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Effect of the deformability of guest particles on the tensile strength of tablets from interactive mixtures

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ABSTRACT

In this study, we investigated the influence of deformability of specifically-engineered guest particles on the tensile strength of tablets of interactive mixtures. The binder polyvinylpyrrolidone (PVP) of different molecular weights were spray dried with L-leucine to create guest particle formulations. The guest particle formulations were characterized by their particle size, surface L-leucine concentration and glass transition temperature (Tg). These spray-dried particles were then blended with paracetamol to form interactive mixtures, which were compacted into tablets and tablet tensile strength and elastic recovery were determined. The guest particles had particle diameters in the range of 1–10 μm, and surfaces that were L-leucine enriched. The Tg of guest particle formulations increased with increasing molecular weight of the PVP. All the guest particle formulations formed an observed homogeneous interactive mixture with paracetamol. The tensile strength of the tablets of interactive mixtures increased with decreasing Tg of the guest particles. In these interactive mixtures, higher tensile strength was also associated with lower tablet elastic recovery. The elastic recovery of the tablets showed a correlation with the elastic recovery of the tablets of guest particles. Thus, our results indicated that the deformability of guest particles dictates the tensile strength of the tablets of these interactive mixtures.

1. Introduction

In interactive mixtures, small guest particles (typically <10 μm) adhere to the surfaces of larger host particles (Hersey, 1975, 1976; Lai et al., 1981; Staniforth, 1985). However, strongly cohesive nature inhibits the de-agglomeration of such small particles and is thus a major impediment in the formation of homogeneous interactive mixtures (Begat et al., 2005). Homogeneous interactive mixtures form, when guest particles de-agglomerate efficiently and preferentially adhere to large particles upon mixing. It is generally accepted that preferential adhesion of small particles to large particle occur, when the forces of adhesion between guest particles and host particles are stronger than the forces of cohesion between guest particles. This concept is referred to as cohesive-adhesive balance (Begat et al., 2004a, 2004b).

Surface properties strongly influence the forces of inter-particle interactions and hence cohesion (Orband and Geldart, 1997; Zhou et al., 2011b). Previous studies have suggested surface manipulation by increasing surface asperity (Chew and Chan, 2001; Li et al., 2006; Podczeck, 1999), reducing surface energy (Han et al., 2013; Zhou et al., 2011a) and coating with nanometric sized particles (Yang et al., 2005; Zhou et al., 2010) can efficiently reduce the cohesion of small particles. Co-spraying with L-leucine is another promising strategy to reduce the cohesion of small particles (Chew et al., 2005a; Sou et al., 2013; Staniforth and Morton, 2002). The exact mechanism by which L-leucine reduces cohesion is a subject of active debate (Feng et al., 2011; Mangal et al., 2015b; Sou et al., 2013). However, L-leucine is proposed to enrich into the surface of the spray-dried particles owing to its interfacial activity (Gliński et al., 2000) and low water solubility (Vehring, 2008; Vehring et al., 2007) and form L-leucine film/shell (Feng et al., 2011; Mangal et al., 2015b; Vehring, 2008). The L-leucine film/shell increases the surface asperity of the particles reducing inter-particles forces acting between such L-leucine coated small particles (Chew et al., 2005a; Sou et al., 2013).

We demonstrated that co-spraying a model binder (PVP) with L-leucine forms L-leucine surface-enriched small particles with low

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bulk cohesion (Mangal et al., 2015a). These L-leucine coated small binder particles were found to more easily form a homogeneous interactive mixture with a model API and also improve its flow and compactability (Mangal et al., 2015a). It was proposed that this could be a potentially innovative excipient technology platform to improve both the flow and compaction behaviour of cohesive and poorly compactible APIs. In this study, we aimed to gain insight into the mechanism which was observed to facilitate such surface engineered binder particles to express a binder action.

L-Leucine is a weakly bonding lubricious material with the ability to reduce inter-particle interactions (Ghoroi et al., 2013; Röscheisen and Schmidt, 1995; Rotthäuser et al., 1998; Staniforth and Morton, 2002), thus it is unlikely that L-leucine would facilitate bonding between host particles and improve the compaction behaviour of the resultant interactive mixture. We proposed that deformability of binder at the core allows the L-leucine shell to distort and rupture, leading to creation of fresh PVP surfaces, which participate in inter-particle bonding between host particles, improving the compactability of interactive mixtures. Thus, it would be reasonable to hypothesize that the deformability of the L-leucine coated guest particles would correlate with the compactability of interactive mixtures. In this study, we for the first time investigate the effect of deformability of L-leucine coated guest particles on the compactability of the resultant interactive mixtures.

In general, the plastic/elastic deformation that a material undergoes depends on its resistance to the deformation such as under compression (Cowie, 2001). Materials with lower resistance, deform more creating larger areas for inter-particle bonding, and hence form tablets with higher tensile strength (Van der Voort Maarschalk et al., 1998, 1997, 1997). The glass transition temperature (Tg) of amorphous material can determine their resistance to deformation under compression (Cowie, 2001; Van der Voort Maarschalk et al., 1998, 1997). When the Tg of such materials is close to compression temperature, the resistance to deformation is relatively low, which results in greater deformation and formation of tablets with higher tensile strength (Picker, 2003; Van der Voort Maarschalk et al., 1998, 1997). We hypothesized that the Tg of the L-leucine surface engineered guest particles would also dictate their deformability, and hence the tensile strength of tablets of the resultant interactive mixture (Fig. 1).

In this study, PVP was selected as an amorphous material with a characteristic plastic deformation behaviour (Mattsson and Nystrom, 2001). PVP with different molecular weights were selected to create guest particle formulations with varying Tg (Buera et al., 1992). PVPs (of different molecular weights) were spray-dried with L-leucine to form L-leucine surface engineered small guest particles. The guest particle formulations were characterised for their particle size, surface morphology, surface L-leucine concentrations, and Tg. Interactive mixtures were created by mixing the guest particle formulations with paracetamol, which were then compacted into the tablets. The tensile strength and elastic recovery of tablets of pure guest particle and interactive mixtures were determined.

2. Materials and methods

2.1. Materials

Paracetamol and polyvinylpyrrolidone (PVP) with different average molecular weight grades (K-10, K-40 and K-90 average molecular weight ~10, ~30 and ~360 kDa, respectively, as per supplier's specifications) were procured from Sigma-Aldrich (St. Louis, MO, USA). L-Leucine was purchased from Ajinomoto Co., Inc. (Tokyo, Japan). Magnesium stearate was procured from Mallinckrodt Pharmaceuticals (St. Louis, MO, USA).

2.2. Method of preparation

Aqueous solutions of PVP and L-leucine were spray-dried using the procedure previously described (Mangal et al., 2015a, 2015b). Briefly, PVP (6% w/v) and L-leucine (10% (w/w) of PVP) were weighed accurately and dissolved in 500 mL of purified water with the aid of magnetic stirring. The resultant solution was then spray-dried using a Buchi B-190 spray dryer (Buchi Laboratory Equipment, Flawil, Switzerland) with a 0.5 mm two-fluid nozzle. The standard operating conditions employed during spray drying were: inlet temperature 125 ± 5 °C; spray air flow rate 800 L/h and solution pump setting 10 mL/min. These conditions resulted in an outlet temperature of 70 ± 2 °C. The aqueous solution of 6% (w/v) high molecular weight PVP (360 kDa) was very viscous, which resulted in fusion of particles at the spray nozzle exit. Therefore, the PVP was reduced to 4.5% w/v for this molecular weight, while the proportion of L-leucine was kept at the same proportion to other formulations i.e., 10% (w/w) respective of PVP. The PVP spray-dried formulations were denoted as PVP10-Leu, PVP40-Leu

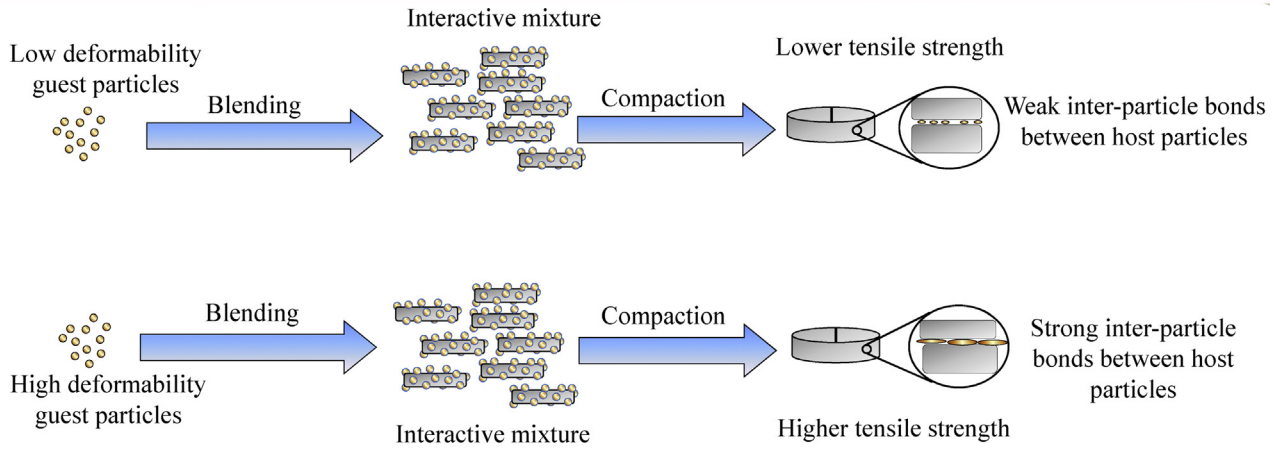

Fig. 1. Schematic figure showing the effect of deformation of guest particles on inter-particle bonding between host particles and tensile strength.