The Impact of Hot Melt Extrusion and Spray Drying on Mechanical Properties and Tableting Indices of Materials Used in Pharmaceutical Development

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ABSTRACT: The impact of melt extrusion (HME) and spray drying (SD) on mechanical properties of hypromellose acetate succinate (HPMCAS), copovidone, and their formulated blends was studied and compared with that of reference excipients. Tensile strength (TS), compression pressure (CP), elastic modulus (E), and dynamic hardness (H_d) were determined along with Hiestand indices using compacts prepared at a solid fraction of ~0.85. HPMCAS and copovidone exhibited lower H_d, lower CP, and lower E than the reference excipients and moderate TS. HPMCAS was found to be highly brittle based on brittle fracture index values. The CP was 24% and 61% higher for HPMCAS after SD and HME, respectively, than for unprocessed material along with a higher H_d. Furthermore, the TS of HPMCAS and copovidone decreased upon HME. Upon blending melt-extruded HPMCAS with plastic materials such as microcrystalline cellulose, the TS increased. These results suggest that SD and HME could impact reworkability by reducing deformation of materials and in case of HME, likely by increasing density due to heating and shear stress in a screw extruder. A somewhat similar effect was observed for the dynamic binding index (BI_d) of the excipients and formulated blends. Such data can be used to quantitate the impact of processing on mechanical properties of materials during tablet formulation development. © 2013 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci

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INTRODUCTION AND BACKGROUND

The design and development of solid dosage forms and galenical processes rely on both the physicochemical and mechanical properties of the active ingredient, excipient components, and the mixtures thereof. Certainly, physical properties are closely linked to final product specifications such as purity, uniformity, dissolution, stability, appearance, and mechanical durability.[1] While physical properties clearly influence powder flow and compression, the mechanical properties of materials, those properties of a material subject to an applied stress, are of great importance in solid dosage form development and manufacturing. The impact of such properties on material behavior during galenical processing has been demonstrated by instrumented tablet press, compression simulator, and mechanical testing devices.[2–4]

Based on the characteristics of the drug substance, excipients that complement or compensate for drug properties may be chosen along with processing equipments to favorably improve the behavior of materials under stress conditions. These evaluations are tied to FDA's new risk-based pharmaceutical quality assessment system in developing pharmaceutical cGMPs for the 21st century, where achieving and maintaining a state of control for a process is considered as beginning at the formulation and process development phase and continuing throughout the commercial phase of a product's life cycle. This new assessment system focuses on pharmaceutical critical quality attributes such as pharmaceutical raw material properties as well as formulation and manufacturing processes as they relate to product performance.[5–7] While there are some generalized procedures to evaluate material properties of active pharmaceutical ingredient (API), excipients, and mixtures, the impact of a given material (API or excipient) is dependent on its concentration in the formulation, its function, as well as any associated processing, and therefore needs to be studied in the context of its ability to affect the performance of a formulation or process.

The value of proper compaction characterization, i.e. assessment of the tensile strength (TS)—compression pressure (CP)—solid fraction (SF) relationships leading to the compactability, tabletability, and compressibility (CTC) profiles, provides basic mechanical property information and has been discussed previously.[8] Along with TS, CP, and SF, the elastic modulus, permanent deformation pressure, and brittleness of compacts are additional important properties used to quantify the mechanical nature of materials. These properties, therefore, are of significant interest in supporting tablet development in a scientific manner. To characterize and compare these properties of materials with different deformation behavior, experimental methods and dimensionless tableting indices (DTI) were developed by Hiestand and Smith.[9,10] The tableting indices are dimensionless numbers that profile the regions of interparti-

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cle contact, the so-called "isthmus" regions between contacting particles. It is at these regions where plastic deformation and the generation of large areas of true contact during decompression are necessary to produce significant tablet strength. The DTI, in combination with compaction characterization, yield a more complete assessment of the multidimensional nature of mechanical properties of materials. The bonding index (BI), for example, is a measure of the extent of plastic deformation or material strength that remains after decompression and recovery of a compact. It is thus a measure of bonding efficiency. A brittleness index called the brittle fracture index (BFI), derived from TS measurements, is a measure of brittleness (fracturing tendency) of compacted material. High BFI values are typically seen with brittle materials that undergo fragmentation. The third index called strain index (SI) indicates roughly the relative strain energy that could develop at a "crack" or other stressed region of the compact during elastic recovery after plastic deformation has occurred. This index combines the elastic and plastic deformation properties of a material and is a measure of the internal entropy or strain in a material when compacted. Finally, a fourth index termed the viscoelasticity index (VI) has been found to be useful as a measure of viscous (time dependent, irreversible) and elastic (reversible) deformation in a compact.[4]

Since the tablet is the most prevalent dosage form that utilizes powder compression, the DTI developed by Hiestand has been used to characterize the behavior of materials during tableting.[11–13] Statistical approaches using factorial designs have been employed to identify experimental conditions that can differentiate materials based on the tableting indices. These have included indenter specifications, compact size, and storage time, but the type of material (deformation behavior) has been the primary determinant of differentiation.[14] The application of DTI to characterize powder compaction behavior by various methods has shown mixed results. The indices have been compared with that of Luenberger's percolation theory using different excipients with brittle or plastic characteristics. The comparison showed the two approaches to be complementary[15] especially for plastically deforming excipients whereby the BI was found to increase with the characteristic relative density, $\rho^* r$, of such excipients. In empirical evaluations, the DTI were correlated with the impact of material properties on processing behavior such as granulation and capping or lamination during tableting. For example, in a study of the influence of the lubricant magnesium stearate on tableting indices of maltodextrins with serially increasing molecular weight, the TS, BI, and BFI were found to decrease with increasing level of magnesium stearate.[16] This effect was more pronounced with the more plastic high molecular weight maltodextrin (M040) that exhibited almost 10-fold lower TS and fourfold lower BI when mixed with 0.48% magnesium stearate compared to virgin material without magnesium stearate.[16] In a similar study on starches,[17] the BFI was used to differentiate the tendency of various starches to ameliorate the brittle fracture of acetaminophen tablets during manufacturing. In a study correlating physical properties of drugs with processing behavior, a high BFI and low BI was seen with larger particle size, suggesting a tendency to cap or laminate during tableting.[18] Moreover, higher BI and lower BFI was seen with wet granulated material compared to dry granulation, indicating a reduced potential for capping and the opportunity to achieve acceptable tablet strength using wet granulation.[18] Amidon showed that specially crystallized lots of ibuprofen exhibited decreased powder flow properties with increasing BI in addition to reduced particle size and greater sphericity, indicating that the mechanical properties of a material also influence powder.[3] The work of Wurster et al. demonstrated that estimating BI based on a linear function of composition was limited to binary mixtures of powders deforming in similar manner (plastic–plastic or brittle–brittle), whereas BI of blends of powders deforming in a dissimilar manner (brittle–plastic) seemed to exhibit a nonlinear relationship.[19,20] The DTI did not predict behavior of new materials from a data set of indices of previously characterized materials using an artificial neural network approach,[21] indicating the complex nature of predicting tablet properties for new materials. However, the nature of BI as a measure of bonding efficiency was shown in the characterization of microcrystalline cellulose (MCC) with varying moisture levels by Amidon and Houghton[22] where both deformation pressure and TS were shown to decrease significantly with the moisture level greater than 5% as the excipient became more plasticized by adsorbed water, resulting in a relatively constant BI or bonding efficiency. This shows that materials with similar bonding indices may have different TS in proportion to their deformation hardness. It is also important to consider the experimental conditions used to generate DTI as they may impact the quantitative aspects and in turn, their predictive ability. In summary, mechanical property characterization and the development of predictive models is a complex function of the properties determined through CTC (i.e., TS CP, solid faction) and DTI (i.e., bonding, plastic deformation, brittleness, elasticity, viscoelasticity) methodologies. However, these measurements when combined provide greater insight into the mechanical properties of pharmaceutical materials and enhance our understanding of the impact of materials and processes on pharmaceutical materials.

Hot melt extrusion (HME) and spray drying are being increasingly employed to produce solid molecular dispersions of poorly soluble drugs, resulting in improved solubility and also to develop sustained, modified, and targeted drug delivery systems.[23–27] During HME of pharmaceutical dosage forms, a blend of active ingredient, thermoplastic polymeric carrier, and other processing aids, including plasticizers and antioxidants, is heated and softened inside a screw extruder and then pressurized through a die into granules, cylinders, or films.[24] The intense mixing and agitation imposed by the rotating screw cause deaggregation of suspended particles in the molten polymer resulting in a more uniform dispersion.[23] In spray drying, the drug–polymer solution is atomized and dispersed into hot gas, which causes the solvent to evaporate and leads to the generation of spherical particles.[27] Plasticizers are used to soften polymers and make them more flexible during melt extrusion. They decrease the glass transition temperature and the melt viscosity of a polymer by increasing the free volume between polymer chains and reducing their movement with respect to each other.[23,28] While this improves the processing conditions (lower temperature and lesser torque, improved stability) during manufacturing of the extruded dosage form, it can also influence the physical and mechanical properties of the extrudate such as TS and elastic modulus.[23,29] In drug–polymer solid dispersions, the small molecule compounds (drugs) in a polymer matrix can plasticize the polymer during HME, impacting its mechanical properties such as reduced TS of extruded films.[30] Powders processed by HME are subjected not only to el-