Evaluation of impurities, degradation products and foreign particles arising in an unwashed valved holding chamber (VHC) used with a pressurized metered dose inhaler (MDI)

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Introduction

Children may struggle with remembering medication schedules and instructions, and although parental involvement and support play a crucial role in ensuring pediatric adherence, parents themselves may face challenges in remembering and following medication instructions[1]. Moreover, children, especially younger ones, may have limited ability to communicate discomfort or adverse reactions[2]. It is therefore essential to measure the potential outcomes of patient non-adherence as, given the unique needs of these patient populations, proper cleaning and maintenance practices for VHCs are paramount in reducing the risk of impurity-related and foreign particles related complications and to ensure safety and treatment efficacy.

To address these concerns, we investigated the occurrence and potential transfer of impurities, degradation products and visible particles resulting from the misuse of a VHC, which was subjected to continuous usage over a three-month period without cleaning, before proceeding to a delivered dose analysis and to the identification of the impurities present in the VHC and in the collection tube.

Method

To mimic the use of a spacer, 6 actuations of a Symbicort® Rapihaler® 200/6 per day for 5 days per week were performed into a VHC. The emitted dose was collected using the Dosage Unit Sampling Apparatus (DUSA), and budesonide, formoterol and related impurities were quantified by LC-ESI-MS.

Optical microscopy (Olympus BX53 with the Clemex software) has been used to assess the presence of foreign particles in the extracts obtained from the collection tubes. The particles (>100 um) have then been isolated and analysed using FT-IR microscope (Perkin Elmer Spotlight 400) and electron microscopy (FEI Nova Nano SEM 230).

Results and Discussion

Related substances recovered in the collection tube

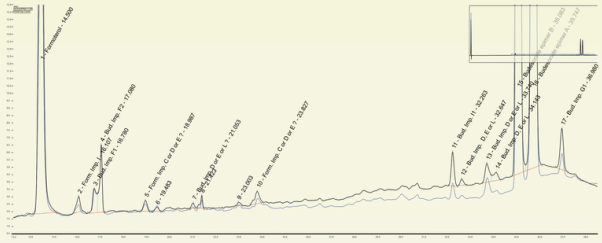

Figure 1: *Chromatogram (214 nm) obtained from the collection tube extraction solution after delivered dose testing with a clean VHC (in blue) and with an unclean VHC (in black).*

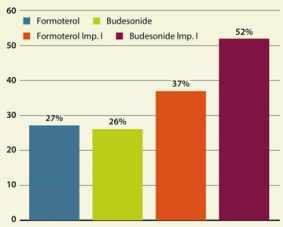

Figure 2: *Rise of compounds obtained from the collection tube connected to an unwashed VHC in comparison to the results obtained from a collection tube connected to a cleaned VHC*

Figure 1 and **Figure 2** shows an increased intake of budesonide (+26%) and formoterol (+27%) with unwashed VHC use, possibly due to the saturated walls of the unwashed device. Unwashed VHCs contribute therefore to elevated budesonide and formoterol intake, affecting treatment efficacy and potentially leading to adverse effects and inadequate symptom control. Additionally, the quantification of a significant rise (+37%) in potentially hazardous formoterol impurity I and a substantial increase (+52%) in budesonide impurity I in the collection tube accentuates safety concerns particularly in the context of such misused scenarios.

Visible particles recovered in the collection tube

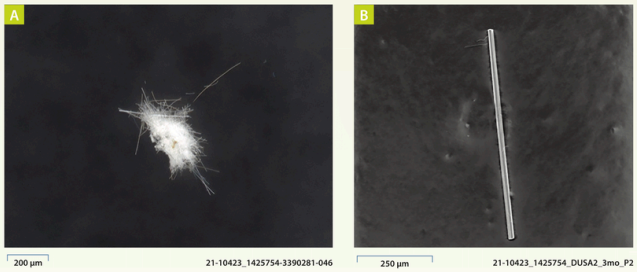

Figure 3 (A & B): *Foreign particles identified in the collection tube connected to the unwashed VHC.* ***A:*** *Crystalline particle.* ***B:*** *Fiber particle.*

The analysis of the extracted collection tube revealed the presence of particles primarily composed of carbohydrate-based materials, likely originating from the canister composition or contaminants as the VHC has been exposed to the atmosphere for several months. While such particles are not causing significant concerns, two distinct particles were identified. A crystalline inorganic fiber (**Figure 4A**) was identified as silicate through FT-IR microscopy, though its origin remains unknown. A fiber-like particle (**Figure 4B**) with a composition analogous to the glass fiber filter used for delivered dose testing. The presence of this particle is attributed to the filter and does not pose safety concerns.

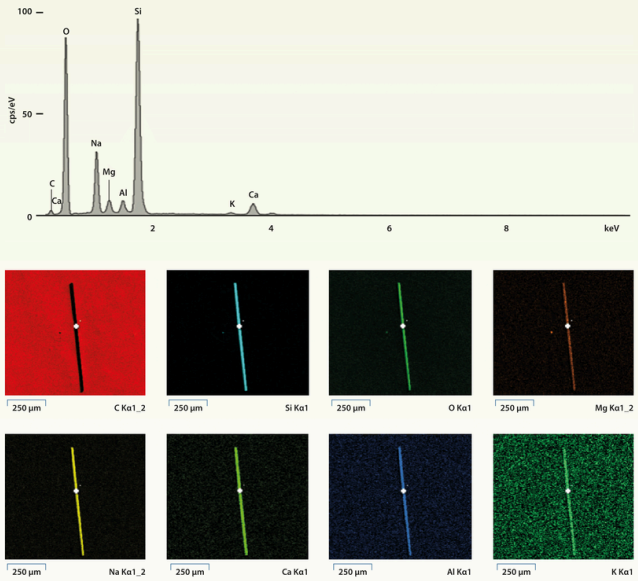

Figure 4: *Energy-dispersive X-ray (EDX) spectroscopy analysis on the fiber particle* ***(Figure 3B)****.*

Conclusion

These findings underscore the necessity for rigorous cleaning protocols, not only to maintain the VHC integritybut also to safeguard the delivered dose from contamination. Caregivers and healthcare providers should exercise caution in educating children and their families about cleaning protocols to promote optimal therapeutic outcomes and potentially minimize risks associated with inhaler use in pediatric populations. While these results provide valuable insights, further studies should be performed on the chromatographic method employed to identify remaining unknown impurities. Moreover, exploring the minimum duration of VHC neglect, after which safety concerns emerge, would be essential to deepen our comprehension of VHC safety standards.

Literature: 1. Ahrens, R C, The role of the MDI and DPI in pediatric patients: Children are not just miniature adults, Respiratory care 2005, 50: pp 1323-1330.
2. Schüepp K G, Devadson S, Roller C, Wildhaber J H: A complementary combination of delivery device and drug formulation for inhalation therapy in preschool children, Swiss Medical Weekly 2004; 134: pp 198-200.

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