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Research paper

Applying surface energy derived cohesive–adhesive balance model in predicting the mixing, flow and compaction behaviour of interactive mixtures

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ABSTRACT

Objective: In this study, we investigated the applicability of cohesive–adhesive balance (CAB) model to predict the interactive mixing behaviour of small excipient particles. Further, we also investigated the application of this CAB model to predict the flow and compactibility of resultant blends.
Methods: Excipients created by co-spraying polyvinylpyrrolidone (PVP, a model pharmaceutical binder) with various L-leucine concentrations were used for this study. Paracetamol was used as model active pharmaceutical ingredient (API). The surface energy was used to derive the work of cohesion (w_{co}) and work of adhesion (w_{ad}) to predict the interactive mixing behaviour of the excipients with paracetamol. The blends were visualised under a scanning electron microscopy microscope to assess the interactive mixing behaviour. In addition, the flow performance and tabletting behaviour of various blends were characterised.
Results: The surface-energy derived work of adhesion (w_{ad}) between excipient and paracetamol particles increased, while the corresponding work of cohesion (w_{co}) between excipient particles decreased, with increasing L-leucine concentrations. In blends for which the work of cohesion was higher than the work of adhesion ($w_{co} > w_{ad}$), small excipient particles were apparent as agglomerates. For excipients with 5% and higher L-leucine concentrations, the work of adhesion between excipient and paracetamol particles was higher than or equivalent to the work of cohesion between excipient particles ($w_{ad} \geqslant w_{co}$) and agglomerates were less apparent. This is an indicator of formation of homogeneous interactive mixtures. At 5% (w/w) excipient proportions, blends for which $w_{ad} \geqslant w_{co}$ demonstrated higher compactibility than other blends. Furthermore, at 10% (w/w) and higher excipient proportions, these blends also demonstrated better flow performance than other blends.
Conclusion: In conclusion, this is the first study to demonstrate that surface-energy derived CAB data effectively predict the interactive mixing behaviour of small excipient particles. Furthermore, at certain proportions of small excipient particles the CAB model also predicts the flow and compaction behaviour of the API/excipient blends.

1. Introduction

1.1. Excipients for powder flow or for powder compaction

Flowability and compactibility are essential material attributes for efficient tablet manufacturing [1–4]. However, the majority of APIs lack the flow and/or compactibility needed for direct tablet manufacturing [5]. Excipients (binders and flow additives) are incorporated to improve the compactibility and flow. Therefore, the success of tablet formulation critically depends on these excipients [6,7].

Both flowability and compactibility depend on inter-particle forces [8]. In practice, flow additives improve flow by reducing inter-particle forces [9], while binders improve compactibility by increasing inter-particle forces [10]. Thus, from a fundamental perspective, flow additives and binders have opposite impacts on powder blends and would be expected to conflict with each other's performance.

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1.2. Interactive mixing and excipient performance

The concept of interactive mixing involves the adhesion of small particles (typically <10 μm) to larger particles resulting in formation of a homogeneous and segregation resistant powder mix [11]. The formation of interactive mixture depends on the magnitude of forces acting between the small and large particles. Efficient de-agglomeration and preferential adhesion of small particles to large particles is energetically favoured when the forces of adhesion acting between small and large particles are stronger than the forces of cohesion acting between the small particles [12,13]. This concept is known as the cohesive–adhesive balance (CAB) [12,13].

Glidants/flow additives are nanometric in size and improve the flow of cohesive particles by adhering to them consequently forming interactive mixtures [14–16]. However, due to their small size, most flow additives are highly cohesive in nature. Low shear mixing is unable to efficiently de-agglomerate these cohesive structures resulting in non-homogeneous mixtures and consequently poor flow [10,17–19]. High shear mixing facilitates de-agglomeration and the formation of a more homogeneous interactive mixture, and consequently optimum flow improvement [15,20,21]. This suggests that the interactive mixing behaviour of small excipient particles affects the flow performance of the resulting interactive mixtures.

Theoretically, a monolayer of binder particles facilitates optimum gain in tensile strength [22,23]. This is supported by percolation theory, which predicts that a three-dimensional continuous bonding network of the excipient must be present in order for the tablet to achieve optimal tensile strength [24,25]. It has been demonstrated that small binder particles with the ability to form efficient interactive mixtures also express an efficient binder action [26]. This suggests that the cohesive adhesive balance of small excipient particles also affects the compaction behaviour of the resulting mixtures.

Clearly, both flow and compaction behaviour of blends depend on the dispersibility of small excipient particles. In this study, we used the cohesive–adhesive balance (CAB) model with surface energy-derived cohesion and adhesion data to predict the dispersibility and therefore the interactive mixing behaviour of small excipient particles with paracetamol. In addition, the applicability of CAB to predict the flow and compaction behaviour of the resultant blends was investigated. Small, micron-sized excipients (PVP spray-dried with L-leucine) were compacted into tablets whose tensile strengths were determined. Paracetamol was selected as a poorly compressible cohesive API model [27]. The surface energies of spray-dried excipients and paracetamol were determined using an inverse gas chromatography (IGC), and the cohesion–adhesion balance was derived from these surface energy data [28,29]. The applicability of the CAB model to predict the dispersibility and therefore the interactive mixing behaviour of small excipient particles were then qualified by inspection of the API/excipient blends under a scanning electron microscope. Powder blends were then characterised for their tabletting behaviour and flow performance.

2. Materials and methods

In this study, we used previously prepared PVP (molecular weight ~10 kDa, as per supplier's specifications) and L-leucine spray-dried formulations [30]. The mean particle diameter (D_{50}) of various spray-dried formulations was in the range of 2–3 μm with narrow particle size distributions. Paracetamol of analytical grade was procured from Sigma–Aldrich (St. Louis, MO, USA). The particle diameters of paracetamol were D_{10}: 3.7 ± 0.1 μm, D_{50}: 21.4 ± 0.3 μm, and D_{90}: 151.5 ± 5.0 μm.

2.1. Inverse gas chromatography (IGC)

The surface energy of paracetamol was determined with an inverse gas chromatography (iGC 2000, Surface Measurement Systems Ltd., London, UK) at infinite dilution. Briefly, paracetamol powder was packed into pre-silanized glass columns (300 mm × 3 mm internal diameter) by gentle tapping, until no cracks, hollows, or channels were visible in the powder bed. The columns were loosely stoppered with silanized glass wool at both ends to prevent sample movement.

Before measurement, the packed columns were pre-conditioned with a helium stream at 10 standard cubic centimetre per minute (sccm) for 2 h at 303 K and 0% RH. Dispersive energy measurements were achieved with the use of a series of n-alkanes (chromatography grade decane, nonane, octane, heptane and hexane (Sigma–Aldrich, St. Louis, MO, USA)), while the specific surface energy measurements were achieved with the use of acidic (chromatography grade chloroform (Sigma–Aldrich, St. Louis, MO, USA)) and basic probes (chromatography grade ethyl acetate (Sigma–Aldrich, St. Louis, MO, USA)), respectively. For all probes, a concentration of 0.03 $p/p0$ (where p is the partial pressure and $p0$ is the saturation vapour pressure) was used. Helium at a flow rate of 10 sccm was used to carry the probes through the stationary phase and the system was maintained at 303 K at 0% RH. Dead volumes were based on the retention volume of methane gas at 0.03 $p/p0$, and detection of probes was achieved with a flame ionisation detector.

The dispersive surface energy was calculated according to the theory described by Schultz et al. [31] while the polar surface energy was calculated based on the theory proposed by Good et al. [32] where the polar surface energy can be split into two components – an acidic component, γ^+, and a basic component, γ^-. The calculation of the polar surface energy is given by the following equation [32,33]:

$$\gamma_s^P = \sqrt{\gamma_S^+ \gamma_S^-} \tag{1}$$

The total surface energy of the material is the additive effect of both the dispersive (γ^D) and polar (γ^P) components [34]. Upon determination of the dispersive and polar surface energies, the work of adhesion (w_{ad}) for interactions between dissimilar particles and the work of cohesion (w_{co}) for interactions between similar particles can be calculated using the following equations [28,29]:

$$w_{co} = 2\sqrt{\gamma_1^D \cdot \gamma_1^D} + 2\sqrt{\gamma_1^P \cdot \gamma_1^P} \tag{2}$$

$$w_{ad} = 2\sqrt{\gamma_1^D \cdot \gamma_2^D} + 2\sqrt{\gamma_1^P \cdot \gamma_2^P} \tag{3}$$

where γ_1^D and γ_1^P represent the dispersive and polar energies of particles of solid 1, and γ_2^D and γ_2^P represent the dispersive and polar energies of particles of solid 2.

2.2. Blending

To minimise the effect of humidity related variations, all the excipients were stored in a controlled humidity (42 ± 2% RH) environment. When the gain in mass was <10 mg (per ~50 g excipient batch) on three consecutive measurements (with 24 h between each measurement), the mass was considered to have attained equilibrium. A total of 50 g blend was prepared by mixing paracetamol with predetermined ratios (5%, 10%, 15% and 20% (w/w)) of spray-dried excipients in a 250 mL glass jar using a Turbula mixer (Willy A. Bachofen, Muttenz, Switzerland) at 72 rpm for 5 min.