

Understanding critical material properties for solid dosage form design

Anthony J. Hlinak¹, Kamal Kuriyan², Kenneth R. Morris³, Gintaras V. Reklaitis⁴, and Prabir K. Basu²

¹Global Pharmaceutical and Analytical Sciences, Abbott Laboratories, North Chicago, IL 60064, USA

²Discovery Park, Purdue University, West Lafayette, IN 47907, USA

³Department of Industrial and Physical Pharmacy, Purdue University, 575 Stadium Mall Drive, West Lafayette, IN 47907-2091, USA

⁴School of Chemical Engineering, Purdue University, 480 Stadium Mall Drive, West Lafayette, IN 47907-2100, USA
Corresponding author: Kuriyan, K. (kuriyan@purdue.edu).

What is the role of standardized methods for determining the impact of material properties in pharmaceutical formulation and process development? In this Perspective article, we identify material properties that are potentially important in solid dosage form design, and we review approaches linking these properties to product specifications in dry granulation process development. We also assess the potential benefits that could be obtained by standardizing the methods for determining the impact of material properties of commonly used excipients and propose a program of research to achieve the desired goal of an efficient, science-based approach for incorporating material properties in solid dosage form design.

Current state

Solid dosage form design and process development depend heavily on the physical properties of the active and excipient components. Physical properties are closely linked to final product specifications such as purity, uniformity, dissolution, stability, appearance, and mechanical durability. Physical properties are also often at the center of manufacturing problems that can emerge unexpectedly during the life cycle of the product. Despite a general awareness of the importance of physical properties, formulation scientists face a knowledge gap as they attempt to develop pharmaceutical products and manufacturing processes. Limited progress

has been made in creating standard methods for characterizing pharmaceutical components, and in creating reliable databases and predictive relationships of properties for common components.

At the core of this gap is the lack of precise knowledge regarding the role played by many of the physical properties of pharmaceutical materials as well as the methods to quantify those properties. Pharmaceutical material properties are a challenge for several reasons. Organic solids are more difficult to characterize than inorganic solids because of the unformalized weak interactions between polyatomic organic molecules and their innate flexibility. Pharmaceu-

tical systems consist of multiple components of particles, and mixture properties must be determined for each composition of interest. Many properties of particulate solids also depend, in unpredictable ways, on factors such as the particle size distribution, which can vary between lots. Finally, behavior during processing is a complex function of the multiple particulate and powder properties that are amplified by the impact of process parameters such as the equipment geometry and energy input.

Properties and their impact on product attributes and processing behavior

The impact of specific material properties is dependent on the amount and function of a particular component within the dosage form. Generally, the impact of a component is greatly reduced when it is present in a relatively low concentration, but there are some notable exceptions. For example, low concentrations of lubricants, such as magnesium stearate, and flow aids, such as talc, can have significantly more than a proportional impact on the tablet strength [1]. Mixing rules relating the properties of a pharmaceutical mixture to the properties of the individual components have been developed for certain properties, particularly for binary mixtures [2,3], but in general, such rules do not exist and each composition must be individually investigated.

A fairly comprehensive but by no means exhaustive set of critical material properties is shown in Table 1, along with their potential impact on product attributes and processing behavior. Poor flow behavior contributes to commonly encountered phenomena such as bridging and arch-

ing, rat-holing, surging, and the uneven movement of particles into die cavities [4]. The latter problem impacts weight uniformity during unit dosing operations such as tablet compaction and capsule filling. Wetting behavior impacts granulation processes and the dissolution rates of oral dosage forms.

Linking product specifications to material properties

Product design should start by identifying the desired final dosage form and its critical quality attributes, along with the potentially limiting properties of the active pharmaceutical ingredient (API). Potential excipient matches designed to suppress or amplify the API characteristics and processing approaches that are likely to result in a product that consistently meets specifications are identified. This is followed by an iterative set of activities that optimize the formula and manufacturing process simultaneously. Adjustments can include changing the formula, changing equipment, or adjusting operating parameters. As an example, we review the literature on the development of dry granulation processes.

Evaluating material impact

Sheskey and Dasbach [5] investigated the effect of commonly used polymer binders on drug release and mechanical characteristics of immediate release formulations (prepared by roller compaction). As expected, higher binder levels resulted in greater tablet strength. Tablets containing higher binder levels generally exhibited a greater range of dissolution

Property	Impact Flow	Blending	Wetting	Drying	Mechanical	Dissolution	Stability
Particle size distribution	X	X	X	X	X	X	X
Particle shape distribution	X						
True density				X	X		
Bulk density – poured and tapped	X		X		X		
Pore size distribution			X	X		X	
Surface area	X	X	X	X	X	X	X
Surface energy	X	X	X				
Flow	X						
Cohesiveness	X	X					
Internal friction	X				X		
Wall friction	X				X		
Amorphous content			X				X
Elastic modulus					X		
Compactibility					X		
Brittleness					X		
Static charge	X	X					
Hygroscopicity	X			X			X

Table 1. Potential impact of material properties on quality attributes and processing behavior.

Continued on page 14.

times. Mollan and Celik [6] studied the effect of lubrication on the compaction of tablets produced from maltodextrin powders – processed by several methods including roller compaction. Lubricant sensitivity, as measured by the R value (i.e., the ratio between the maximum lower punch force and the maximum upper punch force), was found to reach a plateau when the concentration of magnesium stearate was 0.5% (w/w) or higher. Inghelbrecht and Remon [7] found that when microcrystalline cellulose was used as a dry binder or filler, the particle density influenced the tablet dissolution rate more than the particle size. Mitchell *et al.* [8] studied the use of hydroxypropyl methylcellulose (HPMC) to enhance the solubility of poorly soluble drugs, and they found that compaction enhanced solubility, when compared with the drug alone and also with the corresponding loosely mixed powders. Soares *et al.* [9] found that dry granulation improved the compression and flow characteristics of spray-dried plant extracts.

Modeling the impact of processing stresses and parameters

The work described previously in this Perspective article on identifying impact provides evidence of the significant effects of material properties on dosage form performance. However, modeling of the impact of processing stresses is required for optimal design space activities and selection of processing parameters. Falzone *et al.* [10] studied the effect of roller compactor settings on the properties of granulations produced by compaction. The system was modeled with a quadratic correlation model. They studied several different materials including Avicel PH 101, anhydrous lactose, and an acetaminophen blend. A different correlation was developed for each material. The correlations could be used to determine roller compactor settings that would produce desired values of post-milled granule size distribution and recompressibility. Hervieu *et al.* [11] studied the effect of feed and roll speeds and compaction pressures during roll compaction of a pharmaceutical powder. The ratio of speeds between the screw-feeder and the roll speed was found to be a critical parameter in determining the compact quality, as measured by a cohesion index. Inghelbrecht and Remon [12] found that the roller compaction behavior of different types of lactose evaluated by granule friability could be described by a linear quadratic model. The equations showed that the roll pressure was the most important parameter, followed by the horizontal feed speed and roll speed. In contrast to this simple statistical model, modeling the compaction of drum-dried waxy maize starch (DDWM) required a complex neural network model [13]. Sheskey *et al.* [14] studied the scale-up of roller compacted controlled release formulations. They optimized the roll speed, screw speed, and roll pressure at the laboratory scale, and then scaled up these settings using linear roll speed and roll pressure (per inch of

roll width) as the scale-up parameters. They found that manufacturing scale compacts exhibited a lower bulk density and increased compressibility, compared with laboratory scale and pilot scale compacts, thus highlighting the need for a fundamental understanding of material properties and their response to stresses. Rambali *et al.* [15] studied the effect of roll compaction force on buccal bioadhesive tablet properties and found that higher compaction force led to an increase in the bioadhesive energy. This was attributed to an increase in tablet-pore radius and ‘wettability’, which in turn promotes binding. Simon and Guigon [16] found that the design of the feed system resulted in compact heterogeneity, which was principally caused by the variable powder packing that took place in the last flight of the screw-feeder.

Mechanistic models of roller compaction also have been developed. Johanson’s model [17] assumes that the material is isotropic, frictional, cohesive, and compressible, and follows the effective yield function proposed by Jenike and Shield [18]. Bindhumadhavan *et al.* [19] verified that the model can be used to predict the peak pressures generated by the rolls when compacting Avicel PH 102. However, similar predictions have not been as successful for molecular organic crystalline powders.

Dec *et al.* [20] reviewed mechanistic models for roller compaction and suggested that finite element analysis was the most versatile approach because it could incorporate adequate information about powder behavior, geometry, and frictional conditions. They concluded, again, that the biggest challenges in implementing finite element modeling do not arise from computational problems, but from the lack of adequate material data. Specifically, there is a need for more-accurate material models that realistically represent the behavior of the powder through the wide range of densities, which are encountered during compaction, and also for appropriate friction models to describe phenomena at the material and/or roll interface. The need for material models that can represent the behavior of the material through the entire compaction process, including the feed system, also was stressed by Sommer and Hauser [21]. Initial development of a constitutive model to describe the mechanical behavior of microcrystalline cellulose over the range of densities encountered in tableting is described by Cunningham *et al.* [22]. Material behavior during compaction also can be modeled using combined finite-discrete element modeling [23] or non-equilibrium molecular dynamics simulations [24], but challenges remain in scaling these methods up to model systems with large numbers of particles.

Although we have selected roller compaction as the example, similar limitations based on the lack of fundamental material science for compounds of pharmaceutical interest are ubiquitous for our solid unit operations. Even high-shear wet granulation, which seeks to erase the material’s

memory of all variability of the raw materials, suffers from this lack of understanding.

Material characterization

Of course, it is necessary to have reliable and reasonably objective methods to measure the properties before modeling begins, whether empirical or first-principle based. The test methods used in the studies described previously have been summarized in Table 2. The following conclusions can

be drawn from the discussion in the previous sections of this article and the information in Table 2:

- (i) Methods are often specified with reference to a specific vendor apparatus with varying amounts of detail about specific operational settings.
- (ii) There is limited use of standardized test methods for characteristics other than perhaps equilibrium solubil-

Material property, processing characteristic, and/or quality attribute	Method
Particle size distribution	Ro-Tap sieve shaker, 5 min (Sheskey and Dasbach [5]);Retsch sieve shaker, 10 min, 2 mm amplitude (Inghelbrecht and Remon [7]);ATM Sonic Sifter, 5 min, amplitude 8, (Mitchell, Reynolds and Dasbach [8]);Retak sieve shaker (Soares <i>et al.</i> [9])Sieve shaker, 6 min (Falzone, Peck and McCabe [10]);Laser diffraction with Helos particle size analyzer, (Inghelbrecht and Remon [12]);Retsch sieve shaker, 10 min, 2 mm amplitude (Inghelbrecht <i>et al.</i> [13])Ro-Tap sieve shaker, 5 min (Sheskey <i>et al.</i> [14]);Retsch sieve shaker, 5 min, 1.5 mm amplitude (Rambali <i>et al.</i> [15])Laser granulometry with Malvern Mastersizer (Simon and Guigon [16]);Laser diffraction with Helos particle size analyzer (Bindhumadhavan <i>et al.</i> [19])
True density	Helium pycnometry (Mollan and Celik [6]);Beckmann air comparison pycnometer (Soares <i>et al.</i> [9]);Helium pycnometry (Simon and Guigon [16])
Bulk density, tap density	Graduated cylinder, 250, 500, 750, 1000, 1250 taps (Inghelbrecht and Remon [7]);Graduated cylinder, Engelsmann tapping device (Soares <i>et al.</i> [9]);-Vanderkamp tap density tester, 500 taps (Sheskey <i>et al.</i> [14])
Surface area	Nitrogen adsorption multipoint Brunauer Emmett Teller (BET) method (Mollan and Celik [6])
Internal friction, wall friction	Peschl rotational split level shear tester (Bindhumadhavan <i>et al.</i> [19])
Lubrication	Total work of compression, average power consumption (Mollan and Celik [6])
Flow	Discharge time from funnel (Soares <i>et al.</i> [9]);Flow time (Hervieu <i>et al.</i> [11])
Crushing force	Key hardness tester (Sheskey and Dasbach [5]);Pharma Test strength tester (Inghelbrecht and Remon [7]);European Pharmacopeia Supplement, Erweka hardness tester (Soares <i>et al.</i> [9]);Key hardness tester (Sheskey <i>et al.</i> [14]);-Pharma Test strength tester (Rambali <i>et al.</i> [15])
Friability (granules)	Erweka friabilator, 10 min, 25 rpm with glass beads (Inghelbrecht and Remon [7], Inghelbrecht <i>et al.</i> [13]);
Friability (tablet)	Vanderkamp friabilator, 4 min (Sheskey and Dasbach [5]);Erweka friabilator (Inghelbrecht and Remon [7]);Vanderkamp friabilator, 6 min (Sheskey <i>et al.</i> [14])
Dissolution	USP (US Pharmacopoeia) apparatus I, 100 rpm (Sheskey and Dasbach [5]);USP XXIII specs, 150 rpm (Inghelbrecht and Remon [7])USP apparatus II, 100 rpm (Mitchell, Reynolds and Dasbach [8]);USP apparatus II, 50 rpm (Sheskey <i>et al.</i> [14]);Paddle method, 50 rpm (Rambali <i>et al.</i> [15])
Stability	Ambient conditions: 21°C, 50% RH. Accelerated conditions: 40°C, 75% RH (Sheskey <i>et al.</i> [14])

Table 2. Characterizing material properties and their impacts for dry granulation.

Continued on page 16.

ity measurements, which ultimately should not be significantly affected by variability in the raw material (other than, of course, in the case of purity).

- (iii) Processing behavior of materials is typically evaluated in terms of relative performance indices such as flowability or lubricant efficiency, rather than fundamental material properties.
- (iv) Extensive experimental studies are required to determine material properties impacts and processing behavior, even when using common formula ingredients such as microcrystalline cellulose (MCC), lactose, and starch.
- (v) The development of mechanistic process models has been hampered by the lack of adequate molecular and particulate level models that describe material behavior.

Clearly, the existence of standardized test methods for product quality attributes, such as solubility, reflects the importance placed on controlling these characteristics by regulatory agencies. However, in general, a similar emphasis has not been placed on characterization of the raw materials and intermediates that will be incorporated into the final product. Similarly, the evaluation methods for material characteristics that are important for a given process also exhibit varying degrees of standardization. A variety of indices have been proposed in the literature, but it is difficult to assess the predictive value of these indices without extensive experimental studies and/or the development of detailed process models.

The role of standards

Specifications for excipients are often built around the various pharmacopoeial standards such as the British Pharmacopoeia (BP), European Pharmacopoeia (PhEur), Japanese Pharmacopoeia (JP), and the United States Pharmacopoeia/National Formulary (USP/USPNF). However, industry has long recognized that these standards are insufficient because they emphasize purity, chemical stability, and assays, but have little to contribute at a similar level of rigor for the physical or mechanical properties of excipients.

As every formulator will attest, the *Handbook of Pharmaceutical Excipients* [25], which contains information on >500 excipients, is the most widely used reference for excipient properties. However, the information in the handbook is necessarily constrained by the fact that it is largely derived from open literature. As an example, for sucrose, the handbook lists absolute values for bulk densities and gives particle size distributions for crystalline and powdered forms, but without reference to the method of measurement.

Flowability is described in relative terms, but information on many of the remaining property categories shown in Table 1 is not included because it is not currently available. So, despite these laudable efforts, it is difficult to compare properties for excipients because of this knowledge gap.

It is proposed that, even with these challenges, significant progress can be made with a focused effort. Similar challenges faced by other industries have led to the systematic development of databases of physical properties for relevant materials. The Design Institute for Physical Properties (DIPPR) provides critically evaluated thermophysical and environmental property data for industrial applications [26,27]. The data include synonyms that identify the compound, the molecular formula and structure, data quality codes, sources, safety information, explanatory notes, fixed value properties such as the critical temperature and pressure, and correlation coefficients for temperature-dependent properties. Additional information, such as the oxygen demand and toxicity, that is useful for environmental impact studies is also available for certain compounds. The National Institute of Standards and Technology (NIST) Standard Reference Data program (<http://www.nist.gov/srd>) covers a wide range of information, including thermochemical and thermophysical data, spectroscopic constants, and chemical structures. The program provides scientists and engineers with numeric data that are extracted from the literature and assessed for reliability.

The key difference between these databases and the corresponding sources that are used in the pharmaceutical industry is that the former are founded on more-mature science and less-varied downstream applications. In part, this gap exists because there has been insufficient incentive from all sectors to generate fundamental physical property models and information on molecular organic materials. Additionally, excipient vendors might not conduct a test even if they have the capacity to do so, because they cannot anticipate all uses that might be intended by the manufacturer.

Recommendations

Given this litany of challenges, but embracing the approach adopted by other industries faced with similar problems, the following is proposed. The current empirical approaches to solid dosage design could be streamlined considerably if standardized methods were developed to provide formulation scientists with comprehensive databases of properties for commonly used excipients. This should be accompanied by the development of a set of verified physical models that link physical properties to processing behavior and final product performance. The characterization methods should be carefully chosen to supply the required material properties for the process models. We recommend a program of research in which the following elements are applied itera-

tively to improve the pharmaceutical design process continuously:

- (i) Currently available models for common pharmaceutical unit operations should be assessed and the relevant physical properties identified to confirm and/or expand Table 1.
- (ii) Available methods for quantifying the physical property list generated in the previous step should be evaluated and the most promising approaches further developed, particularly for pharmaceutical powders.
- (iii) As methods reach a sufficient state of maturity, the most commonly used pharmaceutical materials should be characterized and the results should be made available through standardized databases. The results should include multiple vendors and include appropriate estimates of variation.
- (iv) The component test results and the methods from the previous step should be used to develop methods for predicting material properties from first principles and to generate appropriate mixing rules for predicting the relevant properties of powder mixtures from the properties of the components.
- (v) The component and mixture properties would be used to refine and improve the existing process models.

Clearly, implementation of such a broad program will require concerted action by drug product manufacturers, excipient vendors, instrumentation companies, the academic community, regulatory agencies and standards bodies to investigate the underlying regulatory and competitive issues, and to provide the supporting research in material characterization. The effort should be structured so the activities are at a precompetitive stage, and should strike a balance between the needs of excipient vendors and drug product manufacturers. The authors have been collaborating with NIST to initiate a series of workshops and conferences that are directed toward meeting these objectives.

References

1. Bolhuis, G.K. and Holzer, A.W. (1996) Lubricant sensitivity. In *Pharmaceutical Powder Compaction Technology* (Alderborn, G. and Nistrom, C., eds), pp 517-560, Marcel Dekker.
2. Wurster, D.E. *et al.* (1999) Prediction of the Hiestand bonding indices of binary powder mixtures from single-component bonding indices. *Pharm. Dev. Technol.* 4, 65-70.
3. Fell, J.T. (1996) Compaction properties of binary mixtures. In *Pharmaceutical Powder Compaction Technology* (Alderborn, G. and Nistrom, C., eds), pp 501-515, Marcel Dekker.
4. Prescott, J.K. and Barnum, R.A. (2000) On powder flowability. *Pharm Technol* 24, 60-84.
5. Sheskey, P.J. and Dasbach, T.P. (1995) Evaluation of various polymers as dry binders in the preparation of an immediate-release tablet formulation by roller compaction, *Pharm Technol*, October, 98-112.
6. Mollan, M.J. and Celik, M. (1996) The effects of lubrication on the compaction and post-compaction properties of directly compressible maltodextrins. *Int. J. Pharm.* 144, 1-9.
7. Inghelbrecht, S. and Remon, J.P. (1998) Roller compaction and tableting of microcrystalline cellulose/drug mixtures. *Int. J. Pharm.* 161, 215-224.
8. Mitchell, S.A. *et al.* (2003) A compaction process to enhance dissolution of poorly water-soluble drugs using hydroxypropyl methylcellulose. *Int. J. Pharm.* 250, 3-11.
9. Soares, L.A.L. *et al.* (2005) Dry granulation and compression of spray-dried plant extracts. *AAPS PharmSciTech* 6, E359-E366.
10. Falzone, A.M. *et al.* (1992) Effects of changes in roller compactor parameters on granulations produced by compaction. *Drug Dev. Ind. Pharm.* 18, 469-489.
11. Hervieu, P. *et al.* (1994) Granulation of pharmaceutical powders by compaction – An experimental study. *Drug Dev. Ind. Pharm.* 20, 65-74.
12. Inghelbrecht, S. and Remon, J.P. (1998) The roller compaction of different types of lactose. *Int. J. Pharm.* 166, 135-144.
13. Inghelbrecht, S. *et al.* (1997) Instrumentation of a roll compactor and the evaluation of the parameter settings by neural networks. *Int. J. Pharm.* 148, 103-115.
14. Sheskey, P. *et al.* (2000), Roll compaction granulation of a controlled-release matrix tablet formulation containing HPMC – Effect of process scale-up on robustness of tablets, tablet stability, and predicted *in vivo* performance, *Pharm Technol*, November, 30-52.
15. Rambali, B. *et al.* (2001) Influence of the roll compactor parameter settings and the compression pressure on the buccal bio-adhesive tablet properties. *Int. J. Pharm.* 220, 129-140.
16. Simon, O. and Guigon, P. (2003) Correlation between powder-packing properties and roll press compact heterogeneity. *Powder Technol* 130, 257-164.
17. Johanson, J.R. (1965) A rolling theory for granular solids. *J. Appl. Mech.* 32, 842-848.
18. Jenike, A.W. and Shield, R.T. (1959) On the plastic flow of coulomb solids beyond original failure. *J. Appl. Mech.* 26, 599-602.
19. Bindhumadhavan, G. *et al.* (2005) Roll compaction of a pharmaceutical excipient: Experimental validation of rolling theory for granular solids. *Chem. Eng. Sci.* 60, 3891-3897.
20. Dec, R.T. *et al.* (2003) Comparison of various modeling methods for analysis of powder compaction in rolling press. *Powder Technol* 130, 265-271.
21. Sommer, K. and Hauser, G. (2003) Flow and compression properties of feed solids for roll-type presses and extrusion presses. *Powder Technol* 130, 272-276.
22. Cunningham, J.C. *et al.* (2004) Analysis of tablet compaction. I. Characterization of mechanical behavior of powder and powder/tooling friction. *J. Pharm. Sci.* 93, 2022-2039.
23. Lewis, R.W. *et al.* (2005) A combined finite-discrete element method for simulating pharmaceutical powder tableting. *Int J Numer Meth Eng* 62, 853-869.
24. Sanchez-Castillo, F.X. *et al.* (2003) Molecular dynamics simulations of granular compaction, *Chemistry of Materials* 15, 3417-3430.
25. Rowe, R.C. *et al.*, eds (2003) *Handbook of pharmaceutical excipients*, 4th ed, American Pharmaceutical Association.
26. Thomson, G.H. and Larsen, A.H. (1996) DIPPR: Satisfying industry data needs. *J. Chem. Eng. Data* 41, 930-934.
27. Kline, A.A. *et al.* (1998) An overview of compiling, critically evaluating, and delivering reliable physical property data from AIChE DIPPR Projects 911 and 912. *Fluid Phase Equilib* 150, 421-428. 