Studying the Effect of Water Ingress on API Adhesion in Suspension Metered Dose Inhalers using AFM.

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Summary

Water ingress into pMDI formulations is a well known stability phenomenon. Whilst it is understood that the presence of water can promote chemical instability and particle adhesion/cohesion in these formulations, the impact of water on particle-surface interactions has not been studied in any great detail. This study aimed to characterise the effect of water on API adhesive interactions with pMDI components. Water was shown to dramatically increase API-pMDI component interactions, even in the presence of other formulation constituents such as ethanol. However, oleic acid, a pMDI surfactant, was shown to counter the adhesive effects of water.

Introduction

The effect of moisture ingress through seals and valves on suspension formulations for metered dose inhalers has routinely been assessed via storage stability trials conducted at high humidity and compendial particle size testing, using such techniques as the Anderson Cascade Impactor. However, whilst this can show the effect of moisture ingress on characteristics such as the fine particle fraction, it does not answer fundamental questions as to how the water elicits such effects. An understanding of the effect of moisture ingress on suspension formulations is highly desirable. Moisture ingress can occur through valve components and can be detrimental to the storage stability of the product. Whilst the effect of surfactants on such formulations has recently been reported, an in depth study into the effects of water on adhesion seems to be absent.

Atomic Force Microscopy was used to study the effect of water on the adhesive characteristics of formoterol fumarate to a number of metered dose inhaler (MDI) components in various combinations of model propellant, water, ethanol and oleic acid.

Methods

The particle-surface interactions between various pMDI components and formoterol fumarate were determined using the colloid probe technique of Atomic Force Microscopy (Fig. 1) in various media.

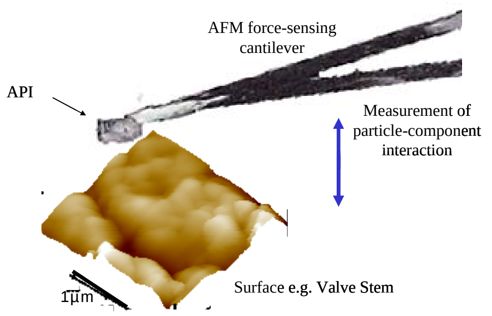

Figure 1 The AFM Colloid Probe Technique

Results

The results are illustrated in Figure 2. Generally, the addition of water to the HFA propellant increases the API-pMDI component interactions. This is possibly due to adsorbed water layers forming on particles and/or surfaces, which then interact via hydrogen bonding, an attractive force considerably stronger than van der Waals interactions.

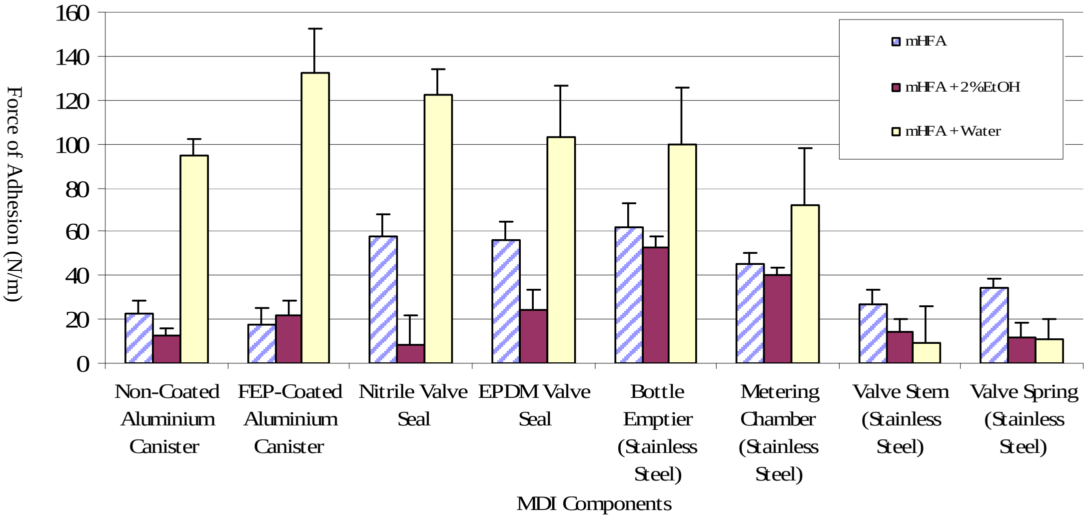

Figure 2 The adhesion of formoterol fumarate to various pMDI components in a) mHFA, b) mHFA and 2% (v/v) anhydrous ethanol, and c) mHFA saturated with water.

Figure 3 illustrates that, when ethanol and water are separately present in mHFA, the particle-surface adhesion is lower in the presence of ethanol. However, in most cases, the adhesive interaction appears to be mainly unaffected by the presence of ethanol and water in mHFA, compared to the adhesive interaction in mHFA containing water alone. This is in spite of the much larger concentration of ethanol compared to water. This demonstrates the degree to which water has a negative influence on formulation stability

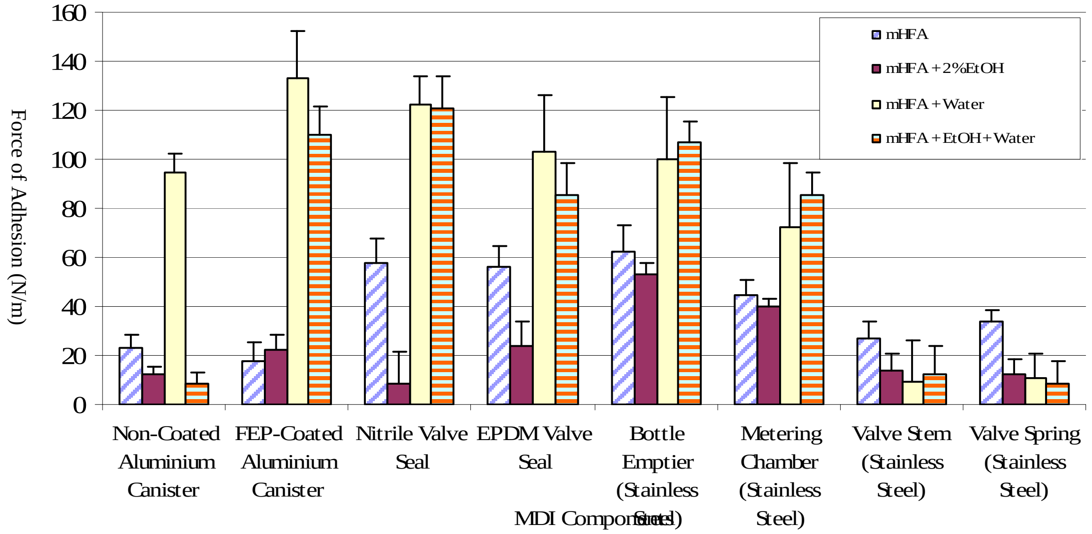

Figure 3 The adhesion of formoterol fumarate to various pMDI components in a) mHFA, b) mHFA and 2% (v/v) anhydrous ethanol, and c) mHFA saturated with water, and d) mHFA saturated with water, plus 2% anhydrous ethanol

Figure 4 illustrates the relative adhesive influences of water content and oleic acid content (0.05% v/v) on formoterol fumarate-pMDI component adhesion. In the vast majority of cases, water clearly increases adhesion with varying magnitudes depending on the component. Oleic acid (and 2% ethanol – required to increase the solubility of the surfactant) was found to decrease adhesion down to a similar level for each interaction. This suggests that oleic acid provides a steric barrier between the particle and the surface, resulting in a low-adhesive surfactant (component)-surfactant (particulate) interaction.

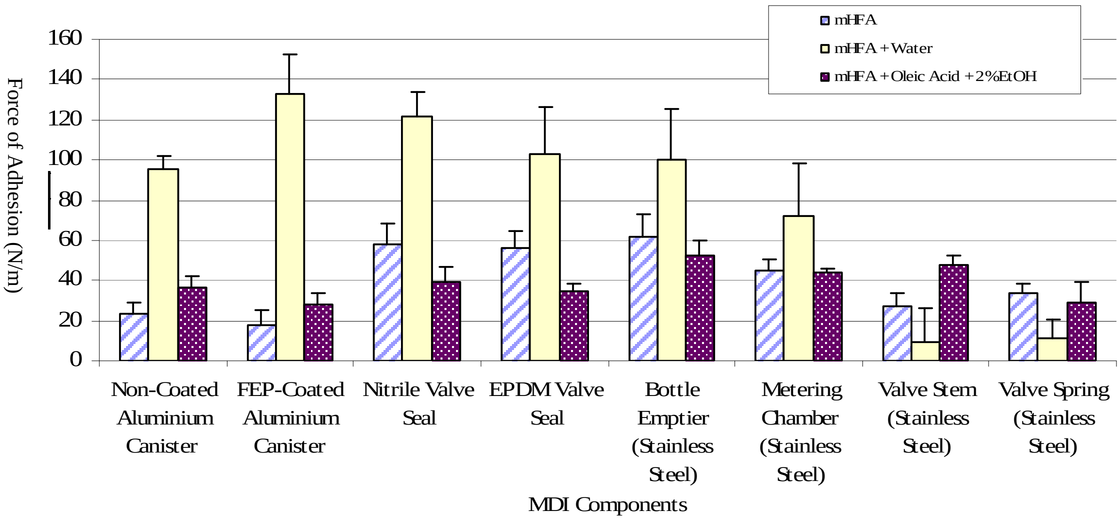

Figure 4 The adhesion of formoterol fumarate to various pMDI Components in a) mHFA, b) mHFA saturated with water c) mHFA plus 0.05% oleic acid (2% anhydrous ethanol).

Figure 5 shows that the presence of oleic acid (plus 2% v/v anhydrous ethanol) in water-saturated mHFA still results in relatively low adhesive interactions. This suggests that oleic acid forms a strong enough steric barrier to diminish the adhesive influence of water in this mHFA system.

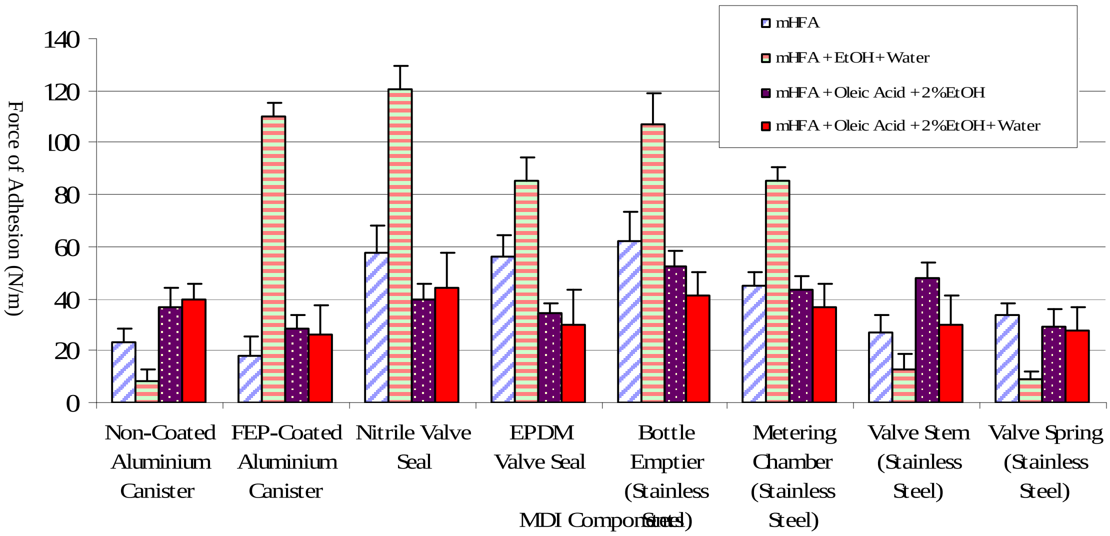

Figure 5 The Adhesion of Formoterol Fumarate to Various pMDI Components in a) mHFA, b) mHFA plus 0.05% oleic acid (plus 2% anhydrous ethanol), c)) water-saturated mHFA plus 0.05% oleic acid (plus 2% anhydrous ethanol)

Conclusion

The presence of water in mHFA formulations considerably increases the adhesive characteristics of formoterol fumarate with respect to pMDI component interactions. This is probably due to adsorbed water layers forming around the surfaces of the API particulate and on the surfaces of the pMDI components. This effect is observed in the presence of a greater concentration of ethanol, suggesting that the water-induced increases in particle interactions are still dominant in the presence of ethanol. The presence of oleic acid as a surfactant diminishes the effects of water, most likely by providing a steric barrier between the API particles and the water molecules in the system. This data indicates that the presence of a surfactant may also act as a stabiliser against moisture ingress during the lifetime of a pMDI unit.

References

(1) Davies et al, Pharm. Res. 22, 2005
(2) Vervaet et al, Int. J. Pharm., 186, 1999, 19.
(3) Vervaet et al, Int. J. Pharm., 186, 1999, 21
(4) Buckton et al, Colloids and Surfaces 95, 1995