Utilization of a Moisture Barrier Film Coating to Enhance In-Use Tablet Stability

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Purpose

It is common practice for pharmacists or patients to remove medicines from their primary packaging and dispense into alternate containers holding the required quantity of dosages for the prescribed regimen. Once medicine is removed from its primary packaging, protection of the active pharmaceutical ingredient (API) from detrimental effects of the environment is compromised and degradation of the API may occur. In 2001, The European Agency for the Evaluation of Medicinal Products (EMA) issued a Note for Guidance on In-use Stability Testing of Human Medicinal Products.[1] This guidance proposes stability studies to ensure product quality for a period of time after the container is opened simulating the expected duration and use of the opened product. Based on the EMA guidance, this study examines the potential for film coating to provide enhanced stability of amoxicillin-clavulanic acid fixed-dose combination tablets, once they have been removed from their primary packaging and placed into an in-use tablet dispenser.

Methods

Amoxicillin and clavulanic acid are combined to produce an antibiotic with an increased spectrum of action against some amoxicillin-resistant bacteria. A fixed-dose combination of amoxicillin 875 mg and clavulanic acid 125 mg was selected for this study due to the high sensitivity of clavulanic acid to moisture. The uncoated tablets and tablets coated to a 4% weight gain (WG) with either an HPMC-based Opadry® coating or PVA-based Opadry® amb II moisture barrier film coating (Colorcon Inc.) were packaged in Aclar blisters at the time of manufacture. Tablets were later removed from their primary packaging (Figure 1) and placed into the plastic, hinged lid, multi-chamber tablet dispensers favored by many consumers. The dispensers were stored in a 25°C/60% RH chamber for the prescribed ten-day regimen (Figure 2). Initially, and every 2 days thereafter, tablets were removed from the dispensers and assayed according to the USP method.

Figure 1. Removal of Tablets from Primary Packaging (Opadry amb II coated

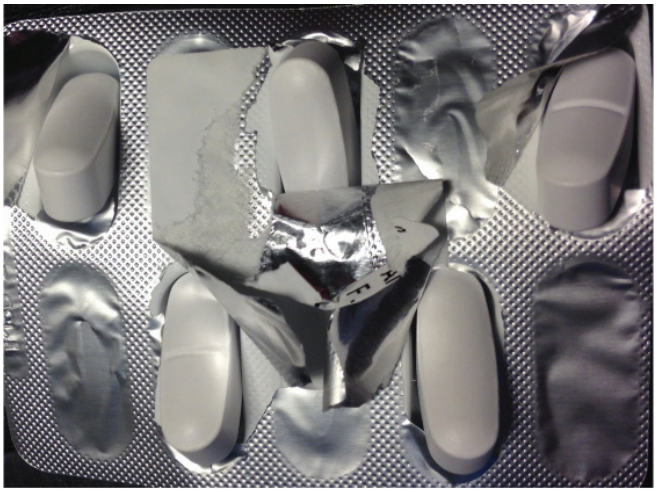


Figure 2. Tablet Storage Configuration

Results

The Opadry amb II coated tablets passed USP assay requirements for both amoxicillin and clavulanic acid across the ten-day storage period at 25°C/60% RH. However, significant degradation of the clavulanic acid was observed for uncoated and HPMC-coated tablets, which failed the USP assay specification of 90-120%, within 4 days. After ten days, no clavulanic acid remained in the uncoated or HPMC coated tablets. Amoxicillin levels decreased by >10% within ten days in the uncoated or HPMC coated tablets. (Figures 3 and 4).

Figure 3. Clavulanic Acid Assay (%) vs Storage Time (Days)

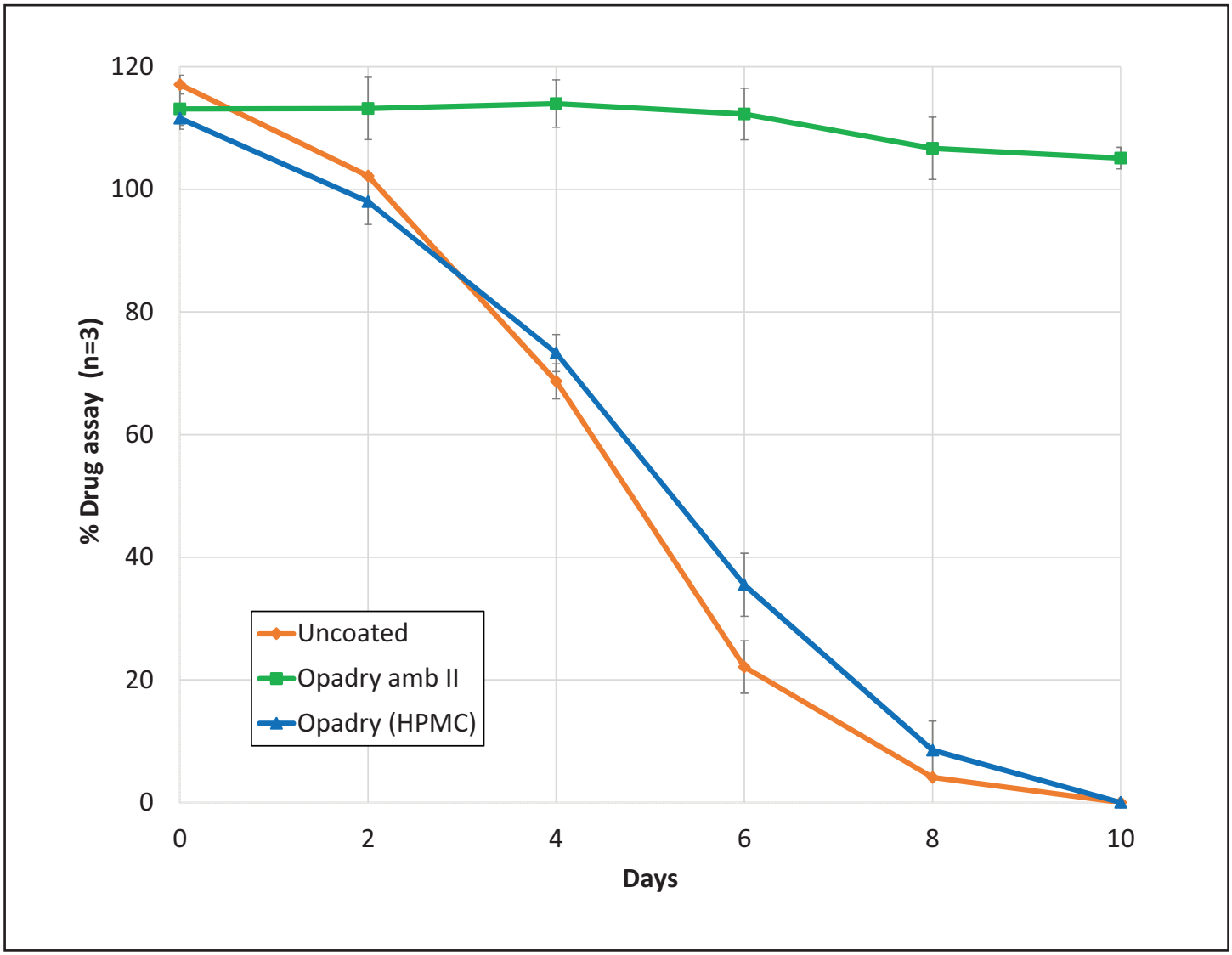
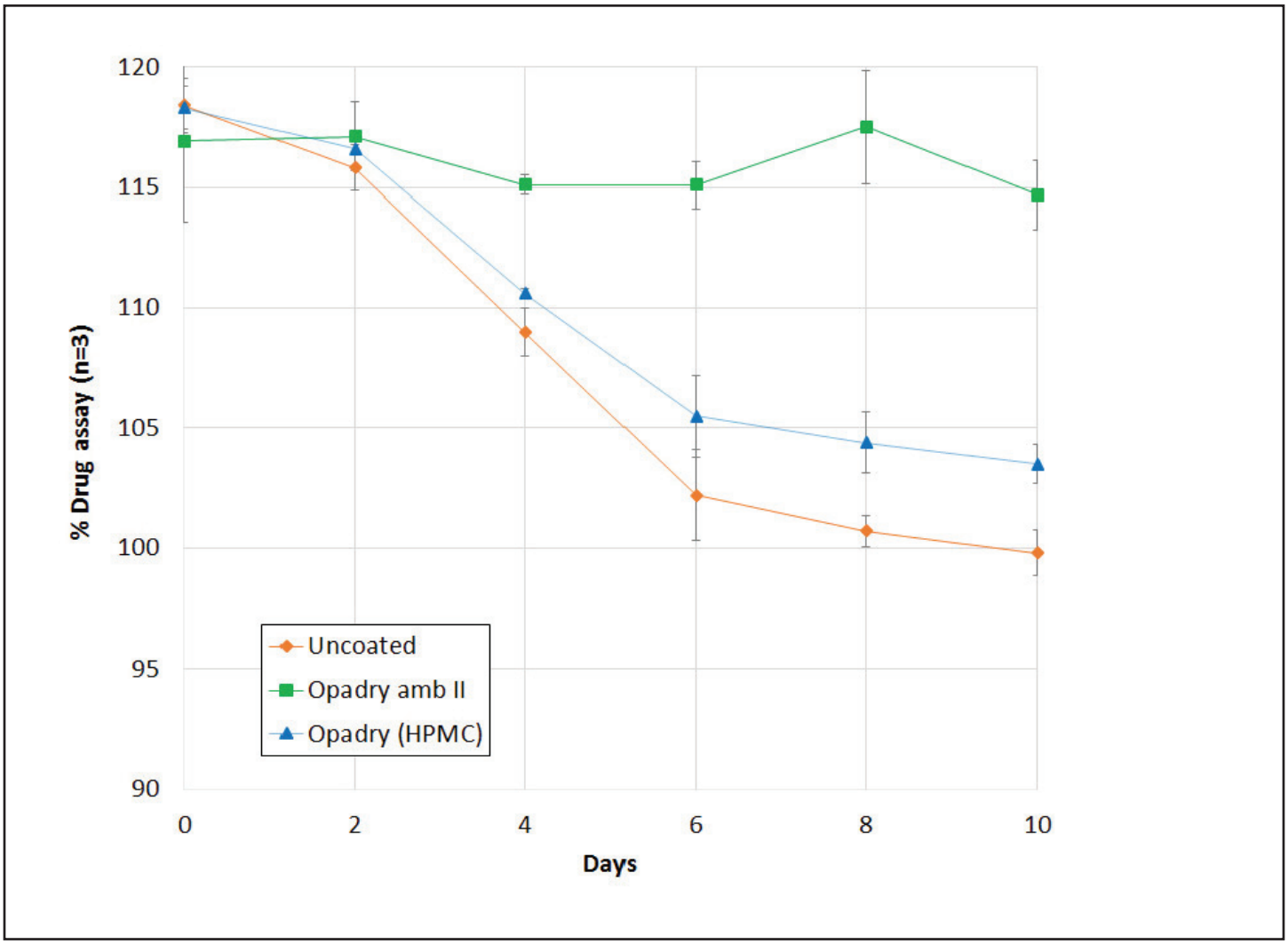


Figure 4. Amoxicillin Assay (%) vs Storage Time (Days)



Conclusions

Many types of packaging configurations (bottles, PVC / Aclar / Alu blisters etc.) are available to protect moisture sensitive APIs to varying levels, but they are only effective when the packaging is unopened. This study demonstrated the detrimental effects, of even short-term exposure to the environment on the assay of the clavulanic acid, after removal from the packaging. The Opadry amb II coating provided a safeguard to ensure product stability, even after tablets were removed from their primary packaging.

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