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Comparison of the cohesion-adhesion balance approach to colloidal probe atomic force microscopy and the measurement of Hansen partial solubility parameters by inverse gas chromatography for the prediction of dry powder inhalation performance

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ABSTRACT

The abilities of the cohesive-adhesive balance approach to atomic force microscopy (AFM) and the measurement of Hansen partial solubility parameters by inverse gas chromatography (IGC) to predict the performance of carrier-based dry powder inhaler (DPI) formulations were compared. Five model drugs (beclometasone dipropionate, budesonide, salbutamol sulphate, terbutaline sulphate and triamcinolone acetonide) and three model carriers (erythritol, α-lactose monohydrate and D-mannitol) were chosen, giving fifteen drug-carrier combinations. Comparison of the AFM and IGC interparticulate adhesion data suggested that they did not produce equivalent results. Comparison of the AFM data with the *in vitro* fine particle delivery of appropriate DPI formulations normalised to account for particle size differences revealed a previously observed pattern for the AFM measurements, with a slightly cohesive AFM CAB ratio being associated with the highest fine particle fraction. However, no consistent relationship between formulation performance and the IGC data was observed. The results as a whole highlight the complexity of the many interacting variables that can affect the behaviour of DPIs and suggest that the prediction of their performance from a single measurement is unlikely to be successful in every case.

1. Introduction

Dry powder inhalers (DPIs) are widely used to deliver drugs to the lungs. Most DPI formulations consist of a mixture of micronised drug and larger "carrier" excipient particles. This is aerosolised as the patient inhales and in order to reach the lungs, drug particles must separate from other particles, as only those $<5\,\mu m$ aerodynamic diameter (*i.e.* single particles) will reach their target (Timsina et al., 1994). The efficacy of this process determines product efficiency, hence interparticulate adhesion and cohesion are critical to determining performance. It might, therefore, be possible to relate particle–particle interactions within a DPI blend to product performance. Such a system would be highly advantageous during the formulation of DPI products, as it would enable the rapid screening of a range of salt forms or carrier excipients in order to find the combination likely to yield the highest fine particle delivery.

Recently, there have been a number of attempts to develop such predictive techniques. The most promising have utilised colloidal probe atomic force microscopy (AFM) and inverse gas chromatography (IGC), though other techniques have also been investigated (Lohrmann et al., 2007). Using AFM, the force of adhesion between particles can be measured with a sensitivity as high as 10^{-11} N, but as the contact area (to which adhesion is proportional) is unknown, its usefulness has been limited (Bunker et al., 2005). This limitation has been overcome in various ways, including by the cohesion-adhesion balance (CAB) technique, in which the cohesion of a material and its adhesion to a different material are measured using the same particle, giving the same contact area (Begat et al., 2004a). The ratio between cohesion and adhesion can then be calculated, a value independent of contact area. Such CAB ratios have been able to explain the behaviour and predict the performance of a number of types of DPI formulation (Begat et al., 2004b, 2005; Hooton et al., 2006, 2008; Jones et al., 2008a,b; Kubavat et al., 2012a,b).

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IGC investigates the surface properties of a solid by examining its interaction with organic vapours (Grimsey et al., 2002). The majority of work using IGC to predict DPI performance has focused on the measurement of surface energy at infinite dilution (Alhalaweh et al., 2013; Bernhard and Steckel, 2005; Cline and Dalby, 2002; Jiang et al., 2005; Kumon et al., 2006; Oliveira et al., 2006; Sethuraman and Hickey, 2002; Traini et al., 2008). However, a consistent relationship between surface energy and DPI performance has failed to emerge. A number of studies have considered the dispersive surface energy of either the carrier or drug, finding either a positive (Kumon et al., 2006) or negative (Jiang et al., 2005; Oliveira et al., 2006; Sethuraman and Hickey, 2002; Traini et al., 2008) relationship with formulation performance. In addition, Traini et al. found a negative relationship between total carrier surface energy and fine particle delivery (Traini et al., 2008). Other workers, recognising that the interaction between two particles is more complex than simply the surface energy of one of them, have used more complex calculations, either combining surface energy and surface area measurements (with conflicting results) (Bernhard and Steckel, 2005; Sethuraman and Hickey, 2002) or attempting to calculate drug-carrier interaction energy from the components of surface energy (Cline and Dalby, 2002). This latter approach found a positive relationship between drug-carrier interaction energy and fine particle delivery. However, this work was subsequently criticized for the substitution of surface tension with free energy of adsorption during the calculation of the "surface energy interaction", as well as for the reliability of the method employed for the determination of specific surface area from IGC data (Chow et al., 2004).

Tong et al. employed another IGC approach, by measuring the Hansen partial solubility parameters (see Section 2.2.4.1) of salmeterol xinafoate polymorphs and lactose monohydrate, from which the strength of the various adhesive and cohesive interactions within in a formulation could be calculated (Tong et al., 2006). Subsequently, these data were found to relate to the *in vitro* performance of DPI formulations.

All of the studies discussed above make the assumption that adhesion between drug and carrier particles dominates the behaviour of carrier-based DPI formulations. However, this assumption is not universally valid, as drug-only and drug-fine excipient agglomerates are also known to exist within, and influence the performance of, carrier-based DPI formulations, especially for cohesive drugs (Jones and Price, 2006; Xu et al., 2011). This may be an explanation for the inconsistent findings of studies to date.

AFM and IGC each have the potential to develop into useful tools for the prediction of DPI performance, although each has its own strengths and weaknesses. While AFM makes a direct measurement of adhesive forces, due to the time consuming processes involved, it is only possible to do so using a few particles (Weiss et al., 2015). In addition, AFM experiments require a high degree of operator expertise. In practical terms, IGC requires a lower level of operator expertise and can also make measurements across a whole powder surface. It is, however, an indirect measurement of adhesion and does not take account of certain factors (*e.g.* electrostatic and capillary forces) which can influence interparticulate forces.These are measured by AFM (Bunker et al., 2005). Currently, the relative merits of AFM and IGC for the prediction of DPI performance are unclear, as their capabilities have yet to be directly compared. The aim of this study was, therefore, to compare these two techniques.

The CAB approach to adhesive force measurement by AFM was employed, as the literature contains more comparisons of data from this technique with DPI formulation performance than any other. IGC was employed at infinite dilution to determine the Hansen partial solubility parameters of the study materials because this approach yielded promising results with a limited number of formulations in the first report of its application to DPI systems (Tong et al., 2006) and so it warrants further investigation in a larger study. In addition, the prediction of DPI performance from surface energies measured at infinite dilution by IGC has been widely investigated without consistent success, as discussed briefly above and in greater detail elsewhere (Jones et al., 2012).

It should be noted that IGC analysis at infinite dilution provides information about the most energetic sites on the surface of a powder and so gives an incomplete representation of surface properties (Buckton and Gill, 2007; Das et al., 2015; Tong et al., 2005). Therefore, over the last decade a number of groups have developed ever more sophisticated methods which employ finite dilution IGC to map the entire surface energy distribution of a powder (Das et al., 2011a; Smith et al., 2014; Tong et al., 2005; Ylä-Mäihäniemi et al., 2008). Such approaches have proven more effective and reliable than infinite dilution IGC in understanding the effects of pharmaceutical processing and batch-to-batch variability on powder surface properties (Das and Stewart, 2012; Das et al., 2015; Das et al., 2011b). Finite dilution IGC has also been used to calculate the work of cohesion distribution for samples of α-lactose monohydrate, which was related to the deagglomeration of the powders observed by laser diffraction (Das et al., 2012). However, data derived from finite dilution IGC have not yet been applied to the study of the adhesion of a drug to a carrier excipient and their subsequent aerosolisation behaviour, so these approaches were not employed in this study.

2. Materials and methods

2.1. Materials

Experiments were conducted using five model drugs and three model carrier excipients, allowing the preparation of 15 carrier-based DPI formulations. The model drugs were micronised anhydrous beclometasone dipropionate, micronised budesonide and micronised anhydrous terbutaline sulphate form B (each from AstraZeneca, Macclesfield, UK), micronised salbutamol sulphate (GlaxoSmithKline Research and Development, Ware, UK) and triamcinolone acetonide form I (Sanofi-Aventis, Holmes Chapel, UK). Triamcinolone acetonide was subsequently micronised by one pass through a Trost Gem-T mill (Plastomer Technologies, Newtown, PA, USA) with feed and grind pressures set to 100 psi. Before use, the micronised drugs were passed through a 500 μm stainless steel sieve (Endecotts Limited, London, UK) to remove large agglomerates of particles. Two to four weeks storage under vacuum and over phosphorus pentoxide (0% RH) at ambient temperature were then allowed to elapse.

The model carriers were erythritol (*Eridex*®) and D-mannitol (β-polymorph, *PharmMannidex*®), each supplied by Cargill Excipients (Mechelen, Belgium) and α-lactose monohydrate (*Lactohale*®, Friesland Foods Domo–Pharma, Zwolle, The Netherlands). The as received carriers were sieved to obtain the 63–90 μm size fraction using stainless steel sieves (Endecotts Limited, London, UK) and an AS 200 sieve shaker (Retsch UK Ltd., Leeds, UK) set to an amplitude of 1 mm. Before sieving, the erythritol carrier was milled for 30 min at 200 rpm using a Pulverisetter 5 planetary ball mill (Fritsch GmbH, Idar-Oberstein, Germany), as its initial particle size distribution was almost entirely >90 μm diameter.

The identity, polymorphism and crystallinity of all these materials were confirmed using X-ray powder diffraction before and after processing. Both drugs and excipients were stored under vacuum and over phosphorus pentoxide (0% RH) at ambient temperature prior to analysis.