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Short communication

Analytical investigation of a preservative - excipient interaction in an oral solution pharmaceutical product

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Introduction

Liquid oral dosage forms often contain complex combinations of active pharmaceutical ingredients (APIs), preservatives, sweeteners, and buffering agents in order to ensure adequate stability, palatability, and microbiological quality. Among commonly used preservatives, parabens are widely favored because of their broad antimicrobial activity and historical safety record. Likewise, sugars and sugar-based excipients are frequently incorporated as sweetening and viscosity-modifying agents in pediatric and geriatric formulations.

Despite their widespread use, the chemical compatibility of parabens with other formulation components is known to be influenced by pH, excipient composition, and microenvironmental effects. Previous studies have shown that parabens are susceptible to base-catalyzed hydrolysis, leading to the formation of p-hydroxybenzoic acid and subsequent secondary reactions, particularly in the presence of certain excipients such as sugars and buffers (Ma et al., 2002). Such interactions are of particular relevance in oral solutions, where all components coexist in a fully dissolved state and reaction kinetics may differ significantly from those in solid dosage forms (Kabrane et al., 2015)

During routine HPLC analysis of an oral solution formulation, a group of unknown peaks was detected and subsequently linked to an interaction between methylparaben (MP) and the sugar excipient under mildly basic conditions. Notably, the extent of this interaction was observed to be greater in the presence of the API compared with the placebo formulation, indicating a potential catalytic or microenvironmental contribution of the API. This article describes the analytical investigation of this interaction, discusses the underlying chemical mechanisms, and highlights formulation considerations relevant to the development and stabilization of paraben-preserved oral liquid products.

Materials and methods

Two different formulations of oral solution were analyzed for related and degradation products. Trial 01 consisted of API, sucrose (sweetener / viscosity building agent), MP, propylparaben (PP) (preservatives), citric acid monohydrate, sodium hydroxide (pH adjusting agents), cherry flavor and water (solvent). Trial 02 consisted of API, Sodium carboxymethylcelullose (viscosity building agent), potassium sorbate (preservative), citric acid monohydrate, sodium citrate dihydrate (pH adjusting agents), cherry flavor and water (solvent).

The laboratory trials, along with placebo, were analyzed at an initial time point, and analyzed again after storage in stability chambers for 30 days at 25°C / 60% RH and 40°C / 75% RH.

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Quantification was performed on UHPLC Thermo Vanquish Flex system, with an in house HPLC method. All reagents used were of analytical HPLC grade. Zorbax Eclipse XDB C18; 150 x 4.6 mm; 3.5 µm HPLC Column was used for analysis. The mobile phase consisted of a mixture of 50 mM phosphate buffer (prepared with potassium dihydrogen phosphate) adjusted to pH 3.0 with ortho-phosphoric acid and methanol. The method employed gradient programme, with run time of 30 minutes, and injection volume of 20 µL. The detection wavelength was 254 nm.

The samples were prepared by diluting 1 ml oral solution to 10 ml volume with a diluent consisting of phosphate buffer pH 3.0 and methanol in a ratio of 88:12 (v:v). The final concentration of API in the analysed samples was 0.6 mg/ml.

Results and discussion

The comparative impurity profiles of both formulations demonstrated that Trial 01 showedseveral unknown peaks, with higher peak areas in the sample compared to the placebo solution, indicating the formation of degradation products. These peaks further increased after one month of storage under stability conditions, especially when stored at 40°C / 75% RH. In contrast, Trial 02 showed no detectable unknown impurities either initially or after storage, suggesting a more stable composition.

In order to investigate the origin of the unknown peaks, systematic compatibility studies with individual excipients and binary mixtures with the API did not reproduce the unknown peaks observed in Trial 01. However, the combination of API, sucrose, sodium hydroxide, and methylparaben generated the same impurity profile, indicating that the observed peaks from unknown origin likely result from interactions involving methylparaben in the presence of API and sucrose under basic conditions. Same peaks with smaller areas appeared in a solution consisting of sucrose, NaOH and MP (without the API). This finding suggests that the alkaline microenvironment promotes methylparaben degradation and/or interaction pathways, which are accelerated in the presence of API - leading to impurity formation, highlighting an interaction in Trial 01 formulation design.

Such interactions are well documented in the literature, where parabens, including MP, undergo base-catalyzed hydrolysis to form p-hydroxybenzoic acid (PHBA), which can further react in the presence of reducing sugars such as sucrose to generate sugar-derived adducts or conjugates (Singh et al., 2024). In alkaline environments, additional pathways such as transesterification and oxidative or secondary degradation products may also occur. These known degradation mechanisms are consistent with the impurity profile observed, supporting the conclusion that the unknown peaks arise from established paraben instability and interaction pathways under basic conditions.

Conclusion

The results demonstrated that Trial 01 is susceptible to degradation due to interaction between MP sucrose, under alkaline conditions, leading to the formation of paraben-related degradation products. Although these products are consistent with known degradation pathways and are generally of low toxicological concern, their progressive increase during stability studies indicates insufficient formulation robustness. In contrast, the trial 02 (without parabens) exhibited satisfactory stability, highlighting the importance of excipient selection and microenvironmental pH control in the development of stable oral solution formulations.

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