



Particulate drug interactions with polymeric and elastomeric valve components in suspension formulations for metered dose inhalers

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ABSTRACT

Purpose: To characterise the adhesive interactions between three pulmonary active pharmaceutical ingredient (API) materials and the components of pressurised metered dose inhalers (pMDIs) obtained from two commercially available products (termed 'Prod-1' and 'Prod-2'). This is of potential interest, as a greater understanding of the interactions between specific APIs and surfaces may aid manufacturers in component selection during pMDI system development.

Methods: The theoretical work of adhesion (ΔG_{132}) for each API–pMDI component interaction was calculated using the surface component analysis (SCA) approach. These results were correlated with corresponding API–pMDI component separation energy measurements determined using colloid probe AFM.

Results: Strong correlations existed between separation energy and the ΔG_{132} parameters where the polar contribution was accounted for. This highlighted the adhesive influence of polar surface energy on each interaction in this study. Generally the largest adhesive interactions involved APIs and pMDI components which have a bipolar surface energy (i.e. both γ^- and $\gamma^+ > 1 \text{ mJ m}^{-2}$).

Conclusions: For each API–pMDI interaction in this study, the polar component of surface energy has the greater influence on adhesive events. The bipolar surface energetics of certain APIs and pMDI components were deemed responsible for the increased adhesive interactions observed with these materials. This study highlights that different materials can have different effects on the adhesive interactions with particulate APIs; information that could aid the manufacturer in producing more effective and efficient pMDI systems.

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1. Introduction

Suspension pressurised metered dose inhalers (pMDIs) generally consist of particulate active pharmaceutical ingredients (APIs) suspended in a hydrofluoroalkane (HFA) propellant within an aluminium canister, usually in the presence of one or more excipients. A cross section of a typical pMDI valve is shown in Fig. 1. After initial actuation of the unit, a metered dose of the formulation is constantly present within the metering chamber of the valve and replaced with fresh formulation after each subsequent actuation. Therefore, a dose of the particulate formulation is in constant contact with the components of the valve (metering chamber, stem, seals and spring) until exhaustion of the unit occurs. Clearly then, the physical stability of particulate formulations in the pMDI valves is pertinent in terms of dose uniformity and, potentially, regula-

tory compliance. It has been previously demonstrated that pMDI device components used with propellants (chlorofluorocarbon or hydrofluoroalkane) can result in inefficient device performance, due to adhesion of the suspended particulate API material to the interior of pMDI device surfaces (Vervaet and Byron, 1999). Other consequences of device–propellant interactions include adsorption, poor lubrication and elastomer swelling (Vervaet and Byron, 1999). Consequently, there have been attempts to counter these phenomena, such as coating the canister with various polymers to reduce adhesion (Traini et al., 2006), the development of low swell elastomers such as ethylene propylene diene monomer (EPDM) and the use of various surfactants within the pMDI formulation. In the case considering suspension pMDI formulations, adhesion to pMDI surfaces can also potentially occur (Young et al., 2003).

Atomic force microscopy (AFM) has, in recent years, been employed to gain some insight into drug particle interactions within model pMDI systems (e.g., Ashayer et al., 2004; Traini et al., 2005; James et al., 2007). Most assessments have been semi-quantitative and non-empirical (Chibowski et al., 1992). More recently, there have been attempts to relate the thermodynamic

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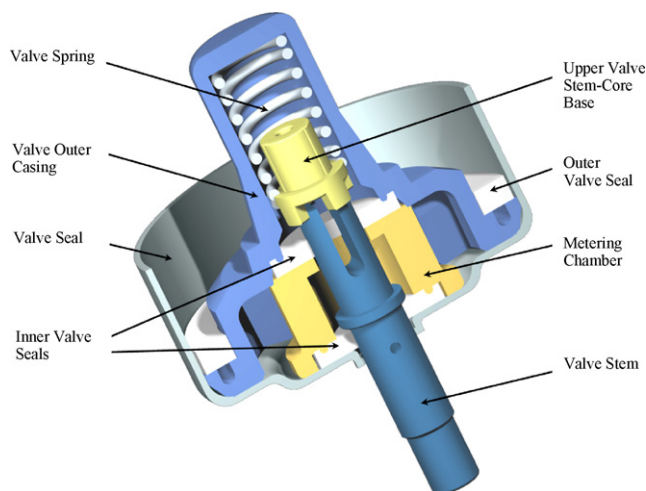


Fig. 1. Diagram illustrating a cross section of a pMDI valve.

work of adhesion of various API materials to the surface energy of polymer-coated and non-coated metallic pMDI canisters (Traini et al., 2006). However, to the authors' knowledge, there has been little assessment of the interactions between particulate APIs and both the elastomeric and polymeric valve components of a pMDI system. This is somewhat surprising as some commercially available products use both polymeric and elastomeric components within their valves. One could assume that the assessment of particle-component interactions in the metering chamber of a pMDI system would be of considerable interest when considering the variety of materials employed and the potential physical changes that may occur during the storage of suspension formulations.

This study primarily compares the adhesive interactions of pMDI valve components from two different commercially available products, to selected API materials in the presence of the model propellant, 2H, 3H decafluoropentane (mHFA). In addition, this study also determines the surface energy of each API and pMDI valve component using contact angle (CA) measurements. Subsequently the theoretical adhesive forces were calculated from the CA measurements using the surface component analysis (SCA) approach (Traini et al., 2005). The theoretical work of adhesion values were correlated with those determined experimentally using the AFM colloid probe technique (Davies et al., 2005).

1.1. The surface component analysis (SCA) principle

The SCA method for determining the work of adhesion from contact angle measurements was first devised by van Oss (van Oss et al., 1988) and is essentially based on an adaptation of the DLVO theory (Derjaguin and Landau, 1941; Verwey and Overbeek, 1948). The theory behind the SCA principle is extensive and can be found in the literature (van Oss et al., 1988; van Oss, 1994), whereas only a brief overview of the background and key points will be given here.

DLVO theory is based on the assumption that London van der Waals forces and electrostatic forces (primarily repulsive) dictate intermolecular and interparticulate interactions in a liquid environment. This has not been validated in non-aqueous pMDI formulations (Vervaet and Byron, 1999; Smyth, 2003) since in such cases interactions are dictated by a combination of London van der Waals forces, electrostatic double-layer interactions and Lewis acid/base interactions (van Oss, 1993; van Oss and Busscher, 1997). Moreover, it was predicted that London van der Waals forces and Lewis acid/base interactions would dominate these interactions,

since the diffuse nature of the electric double-layers in these systems would result in negligible electrostatic repulsive forces (Pugh et al., 1983). Therefore, the SCA model focuses on the Lifshitz van der Waals and Lewis acid/base interactions. The Lifshitz van der Waals interactions are apolar in nature and consist of a combination of the dispersive, induction and orientation components of van der Waals interactions. The Lewis acid/base interactions are polar in nature. The surface energy of any interaction is a combination of the dispersive Lifshitz van der Waals (γ^{LW}) contribution and the Lewis acid/base (γ^{AB}) contribution.

Subsequently, adopting the Good–Girifalco–Fowkes combination rule (Good and Girifalco, 1960; Fowkes, 1963), the interfacial energy parameters between dissimilar substances (1 and 2) within an apolar medium (3, where the polar γ contributions (γ^+ and γ^-) both equal 0), the free energy of an interaction can be stated in the following equation:

$$\Delta G_{132} = 2 \left(\sqrt{\gamma_1^{LW} \gamma_3^{LW}} + \sqrt{\gamma_2^{LW} \gamma_3^{LW}} - \sqrt{\gamma_1^{LW} \gamma_2^{LW}} - \gamma_3^{LW} - \sqrt{\gamma_1^+ \gamma_2^-} - \sqrt{\gamma_1^- \gamma_2^+} \right) \quad (1)$$

(Note: the full explanation and derivation of this equation is detailed in Traini et al., 2005, referenced in the appropriate section of this article.)

Thus, the free energy of interaction for the dispersive and polar forces can be calculated if the user has a knowledge of the dispersive and polar surface energies of each solid (1 and 2) and the liquid media (3).

1.2. Direct surface energy measurements using AFM

Since the interfacial free energy of interaction (ΔG_{132}) is equal to the work of adhesion (W_{adh}), comparisons can be made between ΔG_{132} determined by the SCA model, and W_{adh} measurements directly determined by colloid probe AFM force measurements, via one of the contact models; the Johnson–Kendall–Roberts model (JKR – Eq. (2)) or the Derjaguin–Müller–Toporov model (DMT – Eq. (3)).

$$\text{JKR model : } F_{ad} = \frac{3}{2} \pi R^* W_{adh} \quad (2)$$

$$\text{DMT model : } F_{adh} = 2 \pi R^* W_{adh} \quad (3)$$

In both equations, F_{adh} is the measured force of adhesion between two surfaces and R^* is the contact radius of the particle against the surface. The JKR model is usually applied to systems with large particle radii, high surface energies and compliant materials (Johnson et al., 1971; Derjaguin et al., 1975), whereas the DMT model is usually applied to rigid particles with small radii. The use of each model is dependant on the nature of each interactive system.

1.3. Summary of investigative aims

This study investigated the adhesive interactions between three API materials and pMDI valve components from two different products (denoted 'Prod-1' and 'Prod-2'). The surface chemistry of each of these pMDI components was assessed using X-ray photoelectric spectroscopy (XPS). The surface morphology of each component was determined using scanning electron microscopy (SEM). The surface roughness of each component was determined using AFM imaging. Using the SCA approach, the theoretical work of adhesion (ΔG_{132}) was determined for each pMDI valve component and API; these theoretical values were subsequently compared to

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