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Short communication

Origin assessment of an unknown impurity in two drug products packed in LDPE bottles – a case study

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Introduction

Pharmaceutical packaging is an indispensable component of medications, consisting of a collection of packaging components made from various materials (Ibrahim et al., 2022; Lv et al., 2025). Plastic packaging materials have become the preferred choice for various drugs containers used for medication processing, storage or delivery, because they are user-friendly with low costs (Zhang et al., 2016). However, when a drug substance or a solution directly contacts plastic packaging, leachable or extractable chemicals may be released into drugs causing contamination and raising safety concerns for the patient (Pan et al., 2011; Zhang et al., 2016). The presence of these chemicals in drug products may result in reduced shelf-life, compromised drug efficacy, impaired drug product physical stability or pose a direct safety risk to patients due to toxicity. Consequently, comprehensive assessment and characterization of these impurities is important to assure product quality, safety and efficacy (Kuzmič et al., 2026).

The aim of our study was to perform an source assessment of an unknown impurity detected in two drug products packaged in transparent low-density polyethylene (LDPE) dropper bottles fitted with polypropylene (PP) screw caps.

Materials and methods

The impurity profile of two solutions for local application, product A and product B, containing α-adrenergic agonists, packed in LDPE dropper bottles fitted with PP screw caps, were evaluated.

ACN, acetic acid, glacial, sodium octane sulfonate and ammonium acetate were of HPLC grade. Deionized water was used throughout entire analyses. Secondary reference standards of the APIs were obtained from Alkaloid, AD, Skopje whereas reference standards for the impurity profile of the investigated drug products were obtained from Ph. Eur, USP and LGC. In order to verify impurity source, accelerated stability studies were performed under the following conditions: Case 1: Product A and Product B packaged in LDPE bottles with PP caps, without labels; Case 2: Product A and Product B packaged in LDPE bottles with PP caps, with a low migrating paper label applied; Case 3: Product A and Product B packaged in LDPE bottles with PP caps, with a low migrating polypropylene label applied and Case 4: Product A and Product B packaged in LDPE bottles with PP caps with a polyethylene label applied. Samples were stored at 40°C±2°C/75%RH±5%RH and the analysis was performed at the beginning of the study, after 3 and after 6 months, using in-house HPLC methods. For product A, analysis was carried out on a C8 column (250 x4.0 mm, 4µm) and a mobile phase consisting of

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mixture A (sodium octane sulfonate in a mixture of 5 mL acetic acid, glacial and 700 mL deionized water) and ACN (70:30, *v/v*), at a flow rate of 1.0 mL/min. UV detection was performed at 280 nm and the injection volume was 20 µL. For Product B, chromatographic separation was performed using a cyano column (250 x 4.6 mm, 5µm) and a mobile phase composed of acetic buffer (pH 5.0) and acetonitrile (70:30, *v/v*). The flow rate was 1.0 mL/min, the injection volume was 100 µL, the UV detection was at 220 nm. All samples were prepared in accordance with the prescribed procedures for test solution preparation as described in the respective in-house methods.

Results and discussion

The impurity profile analysis for both products, obtained after the predictive stability studies, revealed a peak of an unknown impurity. After its UV spectrum analysis, it was determined that impurity was identical in both products, leading to the hypothesis that it could be a migrating impurity.

The impurity profile evaluation for Product A showed that at the beginning, in all four cases, the peak of interest was not detected. After 3 months, the presence of the peak of the unknown impurity was observed in all cases, with the highest level detected in samples from Case 4. In the rest of the investigated cases the levels of the unknown impurity were comparable. After 6 months, the peak of interest did not show further increase. Specifically, in Cases 1, 2, and 3, the impurity level remained stable, whereas in Case 4, a decrease in peak area was observed. Additionally, a subset of samples, which had been stored for 4.5 months under the conditions previously described, were transferred to glass containers and placed in a stability chamber at 40°C±2°C/75%RH±5%RH for an additional 1.5 months. Analysis of these samples (4.5 months under initial conditions followed by 1.5 months in glass packaging) demonstrated a reduction and disappearance of the unknown impurity peak. This observation suggests the potential occurrence of secondary degradation of the impurity in question. The evaluation of Product B showed that, at the beginning, a clearly defined peak was present in samples from Case 4, whereas in the other three cases an elevation of the baseline with a poorly defined peak was observed. After 3 and after 6 months, the unknown impurity was detected in all four cases. However, no increase in the impurity level was observed at the 6-month time point. In contrast, samples from Case 4 exhibited a significant decrease in impurity levels compared to the results obtained after 3 months.

Conclusion

Based on the results obtained from our study it can be concluded that the origin of the unknown impurity is the LDPE container itself, given that the peak of interest was detected even in Case 1. The possibility that the impurity originates from the cap can be excluded, since the samples were stored unopened in an upright position, and therefore the product was not in direct contact with the cap. The stabilization and in some cases the decrease in the investigated impurity levels between 3 and 6 months suggests the possibility of secondary degradation of the impurity.

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