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The role of physico-chemical and bulk characteristics of co-spray dried L-leucine and polyvinylpyrrolidone on glidant and binder properties in interactive mixtures

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ABSTRACT

In this study, polyvinylpyrrolidone (PVP) was spray dried with L-leucine (PVP-Leu) to create a prototype multifunctional interactive excipient. The physico-chemical and bulk properties such as particle size, surface composition, surface energy and bulk cohesion of PVP-Leu was measured and compared against pure spray dried PVP (PVP-SD). The mixing behaviour of these excipients and their effect on flow and binder activity of paracetamol was assessed. The mean particle sizes of PVP-Leu PVP-SD and PVP were 2.5, 2.1 and 21.9 μm, respectively. Surface composition characterization indicated that L-leucine achieved higher concentrations on the surface compared to the bulk of the PVP-Leu particles. The surface energy of PVP-Leu was significantly lower compared to PVP-SD. In addition, PVP-Leu exhibited a significantly lower bulk cohesion compared PVP-SD. The excipients were blended with paracetamol and qualitative characterization indicated that PVP-Leu blended more homogeneously with paracetamol compared to PVP-SD. Both PVP-Leu and PVP-SD then exhibited a significantly improved binder activity compared to PVP. The flow of the paracetamol was markedly improved with PVP-Leu while PVP-SD and PVP had negligible effect on its flow. This study reveals how physico-chemical and bulk properties of such prototype interactive excipients can play a key role in determining multi-factorial excipient performance.

1. Introduction

Tablets are the most commonly used pharmaceutical preparation, despite the availability of many advanced pharmaceutical formulations (Andrews, 2007). For any active pharmaceutical ingredient (API) to be transformed into the tablets of satisfactory quality, the formulation must exhibit three essential attributes i.e. good flow, high compactability and excellent content uniformity (Bolhuis and Armstrong, 2006):

- good flow is necessary for the rapid and reproducible filling of powder into the tablet die to minimize weight variation,
- high compactability is required to ensure that the tablets are sufficiently strong to withstand handling during manufacturing and transportation,
- excellent content uniformity is necessary for a consistent drug dose.

The majority of APIs lack the requisite flow and compactability for tablet manufacturing (Rojas et al., 2012). Therefore, the flow and compactability of such APIs are typically improved by a granulation step (either wet or dry), which involves agglomeration of API and excipients into larger particulate structures i.e. granules. In such structures, the physico-mechanical inadequacies of both APIs and excipients are masked to an extent, facilitating efficient tablet manufacturing. In contrast, direct compression involves the mixing of API(s) with excipient(s) without a preliminary granulation, therefore the physico-mechanical properties of the individual components i.e. API(s) and excipient(s) have greater impact on the powder blend performance i.e. flow and compressibility. Hence, the role of excipients is critical to ensure formation of robust tablets in direct compression (Bolhius and Waard, 1996; Bolhuis and Armstrong, 2006). Therefore, there is a ubiquitous need for

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optimisation of excipients in the drive for more efficient tablet manufacturing using direct compression.

Improved and optimised excipients have mainly been generated via physical manipulation of existing excipient materials (Reimerdes, 1993; Saha and Shahiwala, 2009; Tian et al., 2012; Tobyn et al., 1998). The main objective of excipient engineering is to improve both flow and compactability of the excipient. Particle size manipulation is one of the most commonly used approaches to optimize the flow and compactability of the excipients. However, typically flow and compressibility are inherently competing characteristics, which makes it challenging to achieve an optimum balance of excipient flow and compressibility at a given particle size (Peck et al., 1990). Large particle size is usually associated with improved flow, to facilitate their flow under gravity. However, a smaller particle size is associated with improved compactability due to an increase in the surface area (Kolter and Flick, 2000; Mattsson and Nyström, 2000; Skinner et al., 1999). Additionally, there is also the requirement to match particle size of the excipients and API to achieve good content uniformity (except for ordered/interactive powder mixtures), which typically requires particle size of APIs and excipients to be in the same order. The obligation to satisfy such competing objectives has made excipient design for direct compression a challenging task, and efforts to improve excipient functionality has resulted in a qualified success so far (Nachaegari and Bansal, 2004).

The concept of interactive mixing involves the adhesion of smaller particles to relatively larger particles facilitating their homogeneous distribution and achieving content uniform (Crooks and Ho, 1976; Hersey, 1975; Staniforth, 1985; Staniforth and Rees, 1982; Stephenson and Thiel, 1980). As particles become smaller, their interactive ability increases and particles below 10 μm are considered to be highly interactive in nature (Schulze, 2008). We propose that an excipient with the ability to form interactive mixture with the API(s) may exert an efficient binder action due to its higher effective surface area and better coverage (Kolter and Flick, 2000; Mattsson and Nyström, 2000; Skinner et al., 1999). Additionally, adhesion of an appropriate form of smaller particles to larger cohesive API could also reduce inter-particle cohesion between API particles therefore exerting a flow additive action, as typically observed with flow aids such as silica (Xie, 1997; Yang et al., 2005). So, in principle we propose that such an interactive excipient might not only improve binder action and facilitate flow but could also give robust content uniformity.

For interactive mixing to occur, the cohesion forces acting between the individual components, especially the smaller component must be overcome via energy applied through mixing. Small particles (<10 μm) are considered to be highly cohesive in nature as the inter-particle forces (cohesive forces arising from electrostatic, capillary or van der Waals interactions) significantly exceed external forces such as gravity resulting in agglomeration (Jallo et al., 2011). The ability of the mixing process to split agglomerates into individual particles decreases with increasing inter-particle cohesion forces, which makes de-agglomeration difficult (de Villiers et al., 1993). This may compromise the ability of smaller excipient particles to form interactive mixtures with larger API particles, compromising their functional performance. Therefore, controlling inter-particle cohesion is considered to be a key aspect of creating such interactive excipients.

L-leucine has been reported to act as a lubricant in tablet formulation (Röscheisen and Schmidt, 1995; Rotthäuser et al., 1998). In addition, it has also been previously employed to reduce cohesion and improve the dispersibility of spray dried fine particles in dry powder inhaler research (Sou et al., 2013, 2011; Yang et al., 2012). In this study, polyvinylpyrrolidone (PVP) was chosen as a polymeric binder and L-leucine was chosen as a lubricant to control inter-particle cohesion. PVP was spray dried with L-leucine to generate micron-sized interactive excipients. The effect of L-leucine on the surface composition, surface energy and bulk cohesion was assessed. Paracetamol was selected as model poorly flowable and poorly compressible API (Armstrong, 2007; Minchom and Armstrong, 1989) to investigate the mixing behaviour of excipients and its impact on flow and tabletability.

2. Materials and methods

Paracetamol of analytical grade was procured from Sigma–Aldrich (St. Louis, MO, USA). PVP K-10 (average molecular weight 10,000), was purchased from Sigma–Aldrich (St. Louis, MO, USA). L-leucine was purchased from Ajinomoto Co. Inc. (Tokyo, Japan). The water used in the formulations was of Milli-Q grade (Millipore Corporation, MA, USA). Magnesium stearate was procured from Mallinckrodt Pharmaceuticals (Mallinckrodt Pharmaceuticals, St. Louis, MO, USA). Hydrophobic fumed silica (Aerosil® R 972) was procured from Evonik Industries (Essen, Germany). Copolyvidone (Kollidone® VA 64) and Ludipress® LCE were kindly donated by BASF (Ludwigshafen, Germany). Silicified microcrystalline cellulose (Prosolv®, SMCC) was kindly donated by JRS Pharma (Rosenberg, Germany). Microcrystalline cellulose (Avicel®, PH-105) was kindly donated by FMC biopolymer (Philadelphia, PA, USA), Lactose monohydrate (Tablettose®70) was kindly donated by Meggle (Wasserburg, Germany) and hydroxypropylcellulose (HPC-SSL-SFP®) was received as kind donation from Nisso (New York, NY, USA). Presilanized glass columns and silanized glass wool for the measurement of surface energies were purchased from Surface Measurement Systems Ltd. (Middlesex, UK). Pre-silanized glass beads were purchased from Sigma–Aldrich GmBH (Steinheim, Germany).

2.1. Method of preparation

Briefly, PVP (K-10) and L-leucine were weighed accurately and dissolved in Milli-Q water with the aid of stirring. The resultant solution was spray dried with a Buchi-190 Mini spray dryer (Buchi Laboratory Equipment, Flawil, Switzerland). The operating conditions employed were: inlet temperature, 125 °C; spray flow rate, 800 L/h and pump setting, 10 mL/min. These conditions resulted in an outlet temperature of approximately 70 °C. The spray dried particles were collected and stored in heat sealed aluminium bags for further evaluation and use. PVP alone was spray dried under similar conditions (PVP-SD) and PVP as received from the supplier (PVP) were used as comparators.

2.2. Particle size and size distribution

Particle size measurements were performed using a Malvern Mastersizer 2000 (Malvern Instruments Ltd. Worcestershire, UK) dry cell. A shear pressure of 2.0 bar was used to disperse the powders at a feeder setting of 50%. Measurements for each formulation were performed in triplicate. The in-built software provided values of D_{50} (volume median diameter), D_{10} (10% volume below this diameter) and D_{90} (90% volume below this diameter). An obscuration factor of 2–5 was targeted and the results were considered valid if the obscuration in this range was attained during the measurement.

2.3. Scanning electron microscopy: surface morphology

The shape and surface morphology of the various excipients were visualised by SEM (Phenom™, FEI Company, Hillsboro, OR, USA). Double-sided adhesive carbon tape was placed on an aluminium stub and, after stripping off the upper side of the adhesive, a small amount of sample was scattered on the stub and