6mm reverse-phase C18, 4µm column (Aligent Poroshell 120 EC) at 1.0 mL/min. The effluent was monitored with UV detection at 226 nm. Injection volume was 10uL

**Assay Validation**

The method was evaluated to ensure reproducibility, accuracy and specificity. The system was shown to be capable of separating amoxicillin from its degradation products (Figure 1). Accuracy and reproducibility of standard curves was tested over 5 days. Inter- and intra-day errors of reproducibility were assessed by the coefficients of variation and the standard deviation of regression.

**Stability Study**

On study day 0, Amoxicillin 500 mg capsules (Teva, Lot: 35449458A, Expiry: 08-25) were opened and used to prepare 50 mg/mL amoxicillin oral suspensions by levigating with Medisca Oral-Mix/Oral Syrup (MOMOS) in an 80:20 ratio as well as Perrigo Ora-Sweet/Ora-Plus (POSOP) in a 60:40 ratio. Three units of each temperature and suspending agents were stored at 4°C and 25°C in 100 mL amber PET bottles. In addition, oral syringes were prepared for each suspending agent 5 mL in a 12 mL syringe and stored at room temperature only. Concentrations and physical inspection were completed on days 0,2,5,7,9,11,14,18.

**Data Reduction and Statistical Analysis**

The concentration of a solution on a particular day was considered "acceptable" or "within acceptable limits" if it was greater than 90% of the initial concentration (as determined on day 0) with 95% confidence. Chemical stability was calculated using the lower limit (highest degradation) of the observed degradation rate with 95% confidence and the time to achieve 90% of the initial concentration. Analysis of variance was used to test differences in degradation rate between the different storage temperatures and concentrations. The 5% level was used as the *a priori* cut-off for significance.

## RESULTS

**Assay Validation**

Assay validation demonstrated that degradation products are separated from Amoxicillin (Figure 1). The analytic method separated degradation products from amoxicillin such that the concentration was measured specifically, accurately (deviation from known averaged 1.35%) and reproducibly (within day variation averaged 0.31%; between day variation averaged 1.12%).

**Figure 1. Representative Chromatograms**

Chromatogram A represents a suspension of 50 mg/mL of Amoxicillin on day 0 after degradation by Sodium Hypochlorite.

Chromatogram B shows the Amoxicillin standard of 50 mg/mL on day

Chromatogram C represents a suspension of Amoxicillin 50 mg/mL stored at Room Temperature in a plastic syringe for 18 days.

Amoxicillin eluted at 5.2 minutes and degradation products eluted at 4.5 and 6.8 minutes.

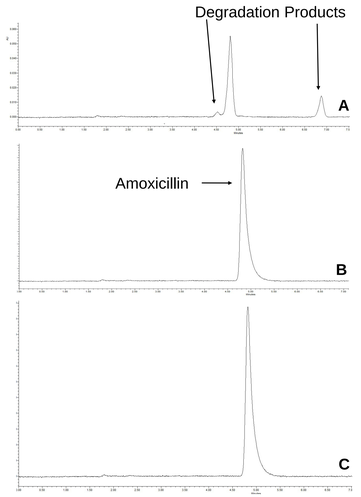


**Table 2. Physical Stability of Amoxicillin Suspensions over time**

| Study Arm / Study Tests and Results | MOMOS PET 4°C | POSOP PET 4°C | MOMOS PET 25°C | POSOP PET 25°C | MOMOS Oral Syringe 4°C | POSOP Oral Syringe 4°C | MOMOS Oral Syringe 25°C | POSOP Oral Syringe 25°C |
|---|---|---|---|---|---|---|---|---|
| Study Day 0 | Homogeneous ND | Homogeneous ND | Homogeneous ND | Homogeneous ND | Homogeneous ND | Homogeneous ND | Homogeneous ND | Homogeneous ND |
| Study Day 2 | Homogeneous ND | Homogeneous ND | Homogeneous ND | Homogeneous ND | Homogeneous ND | Homogeneous ND | Homogeneous ND | Homogeneous ND |
| Study Day 5 | Homogeneous ND | Homogeneous ND | Homogeneous SY | Homogeneous SY | Homogeneous ND | Homogeneous ND | Homogeneous SY | Homogeneous SY |
| Study Day 7 | Homogeneous ND | Homogeneous ND | Separated Y | Separated Y | Homogeneous ND | Homogeneous ND | Separated Y | Separated Y |
| Study Day 9 | Separated ND | Separated ND | Separated Y | Separated Y | Separated ND | Separated ND | Separated Y | Separated Y |
| Study Day 11 | Separated ND | Separated ND | Separated Y | Separated Y | Separated ND | Separated ND | Separated Y | Separated Y |
| Study Day 14 | Separated ND | Separated ND | Separated Y | Separated Y | Separated ND | Separated ND | Separated Y | Separated Y |
| Study Day 18 | Separated ND | Separated ND | Separated Y | Separated Y | Separated ND | Separated ND | Separated Y | Separated Y |

Legend: No discolouration (ND), Slightly Yellow (SY), Yellow (Y)

**Chemical Stability Results (See Table 1)**

Univariate analysis identified temperature ($p<0.001$) and formulation ($p=0.045$) as significant predictors for percent remaining, but not container ($p=0.88$) or study day ($p=0.19$).

**Physical Stability Results (See Table 2)**

Colour changes were noted for suspensions stored at 25°C beginning on day 5 but not for suspensions stored at 4°C.

The suspension separated into two layers on day 7 for samples stored at 25°C and day 9 for samples at 4°C but easily re-formed a homogenous suspension after vigorous shaking.

## CONCLUSIONS

The amoxicillin suspensions stored in PET bottles for both formulations and temperatures are chemically stable for at least 16 days.

Amoxicillin suspensions stored in plastic oral syringes for both formulations and temperatures are chemically stable for at least 10 days.

We recommend storage in the refrigerator to limit microbial growth, minimize colour change and improve physical stability. Should physically instability occur, re-suspension is easy to achieve by vigorous shaking and does not adversely affect chemical stability. Storage at room temperature would not adversely affect chemical stability subject to the limits described above.

BUDs assigned by compounders should incorporate microbial standards as described by relevant regulatory bodies in addition to the physical and chemical stability of the suspension.

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## DISCLOSURES

Authors of this poster have the following to disclose concerning possible personal or financial relationships with commercial entities that may have direct or indirect interest in the subject matter of this presentation:

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