IMPROVING POWDER TABLETING PERFORMANCE THROUGH MATERIALS ENGINEERING

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Dedication

To my love, Ewuraa Adwoa and my dear, Ellie-Jayne

To my caring family

Abstract

Adequate mechanical strength is a critical requirement to the successful development of a tablet product. Before tablet compression, powders are often engineered by various processes including wet granulation and surface coating, which may improve or adversely affect the powder tableting performance. Such effects, commonly, result from a change in either particle mechanical properties or particulate (size, shape) properties. In this work, tableting performance is interpreted based on the qualitative bonding-area and bonding-strength (BABS) model.

The tabletability of the microcrystalline cellulose (MCC) granules deteriorates rapidly with increasing amount of granulating water and eventually leads to over-granulation at high water level. Granule surface smoothing, size enlargement, granule densification and shape rounding are the dominant factors leading to the tabletability reduction of plastic MCC. Incorporation of increasing amounts of brittle excipients, such as lactose or dibasic calcium phosphate reduces the rate of tabletability reduction by promoting more granule fragmentation, introducing more surface area available for bonding. When a sufficient amount of brittle excipients is used, the over-granulation phenomenon can be eliminated.

Surface coating of incompressible MCC pellets with highly bonding polymer leads to sufficient surface deformation and adhesion to enable direct compression of the pellets into tablets of adequate mechanical strength. This improvement is enhanced by the

presence of moisture, which plasticizes the polymer to allow the development of a larger bonding area between coated pellets.

The relationship between mechanical properties and tableting behavior is systematically investigated in polymeric composites using celecoxib-polyvinylpyrrolidone vinyl acetate solid dispersions. Mechanical properties such as indentation hardness of the solid dispersions were measured using nanoindentation. Incorporation of celecoxib up to 60% by weight hardens the polymers, which reduces bonding area but increases bonding strength. On the other hand, moisture softens the solid dispersions and facilitates deformation under pressure to improve tablet mechanical strength.

In summary, insights into the deteriorated tabletability of wet granulated powders have been developed and strategies for improving tabletability have been demonstrated. Also, the relationship between particle mechanical properties and tableting performance has been examined using solid dispersions. The BABS model has been further developed to enable its widespread application in interpreting complex tableting behavior.

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CHAPTER 1. INTRODUCTION

General Introduction

The tablet is an important dosage form for drug delivery because of a number of advantages over other dosage forms: 1) significantly better chemical and physical stability; 2) accurate delivery of amount of drug; 3) relative ease of production and transportation; 4) high patient acceptance; and 5) relatively lower manufacturing cost.[1] Tablet design is however a complex process because a tablet must satisfy several competing objectives. For example, a tablet must be adequately strong to withstand mechanical stresses during packaging, shipping and handling. On the other hand, an overly strong tablet may suffer from slower drug release.[2]

Many active pharmaceutical ingredients (API) used in drug products, for example, ibuprofen, flurbiprofen, acetaminophen, phenacetin, ascorbic acid, and probenecid, exhibit poor compaction behaviors.[3-5] Poor compaction behavior results in mechanically weak tablets. In order to correct for inherent deficiencies such as poor compaction behavior, the API(s) must be formulated with excipients into drug products. Successful tablet product development assures chemical and physical stability, acceptable drug release profile intended for the product and adequate mechanical strength. Judicious selection of both excipients and manufacturing processes is required to correct for the inherent deficiencies in API for tablet manufacturing.[6] The diversity in compaction behavior of both drugs and excipients makes this a challenging goal to achieve.

Traditional formulation development is characterized by inefficient empirical methods, which generally do not lead to optimized products. Currently, problems associated with mechanically weak or defective tablets such as tablet capping, lamination and high friability, still persist.[4] The need for a more scientific tablet formulation design and to modernize pharmaceutical product development and manufacturing is well known and has been articulated by the Food and Drugs Administration (FDA).[7,8]

Scientific tablet development is best if a clear relationship between the *structure* of materials and their *properties* are known. Based on such understanding the ideal *process* employed in manufacturing platform technologies can be used to achieve optimum product *performance*. These relationships involving materials' *structure, processing, property* and *performance* have been elaborated by the principles of materials science tetrahedron (MST).[6]

Tablets gain their mechanical strength from the process of powder compaction, and the adequacy of their strength is commonly ascertained by methods, which include tablet tensile strength[9], indentation hardness[10], and tablet friability[11] tests during development. The outcome of a compaction run depends on material properties and the conditions of the compaction process e.g. compression speed.[12] Thus, the constituent materials' mechanical properties, such as elasticity, plasticity, viscoelasticity and fracture toughness, and particulate properties, including particle size, particle shape, surface texture, surface energy are of paramount interest to tableting.[13]

It has been proposed that the mechanical strength of a tablet essentially stems from two fundamental attributes – the inter-particulate bonding area (BA) and inter-particulate bonding strength (BS).[14] The bonding area-bonding strength (BABS) model suggests that all the factors that influence tablet compaction alter one or both of these attributes. Tablet strength is favored by high bonding area, which primarily results from plastic deformation, and high bonding strength, which may be attributed to the surface energy. The BABS model can enable formulation scientists to diagnose the leading causes of poor tableting performance of a powder and guide targeted corrective actions by choosing appropriate excipients and processes during the product development process. Appropriate application of MST and the BABS model is expected to significantly improve the efficiency in tablet formulation development. The purpose of this research is to facilitate the design of tablet formulations using MST and the BABS model as the guiding principles. The thesis is aimed at understanding the impact of materials engineering on tableting performance of powders and to establish a clear relationship between particle mechanical properties and tablet mechanical strength such that it allows the development of efficient strategies to address poor tableting behavior of drugs.

Literature Review

The Tablet

The concept of compressing medicinal powder into compacts is credited to Professor Brockedon, who successfully compressed potassium bicarbonate into tablets in 1844.[15] Today, the compressed tablet is the most common dosage form for oral drug delivery, more utilized than capsules.[16] The fact that tablet products accounted for almost half of the new medicinal entities (NMEs) (46%) registered in the US from 2009 till date, 7% more than the preceding 5 year period,[17] signifies their importance as a dosage form (Table 1.1). The tablets are the preferred dosage form to capsules, because tablets can be manufactured at a higher production speed and a lower cost, and tampering the tablet content is difficult.[18] Apart from the flexibility in shape and color, a tablet is also significantly smaller than a capsule for the same drug content. These are essential for developing an appealing and unique product with good patient compliance.

Tablets are mainly for oral drug delivery and may be classified based on the mode of administration, the intended mechanism of drug release or their site of application. The common types of tablets include 1) immediate release tablets; 2) modified release tablets; 3) buccal tablets; 4) dispersible tablets; 5) soluble tablets; 6) effervescent tablets; 7) chewable tablets and 8) lozenges.[17] A tablet may belong to more than one class of products. For example, the dispersible or soluble tablets may be regarded as immediate

release tablet products.

Several important attributes characterize a tablet product. Tablet mechanical strength is one of the critical quality attributes of a tablet.[19] Factors including material physical form (structure), particle size, shape, surface (particulate properties), plasticity, brittleness, viscoelasticity (mechanical properties) and moisture are of importance to a material's tableting behavior.

Formation of a Tablet

The compaction process takes place in a tooling set, i.e. a die and two punches on a tablet press and has been categorized into four phases: I) die filling and particle slippage, II) compression, III) decompression, and IV) ejection.[14] Depending on the tablet press, both punches can move towards each other during compression or one will be stationary as the other compresses the powder. Commercial tablet presses, e.g. Korsch (Berlin, Germany) and compaction simulators e.g. Presster (MCC, East Hanover, NJ), are of the first kind, while materials testing instruments such as Zwick® (Ulm, Germany), Instron® (Norwood, MA) and Carver Press (Fred Carver, Monomonee, WI) are of the latter.

In Phase I, the particles fill the die and move past each other to pack more efficiently as the punches move into the die. At this stage, displacement of trapped air in the bulk powder occurs, and the powder porosity decreases without any significant resistance to

the punch movement. At a critical porosity, the loose powder transitions into a rigid body and becomes susceptible to the stress applied by the punches.[20] This transition initiates Phase II, the powder compression stage. Phase II is where particles experience the maximum stress for deformation to occur. In Phase III, the decompression stage, the stress is reduced from the highest achieved in Phase II to zero. The compacts are finally pushed out of the die in the ejection phase – Phase IV.

Permanent deformation (plastic) occurs if the particles' yield stress is exceeded by the applied stress; if not the deformation is only elastic. This implies that the powder blend will eventually return to its original pre-compression state. Upon ejection a loose powder will emerge. For particles that are susceptible to brittle fracture, fragmentation into smaller particles ensues before the particles finally undergo plastic or elastic deformation. In Phase III, when the applied stress is removed, elastic energy stored as a result of the work of compaction is dissipated. Elastically deformed fragments, on release of pressure return to their original shape of the fragments. However, for plastically deformed particles, the altered particle shape is preserved. Tablets gain their mechanical strength from the process of powder compaction. Conceptually, if the interparticulate contact area resulting from the particle deformation is large enough, and the forces of attraction among the particles are sufficient, the tablet will remain intact at the end of the compaction process and the tablet will gain some mechanical strength. The magnitude of this strength is a result of the interplay between the total area of contact and the strength

of interaction. This is the basis of the bonding area-bonding strength (BABS) model.[14]

Tablet Mechanical Strength

The mechanical strength of a tablet obtained is a function of the physico-chemical, particulate (shape, size and surface) and mechanical properties of the particles (elastic, plastic deformation, and brittleness)[13] and the conditions of formation, e.g., the compaction pressure and speed.[21] Tablets are subjected to various kinds of stresses to test their mechanical strength. Tablet hardness, a term that has been used, albeit inappropriately, to describe a tablet's durability, ease of handling and firmness, is essentially resistance to the tablet crushing under a certain applied load.[22] Hardness is a misnomer because it has a different meaning in mechanical engineering; however, quite a number of studies use it as a tablet strength descriptor even in recent pharmaceutical literature.[23-26] Tablet crushing force or strength is used synonymously with hardness and is taken as the breaking force obtained when a tablet is fractured diametrically. For this test any tablet shape can be used.

Tablet tensile strength is the tensile stress at failure.[9,27] It may be obtained by different methods such as diametral compression test[9] or flexural (bending) test[28], though the diametral compression test appears to be the most common. The determination of the tablet tensile strength originates from fundamental understanding of stress fields in

compacts and also takes into account the tablet size and geometry, hence it is usually regarded as a better descriptor of tablet mechanical strength.[14] Tensile strength by the diametral compression test is given by *Equation 1.1*.

$$\sigma = \frac{2P}{\pi Dt} \qquad \textit{Equation 1.1}$$

where σ is the tensile strength, P is the applied load, D is the tablet diameter and t is the thickness. The tablet has to be cylindrical for *Equation 1.1* to be applicable. Similarly, the tensile (flexural) strength by bending test is only applicable to tabloid-shaped specimens.

Other parameters known for characterizing mechanical strength include fracture toughness[22], indentation hardness (resistance to permanent deformation of the tablet surface)[29], and tablet friability[11]. Of these methods, the tablet friability test is the most interesting and has compendial specification.[30-32]

Tablet friability is a measure of the ability of the tablet to resist abrasion, friction or mechanical shock.[11] High friability leads to unacceptable loss of drug content during downstream processing (e.g., film coating), storage, and handling.[33]

A standard United States Pharmacopoeia (USP) method has been developed to test tablet friability.[34] In this method, a set of "identical" tablets from the same batch are required. Tablets are dropped from a fixed height for a pre-determined number of times, usually 100 times. Tablets are then recovered, de-dusted, and weighed. The weight loss of the set of tablets is used to quantify friability of the tablets. A total tablet weight of at least 6.5 g is required for a single test to ascertain whether the batch will pass or fail for the particular manufacturing conditions, e.g. compaction pressure and speed, being used. Generally, an acceptable friability for compressed uncoated tablets corresponds to ≤0.8% weight loss for a newly developed tablet formulation. In fact thresholds much below the 0.8% may be adopted for this test[35] depending on the intended use of the tablets.

Predicting Tableting Mechanical Strength

Tabletability describes the relationship between compaction pressure and tablet tensile strength. It represents the ability to form a coherent compact out of powder particles under the effect of compaction pressure.[36,37] Many compression equations exist that describe the density-pressure relationship.[38-41] However, attempts to quantitatively describe the relationship between tablet tensile strength and compaction pressure has been less rewarding.[20,42]

The difficulty in describing tabletability, quantitatively, is due to the inability to quantify

the areas of contacts between particles in a compact[43] and to estimate the intermolecular forces over these areas to arrive at a final strength value. Also, particle size and shape, surface roughness, the orientation of contact planes in the compact make such attempts even more difficult.[44] While tensile strength-compaction pressure data can be fitted with equations, e.g., Leuenberger's equation[42], the ability to predict tabletability based on material mechanical properties and particulate properties is the ultimate goal.[43]

Attempts to predict powder mixture tabletability from the compaction behavior of individual powders have led to conflicting results.[42,45-48] Fell and Newton reported a correlation between the tensile strength of individual powders and mixtures of α-lactose anhydrate, β-lactose anhydrate and α-lactose monohydrate.[45] Humbert – Droz and co-workers also recorded some linear trends between individual powder components compaction properties and the tableting performance of mixtures.[49] However, many other workers could not establish such relationships. For example, Newton et al. (1977), who conducted studies on dicalcium phosphate and phenacetin[50]; Kurup and Pilpel 1978, on commercial griseofulvin formulations [51]; Sheik-Salem and Fell (1982) on lactose and sodium chloride [52]; Panaggio et al (1984) on calcium phosphate and starch[53] and Cook and Summer (1985) using dicalcium phosphate and aspirin[54] found essentially no linear correlations between component properties and powder mixtures to enable reliable predictions of tableting performance from individual components. None of these studies probed the individual particle mechanical properties. Inferences were made from bulk

behavior.

Picker-Freyer et al. (2007) studied sulfathiazole polymorphs with AFM nanoindentation and recognized that Sulfathiazole Form III, which apparently had higher hardness than Forms I and II, exhibited better compaction behavior.[47] The authors concluded that the mechanical properties of sulfathiazole polymorph did not correlate with performance. A recent study has shown that the best tableting performance of a series of alkali halides is obtained for crystals with intermediate hardness instead of those with lowest hardness.[55] This observation is consistent with the findings of Cao et al. and highlights the importance of considering properties that will enhance both the interparticulate area of contact as well as the forces of attraction in attempting to predict tableting performance of powders.[3] As pointed out by Cao et al.,[3] it is highly probable that sulfathiazole Form III falls within the intermediate hardness range where compaction behavior is best as observed with the alkali halides.[55]

The qualitative bonding area-bonding strength (BABS) model is a useful tool for moving closer to that goal of performance prediction by allowing clear explanation of complex powder tableting behaviors.[14] The BABS model treats tensile strength as an outcome of the bonding area between adjacent particles and the strength of interactions over that area. The interplay between bonding area (BA) and bonding strength (BS) can lead to complex tableting behavior of materials, depending on pressure, temperature, composition, and particulate properties (e.g., size and shape).[56-59]

Although the BABS model is conceptually sound, its direct demonstration is difficult due to the challenge of individually modulating either the bonding area or the bonding strength.

Adequate Tablet Mechanical Strength

Tablet design is complicated by the fact that a tablet must meet competing objectives. For example, a tablet must be adequately strong to withstand mechanical stresses but not too strong to suffer from slower drug release.[2] Thus optimizing tablet mechanical strength using a tablet's mechanical performance criteria, e.g. friability, becomes more important to tablet formulation development than a preset empirical tensile strength/breaking force criterion which may compromise dissolution rate of tablet from a tablet.[60]

In early development stages, the mechanical performance of tablet products is indirectly assessed through measuring tablet mechanical strength by methods such as tablet tensile strength and indentation hardness.[61,62] Although mechanical strength plays a critical role in the resistance to attrition and abrasion, predictions on real-life mechanical integrity performance based on, for instance, tensile strength measurements may be misleading[63,64] because other factors, such as tablet size, tablet shape or even tablet surface roughness, may affect tablet durability and handling toughness.[63-65]

As a critical performance test for any tablet product, the friability test should be used extensively to facilitate the tablet product development. However, the standard USP friability test is usually carried out at a late formulation development stage, as a quality control tool, when a large amount of drug is available because of the requirement of a batch of tablets.

To obtain information useful for guiding tablet development, a number of batches at different mechanical strengths must be systematically tested to determine tableting process conditions for producing sufficiently strong tablets. It becomes prohibitive to carry out the conventional friability test in such a systematic manner, not to mention the time resources required unless a material-sparing method is developed.

Components of the Tablet

The tablet usually contains both drug substance(s) and excipients. Figure 1.1 illustrates that using only the drug substance to produce tablets can only occur in an idealized situation. Practically, a typical tablet is a multi-component compact containing active pharmaceutical ingredient(s) (APIs) and excipients (pharmacologically non-active ingredients). Excipients incorporated into a tablet are required to enable manufacturability, i.e., to facilitate processing by producing a suitable flow rate and compactibility, and to modulate the performance of the tablet product to obtain specific

attributes such as adequate tablet mechanical strength and appropriate drug release (Figure 1.1).[2] A combination of the API and the excipients for the purpose of drug product development is referred to as a formulation. The amount and physical form of tablet components and the relative position of the particles in the tablet constitute the tablet structure. A placebo is a formulation without.[22]

Active Pharmaceutical Ingredient

Active Pharmaceutical Ingredients (APIs) for tablet formulation development are in the form of powders and have diverse particulate and mechanical properties. Crystalline APIs of all forms are known. Many are of needle-like[47,66], tabular[67], prismatic,[68] platy[47,68,69], acicular[69], columnar[70] crystal shapes. Particulate properties such as particle size, shape, and to some extent, surface energy can be modified by crystallization, milling, precipitation, etc.[71] Amorphous (non-crystalline) API is a high-energy form and usually requires processes such as spray[72] or freeze drying[73], milling[74], etc. to induce the transformation.[75] Critical questions regarding APIs in product development pertain to how much can be included in the drug product (drug loading), and which formulation strategy and development processes are to be employed. Answers to these questions are heavily dependent on the particulate and mechanical properties of the API. Quantitative descriptions of material plasticity and elasticity by indentation hardness and elastic

modulus are more useful in this regard.[3,37,76-78] The hardness, elastic modulus and fracture toughness are usually reported.[79] Ascorbic Acid[80] (Vitamin C) crystals are among the hardest known APIs, while theophylline[78] is considered one of the softest APIs.

Excipients

The choice of excipients is critical to the success of the development of a drug product because they affect both tableting and drug release performance.[2] Excipients used in tableting are mainly categorized by their functionality[2]; the common functional classes include 1) Diluent, 2) Binder, 3) Disintegrant, 4) Lubricant, and 5) Glidant.[2,81]

A diluent is included in a formulation primarily to increase the bulk volume of the API and to improve the tableting and flow properties of the API powder. Examples of diluents include, but not limited to, microcrystalline cellulose (MCC), calcium phosphates e.g. dibasic calcium phosphate, polydextrose, pregelatinized starch, and sugars, e.g., lactose and mannitol. Due to their primary function in a formulation, the amounts used in formulations could vary widely. Diluents may be highly crystalline[82], partially crystalline[83] or completely amorphous[84] in their physical state. Particulate and mechanical properties of diluents differ and are offered in various grades by the manufacturers. The primary particles could be agglomerated as in MCC.[85] Ductile

diluents, like the celluloses, deform easily under pressure but the inorganic salts such as dibasic calcium phosphate and sugars are brittle and fragment when compressed. The starches are known to be very sensitive to tableting speed and hence more viscoelastic.[12]

Binders are polymeric in nature and usually non-crystalline.[2] While a diluent (such as MCC[86]) could also serve as a binder if it has the property of high compactibility, typical binders usually include polyvinylpyrrolidone, hydroxypropyl cellulose, and starch, as a paste. The form of the binder when included in a formulation depends on the manufacturing process, e.g. a binder for wet granulation may be added as liquid.[83] Binders become sticky when wet.[87]

Disintegrating agents or simply disintegrants, for example, crospovidone, sodium starch glycollate, croscarmellose sodium, alginic acid and sometimes pregelatinized starch, are substances that facilitate the breaking up of tablets into smaller fragments when in contact with a liquid medium. Some disintegrants, for example sodium starch glycolate and croscarmellose sodium are effective even at low concentrations, and are dubbed superdisintegrants.[26]

The function of a lubricant in a tablet formulation is to prevent sticking to tablet tooling and reduce the ejection force be reducing friction between the tablet and the die during the tableting process. The most common lubricant, magnesium stearate is highly hydrophobic[88] whereas sodium stearyl fumarate, another example of lubricant, has been

shown to have a lesser hydrophobic effect on tablets[89].

Glidants are also called flow aids. These are materials that enhance the flow of powders usually by reducing the degree of interparticulate cohesion and friction.[90] Colloidal Silica is a commonly used flow aid.

Other excipients used in tablet products include wetting agents, e.g., sodium lauryl sulphate and docusate sodium, coloring agents, and sweeteners for masking taste, e.g. aspartame.[81]

Although each of these classes of excipients may be of the same functional classification, they could have a different impact on tableting performance of the formulation. Likewise, their response to various processes in development could differ significantly. These stem from their physico-chemical differences. Hence structure-property relationship lies at the heart of efficient product development as expounded by the principle of materials science tetrahedron (MST).[91]

Materials Engineering in Tablet Product Development

The development of material-sparing techniques and predictive modeling tools to facilitate decision making is essential but the choice of appropriate materials and processing method is critical.[21,92] Commonly used processes for tablet manufacture

include direct compression, and wet and dry granulation.[93] Of these, direct compression is the simplest and lowest-cost processing route, as it involves only weighing, blending, and compression. It also avoids many processing-induced physical and chemical instability issues.[93] Direct compression is, however, generally limited to low drug loading because of the poor flow and tableting properties of APIs which cannot be easily rectified at high drug loading. A large-dose tablet requires a large quantity of excipients to correct the inherent deficiencies of a drug with poor compaction and flow properties and is normally not amenable to direct compression.[1]

Granulation is simply agglomeration of particles. Wet granulation is often used for APIs that are not heat- or moisture-sensitive. For moisture and heat sensitive materials, dry granulation is used instead. It is a particle engineering process similar to wet granulation but there is no involvement with liquid. This circumvents the issue with water and heat sensitivity. In dry granulation, agglomerates are formed by compressing feed powder into ribbons followed by milling into appropriate size ranges.[94]

The multiple unit pellet system (MUPS) is another particle engineering approach gaining attention in pharmaceutical product development especially for controlled drug release.[95] Individual drug-bearing beads, e.g. hard MCC beads (granules), are coated with polymeric functional layer(s) to modulate the drug release and essentially create mini drug depots.[96] For consistent administration, drug-bearing beads need to be placed into a capsule or compressed into a tablet.[97-100]

In pharmaceutical manufacturing, polymeric composites are also often used. The most common polymeric composite used is the amorphous solid dispersion (ASD). ASD technology is an integral part of modern day drug formulation development for oral dosage forms because of the number of drug candidates that have poor aqueous solubility. In ASDs, polymer-drug interactions are postulated to improve physical stability of the drug, i.e., inhibit crystallization. Interactions such as complexation, hydrogen or ionic bonding are often cited.[101-103] While the molecular interactions are proceeding, other properties such as mechanical properties could also be evolving as a function of composition.[104] Systematic understanding of the tableting performance of ASDs is not yet well developed because the focus of research is mostly on enhanced dissolution.[105]

Poor powder tabletability is a common problem that challenges the successful development of high quality tablet products. This problem occurs more frequently when a high dose of a poorly compressible drug must be delivered or when the powder is granulated, by an either dry or wet process or when unique structures like MUPS and polymeric composites such as ASDs are designed for compression.[106-108] To effectively solve tabletability problems, the identification of the cause of poor tabletability is critical.[82]

Particle Engineering by Wet Granulation

A formulation is wet-granulated by spraying either water or a binder solution unto powder as it is agitated in a mixer to produce the agglomerates. The binder is introduced into the formulation to enable inter-particulate bonding which facilitate agglomeration.[109] The wetted agglomerates must be dried to reduce the moisture level to a typical range of < 5%. This results in agglomerates, usually of larger size than the particles of the starting materials. Depending on the intensity of the mixing, the process is referred to as high shear or low shear. The purpose of granulation is to improve powder flow and increase bulk density to facilitate consistent die filling in high speed tableting; to eliminate dust, prevent segregation of powder blends and improve content uniformity especially during the manufacture of low dose drugs; to improve product appearance and so on.[109-111] Granulation is a complex process because of the number of variables – formulation, process and equipment – that influence the process outcome (Figure 1.2). The inter-dependence of these variables further complicates the understanding of the process and makes modeling and scale up difficult.[112] Materials that predominantly undergo plastic deformation such as microcrystalline cellulose (MCC), when granulated, sometimes lose their tableting performance.[85,113-116] This substantial loss of ability of granulated powders to be compressed into tablets of adequate mechanical strength has been referred to as over-granulation.[107]

A mechanistic understanding of the tableting performance of granulated powders is

critical to formulation development because granulation is a common intermediate step that precedes tableting. The reduced tabletability of plastic powders, e.g. MCC, has been attributed to a variety of mechanical and chemical events but such mechanisms are still being debated.[115] For example in some reports, the changes in compaction behavior of cellulose have been attributed to changes in internal bonding within the cellulose material after granulation.[117,118] Changes in degree of crystallinity and binding capacity after milling of the cellulose material have also been cited.[119] On the other hand, studies that focused on granule properties have suggested that the loss of tablet mechanical strength of MCC granules may be attributable to changes in surface texture characteristics such as surface smoothing, particle rounding, reduced surface area and porosity (granule densification) as well as size enlargement.[85,113-116,120] When these changes occur the total inter-granular bonding area necessary to form strong tablets is expected to reduce, which culminates into loss of tablet strength.[14]

The effects of granulating water level[85,120], massing/mixing time[113] and excipient variability in initial moisture content have been systematically investigated using MCC and pure water as granulating fluid to understand the relationship between granule structure and properties during high shear wet granulation (HSWG) on the tableting and flow performance.[114] The choice of the parameters was based on the fact that water level (i.e., liquid saturation level) can be used as a guide to granulation end-point determination in HSWG, massing time can be utilized to ensure effective granulating liquid distribution,

minimize the impact of raw material variability such as initial moisture content on granule properties and to ensure process reproducibility. Through these studies we have learned that, indeed, wetting may occur without any form of agglomeration or nuclei formation during HSWG until a critical granulating liquid level is reached.[85] At some critical concentration of granulating water granule size may increase abruptly.[120] It has been shown that with or without size enlargement, other granule properties such as shape, porosity and surface area may evolve and it is the combined effects of these changes that influence the tableting and flow performance of granules.[85,113] Over-granulation is said to have occurred if tablet tensile strength cannot reach 2 MPa in the typical compaction range of 50 – 400 MPa. The induction or onset of over-granulation in MCC granules appears to correspond with a sharp rise in granule size.[120] Although useful insights have been obtained, the previous reports utilized a simplified model system of MCC powder granulated with pure water. A systematic study which considers the evolution of particulate and mechanical properties in more complex systems is yet to be shown.

Size reduction by milling has been able to salvage over-granulated powders.[115,121] This size reduction strategy is not a good practical solution to solve over-granulation since an ideal strategy should be to eliminate over-granulation by designing the formulation in such a way that the powder mixture is inherently resistant to it.

Dry granulation is also faced with a similar situation of loss of tabletability. Size enlargement in dry granulated powders deteriorates powder tabletability of plastic

materials.[106,115] However, brittle materials exhibit little or no sensitivity to granule size enlargement.[122] Larger granules of plastic materials are expected to have smaller area that can form inter-particulate bonding in tablet because they do not fracture when compressed.[123] This will lead to reduced tabletability. On the other hand, when brittle granules are compressed they fracture and produce fragments that generate larger surface area for bonding. If this induced fragmentation propensity can be demonstrated to be effective in addressing the over-granulation problem in wet granulation, it could make an impact in formulation development for this process.

Developing Multiple Unit Pellets Systems

Tableting of multi-particulates such as MUPS presents several challenges, including inability to form tablets of adequate mechanical strength and pressure-induced destruction of the functional coating layer when they do form.[108,124-128] These prevent tablet manufacturing from beads on a routine basis.

The problem of poor tabletability has been traditionally addressed during formulation development through the use of tablet excipients with superior tableting properties, such as microcrystalline cellulose (MCC).[129] In that case, a large amount of excipients is required to afford sufficient tablet mechanical strength. For example, in a mixture with non-compressible sand and a compressible polymer, 40% of the polymer was required to

form intact, but weak (~0.25 MPa tensile strength) tablets and 60% of the polymer was required to form reasonably strong tablets (1.3 MPa tensile strength) at 250 MPa compaction pressure.[130,131] In another example, 40% of a highly compressible polymer, hydroxypropyl cellulose (HPC), was insufficient to form an intact tablet with poorly compressible acetaminophen.[130,131] A tablet, however, cannot be too big (usually less than 1g) for easy swallowing and compliance by patients.[132] Consequently, this strategy of simply adding highly compressible excipients to a formulation is unfit for drugs that must be delivered in a high dose.

Work in this field has also focused on mitigating fracture of the functional coating by the admixture of beads with soft cushioning excipients and/or compressible excipients to protect the coating layer against fracture during compaction.[127,128,133,134] When excipients are mixed with beads, particle segregation is a foreseeable problem.[135] Layering of the top surface of beads with compressible excipients such as microcrystalline cellulose (MCC) to modify the mechanical properties of the beads is being pursued.[136-138] This approach, however, requires a huge amount of the layering excipients and still with mixed results.[136] At present, the task of routinely tableting MUPS remains an unmet need in drug delivery. A simple and easy-to-implement solution to this problem is of high pharmaceutical importance.

Developing Drug-Polymer Composites

A successfully designed ASD product must keep the drug amorphous throughout its entire shelf life in order to maintain the advantage of increased apparent solubility.[139,140] ASD tablet formulations have polymers as their most common excipients.[141] Plasticizers and surfactants may also be included in ASDs to facilitate processing and to improve wetting; however, they are added in small quantities.[142-144] Concentration of polymer(s) and/or the other additives in these drug composites are known to vary widely from one ASDs formulation to another, depending on the dose and physical stability.[141,143] The composition of ASDs is expected to influence the particle/powder structure and mechanical properties, which will in turn affect the tableting performance of the ASD powder. A clear understanding of such relationship, which is not yet well developed, will be critical for optimizing properties of ASD through structure modifications by formulation or particle engineering.[6] For ASDs, studies that highlight the impact of processing parameters such as compaction pressure or formulation variables on product performance are limited.[143,145,146] In the absence of such fundamental understanding, formulation of an ASD-based tablet remains empirical and may lead to formulation problems.

ASDs may also be exposed to a wide range of relative humidity (RH) conditions during processing and manufacturing of a tablet product. It is known that the degree of moisture sorption is dependent on the ASD composition, more drug leads to less sorption because

of increased hydrophobicity.[104,144] Moisture is known to have a complex effect on the tableting performance of materials.[147] It can improve deformation through plasticization but may also weaken intermolecular forces of attraction and consequently the interparticulate bonding strength when it forms a sheath on particle surface.[56,142,147] Therefore, understanding the impact of RH condition and sorbed moisture on both the mechanical properties of ASDs and their tableting performance is critical.

Objectives and Hypothesis

The primary motivation for this thesis is to understand the relationship between the particulate and mechanical properties and their impact on tableting performance of pharmaceutical powders. The study was divided into a series of projects, which when take together provide the necessary information to accomplish the overall goal. A key issue with tablets is the manufacturability to provide consistent tablet-to-tablet performance. The missing gap is the poor ability in the scientific design of formulation to ensure consistent manufacturability of pharmaceutical powder into tablets of adequate mechanical strength.

The guiding hypothesis of the thesis is that modulating particulate properties (size, shape, surface) and mechanical properties (plasticity, brittleness), based on the mechanistic understanding of their effect on the interparticulate bonding area generated in a tablet and

the interparticulate forces of attraction (bonding strength), leads to effective solutions to poor powder tableting performance. The ability to modulate these properties through appropriate particle engineering has been presented in this thesis in various contexts common to the pharmaceutical manufacturing, such as direct compression, high shear wet granulation, multi-unit pellet systems, and amorphous solid dispersion technology. This research is designed to solve compaction problems encountered during the manufacture of tablet products.

The objectives of the projects were:

1. To gain mechanistic understanding on the over-granulation problem in high shear wet granulation and to develop an effective strategy to overcome this problem through appropriate particle engineering.

2. To test the ability of surface coating with a layer of highly bonding polymer on improving tabletability of non-compressible granules. If successful, we will examine the applicability of this strategy in preparing directly compressible pellets for controlled-release applications.

3. To further understand the effect of moisture and composition on particle mechanical properties as well as the interplay between bonding area and bonding strength on powder tabletability.

Research plan and Thesis organization

In this thesis, each chapter is a self-contained module, arranged in the following order.

1. In Chapter 2, we examine the over-granulation tendency in MCC-Polyvinylpyrrolidone-Magnesium Stearate system to understand how wet granulation affects the structure and properties of the plastic microcrystalline cellulose. Granulation water level was optimized to improve powder flow for robust tablet formulation development capable of meeting needs of high speed tableting.

2. In Chapter 3, we develop a strategy to overcome the over-granulation problem by effective material engineering, based on the mechanistic understanding gleaned from the study in Chapter 2. In this work, we systematically study the granulation performance of binary mixtures of brittle excipients, i.e., lactose and dicalcium phosphate, and plastic microcrystalline cellulose.

3. In Chapters 4 and 5, we investigate a surface coating strategy for overcoming the poor tabletability problem of drug layered beads (multi-unit pellet system, MUPS). We developed this strategy to attain directly compressible beads which can increase tablet mechanical strength by increasing bonding area when compressed. This strategy was further applied to enable development of MUPS tablets with desired release profile.

4. In Chapter 6, we investigate the effect of moisture and drug loading on the mechanical properties and tableting performance of polymer-drug composites, i.e., amorphous solid dispersions (ASD). In this work, we highlighted the importance of plasticization/antiplasticization effects by moisture or drug on tableting performance of ASDs.

5. In Chapter 7, we systematically test the role of interplay between bonding area (BA) and bonding strength (BS) on tabletability. A change in mechanical properties of powders tends to have opposite effects on BA and BS, i.e., higher plasticity favors larger BA but also reduces BS. The net impact on powder tabletability depends on the interplay between BA and BS. We critically examine such BA and BS interplay through systematically varying compaction pressure and powder temperature during compaction or during tablet breaking for an amorphous polymer, Soluplus®.

Tablet friability test is a practical tool for assessing tablet mechanical strength. In Appendix I, we develop and validate an expedited tablet friability test method. Its applications to problems such as the required minimum tablet mechanical strength, and the effect of tablet size, shape and composition on tableting performance are demonstrated. We also show its potential as a material-sparing tool for guiding the scale-

up of tablet manufacturing.

To appropriately characterize tablet mechanical strength a correct relationship between tablet tensile strength and tablet porosity needs to be established. We have addressed a potential pitfall in fitting tablet tensile strength-porosity data by non-linear regression.

Table 1.1 New Molecular Entities Approved by the Food and Drugs Administration (FDA) in the US

Year	Number of Tablets Approved	Number of Capsules Approved	Number of Other Dosage Forms Approved	Percentage of Tablets in the Approved Drug Products
2009	13	0	8	62
2010	5	2	8	33
2011	17	1	5	74
2012	15	4	15	44
2013	13	4	8	52
2014	11	11	11	33
2015	3	5	4	25
Average				**46%**

Source:*http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Reports.NewOriginalNDA*

Figure 1.1 Material Engineering Activities involved in the Development of a Solid Dosage Form (Modified from Sun, 2009)

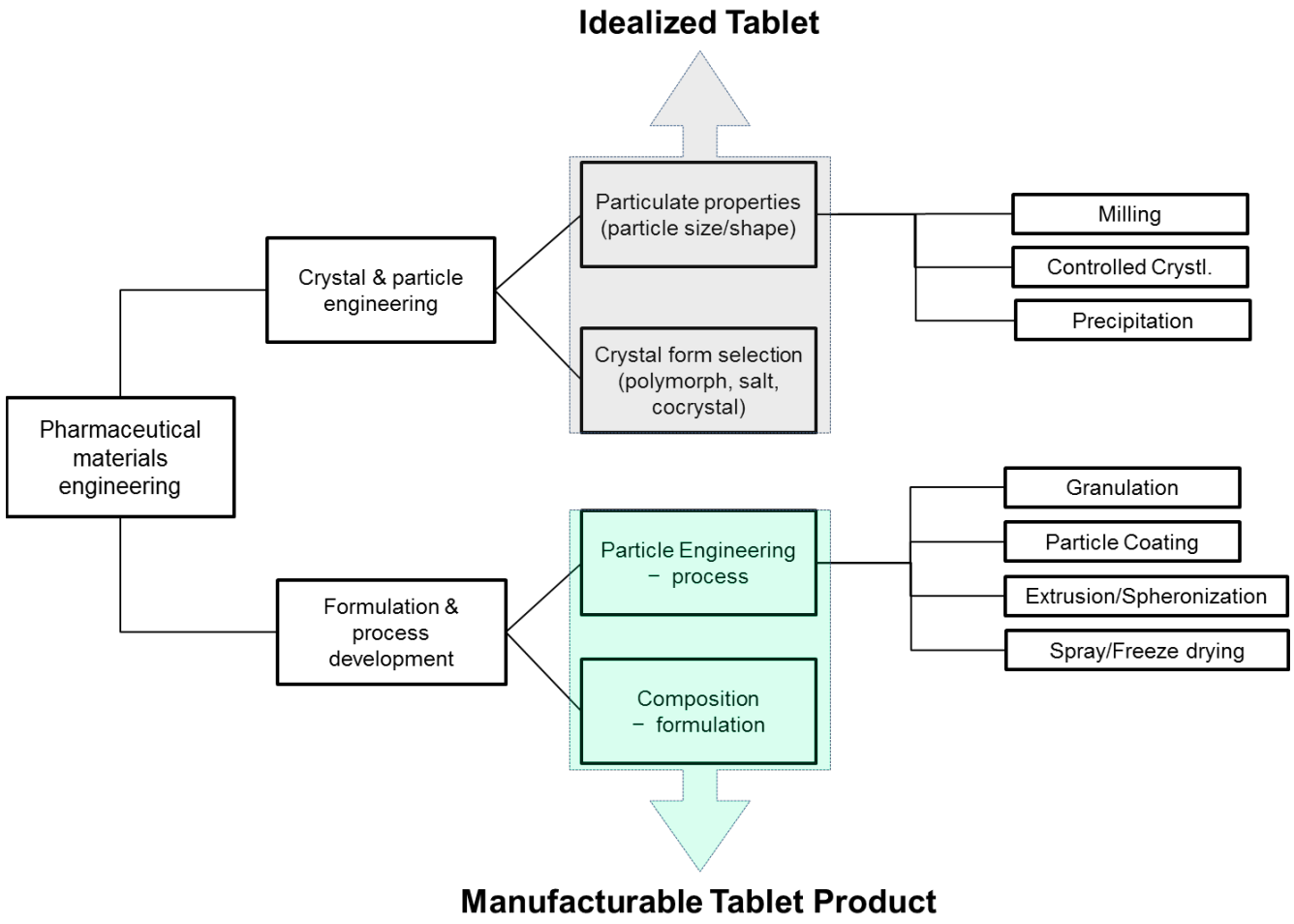
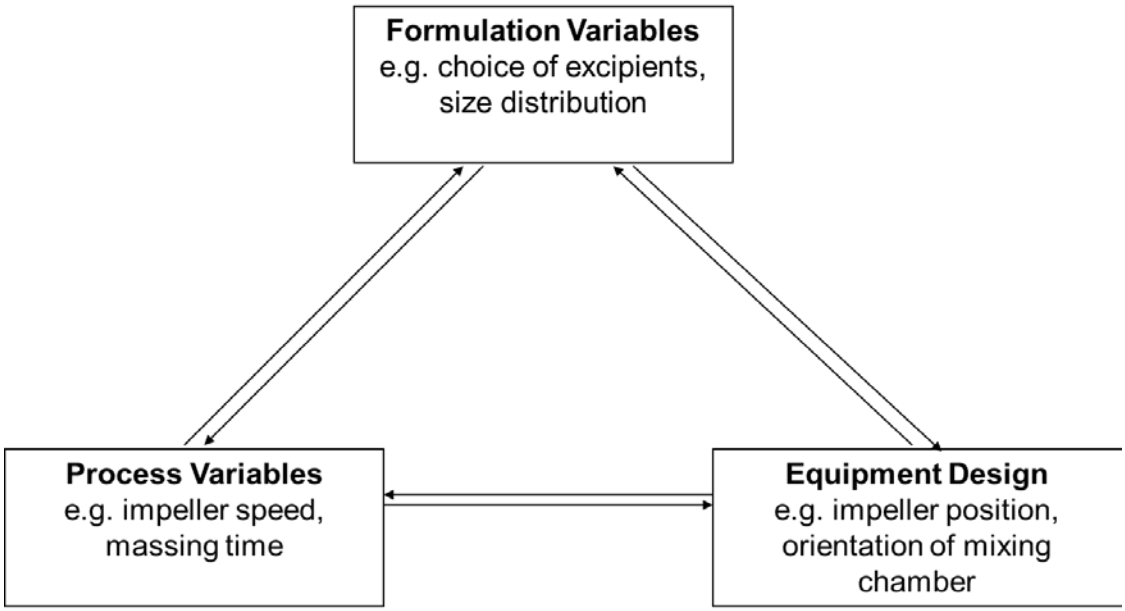


Figure 1.2 The interdependence of the variables in wet granulation that influence process outcome



CHAPTER 2. EVOLUTION OF STRUCTURE AND PROPERTIES OF GRANULES CONTAINING MICRO-CRYSTALLINE CELLULOSE AND POLYVINYLPYRROLIDONE DURING HIGH SHEAR WET GRANULATION

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Summary

Granulation behavior of microcrystalline cellulose (MCC) in the presence of 2.5% polyvinylpyrrolidone was systematically studied. Complex changes in flowability and tabletability of lubricated MCC granules are correlated to changes in intragranular porosity, morphology, surface smoothness, size distribution, and specific surface area (SSA). With 2.5% PVP, the use of 45% granulation water leads to 84% reduction in tablet tensile strength and 66% improvement in powder flowability. The changes in powder performance are explained by granule densification and surface smoothing. Over-granulation is observed at 45% water level, which is significantly lower than the 70% water required for unlubricated MCC granules without PVP. At >45% water levels, MCC granules flow well but cannot be compressed into intact tablets. Such changes in powder performance corresponds to the rapid growth into large and dense spheres with smooth surface. Compared to MCC alone, the onset of fast granule size enlargement occurs at a lower water level when 2.5% PVP is used. Although the use of 2.5% PVP hastens granule nucleation and growth rate, the mechanisms of over-granulation are the same, i.e., size enlargement, granule densification, surface smoothing, and particle rounding in both systems.

Introduction

Prior to tableting, many pharmaceutical powders are processed by high shear wet granulation (HSWG), where either water or a binder solution is sprayed onto a powder bed as it is vigorously agitated in a high shear mixer to produce agglomerates. The main objectives of granulation are to: 1) improve powder flow and increase bulk density to facilitate consistent die filling during high speed tableting; 2) eliminate dust; 3) prevent segregation of powder blends; and 4) improve content uniformity.[1-3] However, the improvement in powder handling properties is often associated with deteriorated tableting performance.[4-7] When tabletability deterioration is extreme, sufficiently strong tablets cannot be manufactured, a phenomeon known as "over-granulation".[8] To solve the problem of over-granulation effectively, a mechanistic understanding is highly desired. Microcrystalline cellulose (MCC), one of the most commonly used tablet excipients, has the problem of deteriorated tabletability when granulated either dry or wet.[7-9] Using the simplest system of MCC and water, it was recently shown that surface smoothing, particle rounding, reduced surface area, reduced granule porosity, and size enlargement during HSWG are responsible for the deteriorated tableting performance of MCC granules.[4-6,8] These changes in granule structure and properties lead to reduced total inter-granular bonding area, hence, loss of tablet strength.[10]

Although useful insights have been obtained from studying the simplest MCC and water system, the question of whether they are applicable to more complex systems remains

open. Further tests of over-granulation mechanisms using more complex systems are of critical importance for solving real-world over-granulation problems. Among possible excipients used in a HSWG formulation, a polymeric binder is expected to have a significant impact on the development of granule structure[7] by influencing the granule nucleation and growth kinetics.[11,12] Therefore, we investigate a system containing MCC and polyvinyl pyrrolidone (PVP), a common HSWG binder. In addition, we characterize granules after lubrication with 0.5% (wt%) magnesium stearate to ensure that knowledge derived from this work is more relevant to real pharmaceutical granules, which are invariably lubricated prior to tableting.

Materials and Methods

Materials

Microcrystalline cellulose, MCC, (Avicel PH101) was received from FMC Biopolymer (Philadelphia, PA). Polyvinylpyrrollidone (PVP) K30 was received from BASF (Geismar, Germany). Initial moisture content of the MCC was 4.24%. The amount of PVP was fixed at 2.5% of the weight of MCC for all batches. Water level was varied between 5% and 105% of the weight of MCC to prepare a total of 12 batches of granules. PVP binder solutions of different concentrations were prepared by dissolving PVP in distilled water corresponding to the desired water levels. A physical mixture of

MCC and PVP (0% water) was also prepared and characterized. Magnesium stearate was received from Mallinckrodt (St Louis, MO).

Methods

Wet Granulation

Each batch of granules, containing 100 g of MCC, was prepared using a custom-made laboratory-scale high-shear granulator (1.7 L bowl volume, modified KitchenAid food processor, two impellers, 1750 rpm). Whenever possible, a binder solution was sprayed at ~ 30 g/min through a nozzle placed approximately 5 cm above the surface of a moving powder bed. However, the binder solutions used for the 5% and 10% water levels were delivered drop-wise from the nozzle tip because they were too viscous to be sprayed. Wet granules were massed for 10 minutes after all binder solution had been added. The wet-massing time was purposely prolonged to ensure uniform distribution of binder solution in the powder bed and reproducibility of the granulation process.[5] The wet granules were tray-dried for ~24 hours at 40 ^{o}C in an oven and then placed in a 32% relative humidity chamber for at least 48 hours prior to further characterization. Water content in the granules ranged 3.7% - 4.8% based on thermogravimetry measurements.

Characterization of Tableting Properties

Powder compaction studies were conducted at room temperature and ~20% relative humidity. The physical mixture was prepared by mixing 100 g MCC and 2.5 g PVP in the granulator for 30 seconds. All samples were lubricated for 10 minutes with 0.5% magnesium stearate using a 1 quart (946 mL) twin shell dry blender (Patterson-Kelley, East Stroudsburg, PA) before characterizing their particulate properties, tableting performance, and flowability.

Tableting performance was tested on a compaction simulator (Presster, Metropolitan Computing Company, East Hanover, NJ) to simulate 10-station Korsch XL100 tablet press using round flat-faced tooling (9.5 mm diameter). The dwell time was set at 20 ms, corresponding to a production speed of 61,600 tablets/hr. Tablet dimensions were measured immediately after ejection. Tablet diametrical breaking force was determined using a texture analyzer (TA-XT2i, Texture Technologies Corporation, Scarsdale, NY) at a speed of 0.01 mm/s and 5 g trigger force. Tablet tensile strength was calculated from the breaking force and tablet dimensions.[13] True density of the MCC-PVP-magnesium stearate composite was obtained by fitting tablet density – compaction pressure data of the physical blend using the Sun method.[14] Powder tabletability (tablet tensile strength as a function of compaction pressure), compressibility (tablet porosity as a function of

compaction pressure), and compactibility (tablet tensile strength as a function of porosity) were obtained.[15,16]

Characterization of Powder Flow Properties

Powder flowability was measured in triplicate using a ring shear tester (RST-XS, Dietmar, Schulze, Wolfenbüttel, Germany). The powders were first pre-sheared under a normal consolidation stress of 6 kPa. Shear tests were subsequetly performed under 0.23, 2, 3, 4, 5 and 0.23 kPa normal stresses to construct a yield locus. Unconfined yield strengths, f_c, and the corresponding major principal stresses, σ_n, were determined by drawing two Mohr's circles using standard procedures.[17] The flow factor, $ff = \sigma_n/f_c$ was subsequently calculated.[18] A higher *ff* generally indicates better flow property. Avicel PH102 (FMC Biopolymer, Philadelphia, PA was also tested under the same experimental conditions) as a reference powder for adequate flowability.[19,20] Powder bulk density was calculated from the powder fill weight and volume of the shear cell.

Characterization of Particulate Properties

To obtain qualitative information on particle shape, size, and surface properties, samples were sputter-coated with platinum (~50 Å coating thickness) and observed with a

Scanning Electron Microscope (SEM, Quanta 200F, FEI, USA) operated at 10 kV. Particle size distributions were measured using a laser scattering particle size analyzer (Malvern Mastersizer 2000, Malvern Instruments Ltd., Worcestershire, UK). An inlet air pressure of 1 bar, a feed rate of 30%, and obscuration of 0.6 – 6% were used for data collection. Granules produced with water levels > 65% contained particles larger than 2000 μm, which is too large for the laser scattering sizer to yield accurate size distribution information. In these cases, granule size was obtained from SEM images using the maximum Feret diameter to give semi-quantitative information on granule size changes. Mercury intrusion porosimetry (MIP, Autopore IV 9500, Micromeritics, Norcross, GA) was used to measure the pore-volume distibution of the materials. The incremental pore volumes were determined in the range of 5 to 33,000 psi. The pore diameter at a given pressure was computed using the Washbun equation.[21] Intragranular pore size cut off points were determined by examining the pore size distribution data and SEM images for each powder, assuming intragranular pores are significantly smaller than intergranular pores.

The specific surface area (SSA) of samples was determined using Krypton adsorption over the partial pressure, P/P_o, range of 0.05 – 0.2, analyzed using the Brunauer, Emmet and Teller (BET) method[22] (ASAP 2020, Micromeritics, Norcross, GA).

Data Analyses

Origin statistical software (Origin® 9.0, OriginLab Corp., Northampton, MA) was used for all data fitting and statistical analyses. The best fitting function for each set of data was obtained using non-linear regression by systematically varying the parameters until the residual sum of squares between the experimental data and predicted values reached a global minimum. Residuals plots were inspected to ensure the true global minimum was obtained for each set of data.[23] Non-linear regression yielded both mean and standard errors for each parameter in the fitting function.

Results

Particulate Properties

Table 2.1 summarizes the key observations on granules and their properties linked to powder flow and compaction behaviors essential for tablet manufacturing. SEM images provide qualitative information on granule shape, size, and surface features (Figure 2.1). In the physical mixture, comprised of MCC, PVP, and magnesium stearate particles, irregularly shaped porous MCC agglomerates with uneven surface can be observed (Figure 2.1A). Granulation with 15% water leads to smoother MCC agglomerates and the generation of new agglomerates of small particles (Figure 2.1B, arrowed). With

increasing granulating water level, 25 – 45% (Figures 2.1C, D & E), the number of observable pores diminishes and fine surface projections on MCC have been completely eliminated. The MCC particles are more regular in shape while the number of new agglomerates formed from the small particles increases. At 45% water these newly formed agglomerates appear larger than those at lower water level (Figure 2.1E). At the 55% water level, many large surface smooth granules devoid of observable pores are seen (Figure 2.1F). In most of these granules, the primary particles cannot be distinguished in the SEM images and they appear more rounded in shape. With increasing granulating water, ≥ 65%, granules continue to enlarge and become dense spheres (Figures 2.1G – K). In this range of water level, granules differ in size but similar in surface features and shape (Table 2.1). Small flaky magnesium stearate particles are found on the surface of all granules, which were not present when images of unlubricated granules were examined.

Granule size is represented either by the median volume diameter, d_{50}, for granules prepared with lower water levels or by the median of the maximum Feret diameter for the higher water level granules (Table 2.1). The median of the Feret diameter for the 65% granules, 343.8 µm, is comparable to d_{50}, obtained by laser diffraction, 356.4 ± 13.2 µm. When compared to the physical mixture, granules size decreases when 15 – 35% water was used for granulation. At 35% water level, the granule size decreases by ~19% (Table 2.1). This suggests that primary MCC particles mainly undergo surface smoothing and

densification instead of forming larger granules within this range of granulating water. Interestingly, while the volume median diameter, d_{50}, from the particle size distribution of granules obtained at the 45% water granulating level increases by merely ~1% from that of the physical mixture, the volume mean diameter, $d_{[4,3]}$, increases by 62.8%. The difference is because $d_{[4,3]}$ are more sensitive to the presence of even a small number of large particles than d_{50} and the overall size distribution is bi-modal for this sample (Figure 2.S1). The $d_{[4,3]}$ is consistent with the observation from SEM images that a few large agglomerates are found in this batch of granules. The size distribution of some of the granules is bimodal, especially the 45% water granules. The SSA is 0.897 ± 0.0168 m^2/g for the physical mixture and decreases consistently with increasing water level (Table 2.1). Nearly ~80% of the SSA of the starting material is lost during the granulation process when 55% granulating water is used. Further increase in water level up to 105% only leads to ~14% additional loss in SSA.

To determine granule porosity from MIP data, a cut-off pore size must be determined to separate intra-granular pores from inter-granular pores within a batch of granules. The cut-off size used was 7.2 μm for 0 – 25% water level granules, 3.8 μm for 35 – 75%, 0.1 μm for 85% - 105% water level granules. These cut-off sizes were selected based on the pore-size distribution and SEM data. The pore-size distributions for the samples are either multimodal or bimodal, which becomes less resolved with increasing granulation water level. Although errors in calculating the intra-granular pore volumes are inevitable

in this exercise, the estimated granule porosity still provides useful information for identifying a qualitative trend. From 0 to 15% water level granule porosity maintains at ~20%, followed by steady decrease from 15% to 55% water level (~79% loss in porosity, Table 2.1) and then stays relatively unchanged at ~4.5% from 55% to 75% water level. Further increase in water level (85 – 105%) leads to approximately constant porosity of ~1.3%.

Tableting Properties

The tabletability of granules generally decreases with increasing water level (Figure 2.2). However, the tabletability profiles of the granule produced at 5% water level and the physical mixture cross at 250 MPa. When compaction pressure is >250 MPa, the granule has higher tensile strength than the physical mixture. There is a ~50% drop in tablet tensile strength over nearly the entire compaction pressure range when water level increases from 5 to 10%. With further increase to 35% water level, tensile strength reduces gradually (Figures 2.2 & 2.5A). The granules prepared at 45% water granulating level do not form tablets of tensile strength > 2 MPa even at 400 MPa compaction pressure. No intact tablet can be formed for granules prepared with 55% - 105% water at any pressures.

Compressibility plots show that the physical mixture is the most compressible because it forms tablets with the lowest porosity at any given compaction pressure up to 300 MPa, where tablet porosity is close to zero (Figure 2.3). Tablet porosities are calculated using true density value of 1.437 ± 0.011 g/cm^3, determined from fitting tablet density vs. pressure data of the physical mixture. Tablet porosities for granulated powders are comparable at low compaction pressures but diverge at higher pressures.

The compactibility plots (Figure 2.4) have been fitted to the Ryshkewitch – Duckworth equation[24], as expressed in *Equation 2.1*:

$$\sigma = \sigma_o e^{-b\varepsilon} \qquad 2.1$$

where σ is the tablet tensile strength, ε is the porosity, σ_o is the tensile strength at zero porosity and b is a constant. At low porosities, the data is well described by this equation. Deviation from the Ryshkewitch – Duckworth equation at high porosities is observed for all granules (Figure 2.4), as previously observed in other systems.[25] However, it is interesting to note that the data points deviate from the fitted line at a lower porosity for granules prepared with a higher level of water.

The initial 5% water leads to a higher σ_o than the physical mixture, from 9.88 ± 0.08 MPa to 13.23 ± 0.25. Further increment in granulation water level results in a decrease in σ_o. Similarly, the tensile strength of tablets at 300 MPa compaction pressure rises at 5% water level and decreases with further increase in the level of granulating water (Figure 2.5A). At 300 MPa, which is within the typical range of compaction pressure used in tablet manufacture, tablet tensile strength have sufficiently approached a plateau for most powders in this study. The constant *b*, although close to each other, appears to increase with increasing granulating water level (Figure 2.5B). At 300 MPa, tablet porosity initially rises with increasing water level from 0% to 10% and remains essentially unchanged at the 10 – 15% water level before dropping at 25% water level (Figure 2.5C). Subsequently, porosity stays relatively constant up to 45% water level.

SEM images of the tablet fracture surface of the powder granulated with 45% water, after diametrical compression test, show deformed granules with clear outline as exemplified by Figure 2.6. Evidently, tablet fracture plane runs around granule instead of through them, indicating that bonding strength at the contact between two adjacent granules is lower than the strength of the granule. This is reasonable since the granules were lubricated with more weakly bonding magnesium stearate. Moreover, the lack of any sign for granule fragmentation is consistent with the well-known plasticity of this material.

The impact of granule size, specific surface area, and granule porosity on tableting performance is presented in Figure 2.7. In spite of the little change in d_{50} (~1%) in the 0 – 45% range of granulating water, there is ~84% drop in tablet tensile strength. In the same range of water level, powder SSA and porosity decrease by ~58% and ~51%, respectively. Clearly, changes in SSA and porosity correlate with the tableting performance of granules better than granule size. The reductions in SSA and porosity suggest surface smoothing and granule densification, which are supported by SEM data (Figures 2.1A-E).

Flow Properties

Flow property, assessed by the flow factor[18] , *ff*, initially improves with the use of 15% water and then stays nearly unchanged up to 35% granulating water before it sharply increases at 45% and higher water level (Table 2.1). Granules at ≥ 65% granulating water level are too large to be tested satisfactorily on the shear cell. All granules were observed to have excellent flowability during the filling of tablet die for compression.

Despite the size reduction that occurs after granulating with 15 – 35% water, the flow property is still better than Avicel PH102 (Table 2.1). Even though there is ~9% drop in granule d_{50} from 15% to 25%, the powder flowability is not heavily affected as indicated by just ~3% drop in *ff*. This means the improvement in flowability due to surface

smoothing and densification outplays the deterioration due to size reduction. The flowability of the physical mixture (*ff* = 13.2 ± 0.8) is lower than Avicel PH102 (*ff* = 15.3 ± 0.23). This is not surprising given the mixture is predominantly the finer grade of MCC, Avicel PH101, which exhibits poorer flowability than Avicel PH102.[26] All granulated powders exhibit better flowability than Avicel PH102, suggesting adequate flowability for a high speed tableting process.[19] Bulk density increases consistently with increasing water level (Table 2.1).

Discussion

Granulation has become an essential operation for modulating powder properties such as flowability before further processing in pharmaceutical solid dosage form development.[1] In this work, we set to examine the impact of water level, up to 105% (wt %) on the particulate properties as well as flow and tableting properties of predominantly microcrystalline cellulose granules for a mechanistic understanding on over-granulation. These process parameters play key roles in the granulation of any powder.[3] For instance, granulating water level influences the onset of granule nucleation, granule size, density, and shape.[4,8,11] In some cases, granulation without binder produces mechanically weak granules and tablets. The main purpose of incorporating polymeric binder is to induce agglomeration,[11,12] but it can also improve granule strength and enhance compactibility.[27]

Massing or kneading time is the period in which granules are subjected to shear forces in the granulator after all the granulation liquid has been added. Massing time, when prolonged, can be used to minimize differences in granule properties, such as size, that occur as a result of slight and inadvertent changes in process parameters, for example, amount of water added.[5] A lubricant is used to facilitate easy tablet ejection and minimize picking. However, it can also deteriorate tablet mechanical strength.[28] To gain insights more relevant to real-world applications, we investigate HSWG behavior of MCC in presence of a binder under prolonged massing time and with lubrication.

Effect of wet granulation on particulate properties

Granulation is primarily a size enlargement technique through fusion of primary particles. During wet granulation, the distribution of liquid under the shear stress leads to granule growth as well as breakage and attrition as powder is agitated.[2,3] Granule growth results from particles coalescence and consolidation during agitation. Initially formed granules may break apart if the impact forces are sufficiently strong.[3] In this study, the absence of size enlargement up to 35% water level, even with 2.5% PVP binder, suggests insufficient amount of granulation liquid available for granule growth.[12] This is indirect evidence that supports the role of liquid bridges to granule growth. The observation of large agglomerates in these granules (Figure 2.1) indicates the inhomogeneous

distribution of binder solution.[11] Some particles coalesce to form large granules in the regions relatively richer in binder solution before they are redistributed to other areas of the powder bed. The drastic size enlargement at ≥55% water indicates the saturation point has been surpassed, where excess binder solution is available for extensive granule growth by coalescence.[3,12] The d_{50} and $d_{[4,3]}$ values exhibited a minimum at 35% and 25% granulating water level respectively (Figure 2.S1). The big difference between $d_{[4,3]}$ and d_{50} at 45% water level is caused by the existence of the discrete, large agglomerates since $d_{[4,3]}$, the volume weighted mean size, is more influenced by the presence of larger agglomerates than the volume weighted median size, d_{50}. The initial size reduction and impact of larger agglomerates on $d_{[4,3]}$ is in agreement with the results obtained in a previous study, where MCC was granulated with only water (5 – 95%).[4] The granule size for the MCC-PVP-water system is always larger than the MCC-water system at each water level. This demonstrates the role of PVP, a polymeric binder on granule size by promoting more agglomeration, perhaps because of the increased viscosity of the binder solution favors granule growth.[12] This is also evidenced by the fact that agglomerates can be located in the 15% water level granules but not until 45% in the previous study.[4] Furthermore, the minimum d_{50} occurred at 45% water level for the MCC-water system but 35% for the MCC-PVP-water system. This finding justifies the inclusion of polymeric binders to promote size enlargement.[27] Polymeric binder solutions may, however, have problems such as more uneven binder distribution as a result of the difficulty in uniform spraying and distribution in powder bed due to its higher solution

viscosity. Uneven binder distribution causes non-uniform nucleation,[11] which may result in wider and/or multi-modal granule size distributions. The bimodality in size distribution is most prominent for the 45% water level granule but absent in the 55% water granule. This means that nucleation phase ends at a water level slightly above 45% (Figure 2.1).

The powder SSA depends on factors such as particle size, surface roughness, and porosity. Smaller particle size, fine surface protrusions, and higher porosity all favor higher SSA. The reduction in powder SSA in the 0 – 45% water range during granulation may be explained by the removal of particle fine surface features and particle densification (Table 2.1 and Figure 2.1) since particle size actually decreases when water level increases from 15 to 35%. For the higher water level range (55 – 105%), the reduction in SSA can be explained by both the profound size enlargement and particle densification. The slightly lower SSA of the PVP-containing granules than the MCC only granules is most likely due to the smaller size of granules in the latter system. Interestingly, the SSA of PVP-containing granules prepared with 85 – 105% water levels are comparable to the granules without PVP and magnesium stearate lubrication. Since the SSA in this range is very small, there may not be enough resolution for accurate determination. The steady reduction in intra-granular porosity is a result of plasticization of MCC by water with or without PVP. When more plastic agglomerates are subjected to intense shear stresses, they undergo consolidation (i.e. elimination of pores) more easily[5]

The difference between the MCC-PVP and MCC only systems is the initially high porosity of the PVP-containing granules in the lower water range (0 – 35%, Figure 2.S2). This may be due to the easier formation of porous agglomerates consisting of mainly smaller particles when PVP binder solution is used. The viscous nature of a polymeric binder solution is capable of causing these particles to stick together even at low granulating water content. The majority of particles in the 15% water level granules have smooth surface with diminished number of pores, suggesting they are denser than particles in the physical mixture (Figure 2.1 and Table 2.1). However, the presence of the newly formed porous agglomerates leads to a slight increase in porosity between 0 and 15% water level granules (Table 1).

Effect of Wet Granulation on Tableting Performance

For the ungranulated mixture used in this study, tablet tensile strength rises sharply with increasing pressure before leveling off at ~200 MPa (Figure 2.2) while tablet porosity sharply decreases initially and then gradually levels off at > 200 MPa (Figure 2.3). The mechanical strength of a tablet is determined by the inter-particulate bonding area and the bonding strength over a unit bonding area.[10] Since lower porosity corresponds to larger bonding area for the same powder, tablet tensile strength is expected to increase with decreasing porosity. Therefore, the shape of tabletability profile (Figure 2.2) corresponds

well with that of the compressibility profile (Figure 2.3). When a well densified powder (low porosity) is subjected to further increase in pressure, particles undergo mostly reversible elastic deformation but little plastic deformation. Tablet porosity after ejection only slightly decreases with increasing pressure and tensile strength only slightly increases.[16] In fact, excessive elastic recovery during decompression phase can compromise tablet integrity and a lower tensile strength may be observed, a phenomenon known as over-compression.[29]

Up to ~350 MPa, a plateau is not obvious in the tabletability plot of the 5% water level granules (Figure 2.2). This corresponds well with the continuous decrease in tablet porosity (Figure 2.3). Interestingly, the tabletability curve of the 5% water granulated powder crosses that of the physical mixture at ~250 MPa (Figure 2.2). At pressures > 250 MPa, tablet tensile strength is higher for the granulated powder. This leads to the peak in the tensile strength as a function of granulating water level (Figure 2.5A). Because tablet porosity of the 5% water granulated powder is higher than that of the physical mixture (Figure 2.3) and because of the similar particle shape (Figure 2.1), the bonding area is expected to be smaller in the 5% water granulated powder. For its tablets to have higher tensile strength, bonding strength must be higher than the physical mixture. This is supported by the higher extrapolated maximum tensile strength for the 5% granulated powder (Figures 2.2 & 2.5A). This seemingly strange observation may be understood by considering different distribution of PVP in the two powders. PVP is

more uniformly distributed in the granulated powder by covering MCC particle surfaces than in the physical mixture. At low pressure region (< 250 MPa), bonding area is the dominating factor and the more compressible physical mixture exhibit lower tablet porosity and, therefore, higher tensile strength. However, bonding area difference is diminished at high pressures, where bonding strength is the determining factor for tensile strength. Since bonding strength of the 5% water granulated powder is higher, it is likely because of the PVP coating. The interplay between bonding area and bonding strength results in the cross over at 250 MPa.[30] The value of *b* gradually increases up to 45% water level (Figure 2.5B). As granulating water level increases, granules are expected to become less compressible due to granule densification, which reduces plasticity.[4-6] However, tablet porosity at comparable compaction pressure does not show the trend of monotonic increase in tablet porosity with increasing water level, which is predicted by considering deformability of granules alone (Figure 2.5C). Rather, granules prepared with 25 – 45% water exhibit lower porosities than that with 15% water. This may be explained by the fact that the more round shape and smoother surfaces for granules prepared with 25 – 45% water have better packing efficiency, which contributes to the lower tablet porosity.

With regards to tabletability, surface smoothing and particle shape rounding effects are expected to diminish total bonding area by limiting mechanical interlocking. This and granule densification collectively lead to the decrease in tabletability in the 10 – 55%

range (Figure 2.5). Such effect is so profound that intact tablets cannot be formed in the 55 – 105% range. For the densest granules, they behave like elastic balls under ordinary compaction pressure, which leads to negligible bonding area.[10] When 45% or more water was used, granulated powders enter the over-granulation region with tensile strength lower than 2 MPa (Figure 2.2). The transition to the over-granulation state is associated with the significant reduction in intra-granular pores, SSA, and particle shape rounding (Figure 2.1 and Table 2.1).

Effect of Wet Granulation on Powder Flowability

Every successful high speed tableting requires adequate powder flow to ensure consistent die filling and good control of tablet weight.[19] Powder flow can be affected by particle size, surface texture, [17] environmental conditions[31] as well as powder history such as storage time.[32] Fine powders generally do not flow well because of high particle cohesion.[26] The physical mixture of MCC-PVP exhibits the poorest flowability primarily because of the surface roughness which leads to higher frictional force during relative movement of particle due to mechanical interlocking (Table 2.1).[4] The surface smoothing, particle shape rounding, granule densification, and size enlargement all favor improved powder flowability. The significant improvement in flowability after granulating with 15% water may be attributed to the removal of the fine surface features

since changes in particle size and shape are negligible (Figure 2.1 and Table 2.1). It was suggested that the presence of larger particles in a fine powder can sometimes significantly improve powder flowability.[33] However, this is unlikely to be the reason to the improved flowability of these 15 – 35% water level granules because the volume of larger particle is actually smaller than that in the starting powder based on the d_{50}. In the 15 – 35% water range, flowability is relatively constant despite the higher bulk density, lower intra-granular porosity and more round shape (Figure 2.1). This suggests that the granule densification and shape rounding are not as effective in improving powder flow as surface smoothing. At ≥45% water range, the significant improvement in flowability is essentially a result of size enlargement. The flowability of MCC-PVP physical mixture is poorer than Avicel PH102 and is, hence, not suitable for high speed tableting.[19] However, granulating with 15% water adequately improves the powder flowability to be better than Avicel PH102, hence, suitable for high speed tableting. For this powder, the HSWG process can stop at 15% water level to avoid the potential problem of deteriorated tabletability.

Comparison of Simplified and Complex MCC Formulations

In addition to the previously discussed similarities and differences between the evolution of particulate properties in the MCC-PVP-water-magnesium stearate system and MCC-

water system,[4-6,8] the sequence of events with the progression of granulation process is the same. First, fine features on particle surface are removed at low water levels to result in surface smoothing attributable to the intense shear stress during the granulation process. This is followed by nucleation of granules, as evidenced by the appearance of large agglomerates. As more liquid is added, the powders become more plasticized and porous agglomerates gradually evolve into round dense granule where the original particles cannot be identified. Consequently, a sharp transition to fast granule growth phase occurs while keeping the spherical shape of granules.

When PVP is present, nucleation phase commences at as low as 15% water level in contrast to the ~45% water level without PVP.[4] This suggests that the use of a binder hastens agglomeration. For the same reason, the fast granule growth phase starts at ~55% water level with PVP but ~65% for MCC without PVP [8] (Figure 2.S2).

At the same water level, the tabletability of PVP-containing granule is always lower than that of granules without PVP.[4,8] This discrepancy is not surprising since MCC-PVP granules were prepared with longer massing time and lubrication was applied prior to compaction. The former factor will lead to more densification, and hence, lower deformability of granules. When compressed under the same conditions, smaller bonding area is expected. The later factor will reduce bonding strength between particles.[28,34] The adverse effect on powder tabletability by lubricant is also expected to be more profound at higher water level as shown by previous workers[7] because of the better coverage by

lubricant on smaller surface area by a fixed amount of lubricant (Figure 2.1). Both reduced bonding area and bonding strength lead to deteriorated tablet tensile strength since granules are separated at the interfaces rather than through the granules (Figure 2.6). This effect is thus expected to contribute to the deterioration in compactibility (Figure 2.4) and σ_0 (Figure 2.5A).

The effect of granulation water on powder flowability in MCC-PVP and MCC follows different patterns. In the MCC-PVP system, granule flowability increases from 0% to 55% (Table 1). However, in the MCC only system, the flowability was improved only up to 15% granulation water level and stays relatively constant at higher water level.[4] At the same water level, the flowability of MCC-PVP granules is always better than that without PVP. The different dependence on granulation water level is in agreement with the observed smoother surfaces of the MCC-PVP granules and larger size (Figure 2.S1). Regardless of the reason for the differences, the use of PVP is advantageous to the performance of granules produced by HSWG process.

Conclusion

For the lubricated MCC–PVP granules, increasing water level leads to both improvement in flowability and deterioration in tableting performance due to mechanisms qualitatively the same as those observed in the MCC granules, i.e., particle surface area reduction,

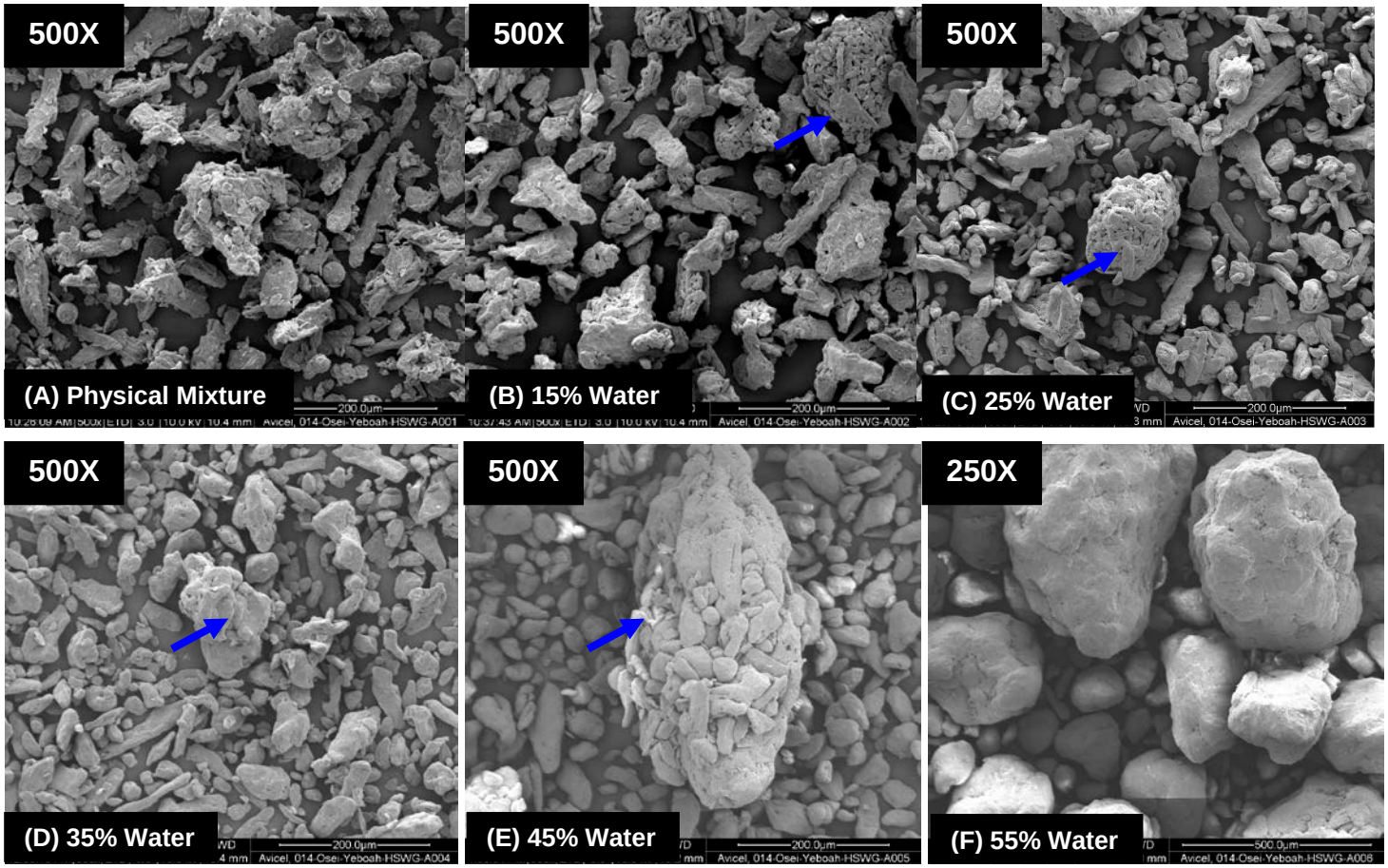
surface smoothing, granule densification, and size enlargement. However, the transition into the over-granulation zone corresponds to a lower water level when PVP and magnesium stearate are used. The observation of concurring deterioration in tabletability and enhancement in flowability suggests that, for the MCC-PVP system, the HSWG process should be terminated as soon as satisfactory powder flowability is attained to minimize the risk of over-granulation. The same strategy likely applies to other high shear wet granulation formulations that are predominantly plastic.

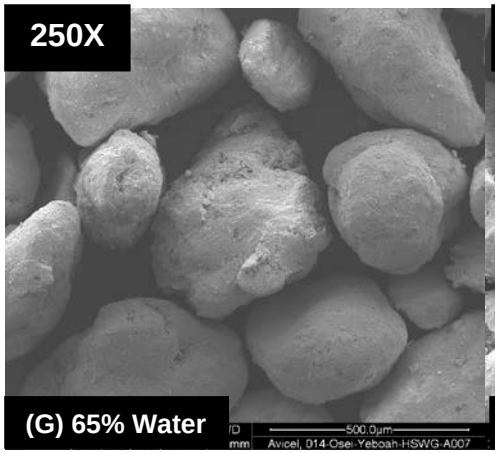
Table 2.1 Evolution of size, surface area, porosity, bulk density and flow factor with increasing granulating water level

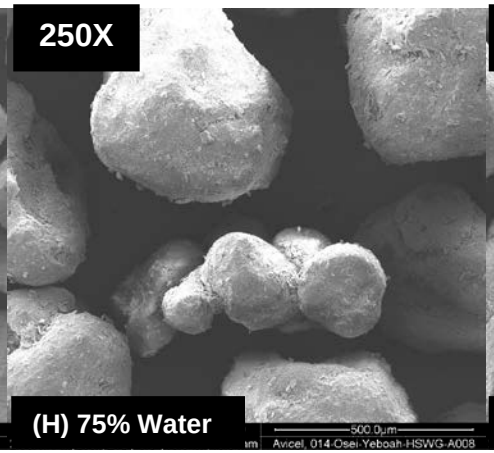
Water Level (%)	Particle Size d_{50}(μm)	SSA (m^2/g)	Porosity (%)	Bulk Density (kg/m^3) [b]	Flow Factor [b]	Performance	
						Tablet strength	Powder Flowability
0	62.7 (±3.0)	0.8967 (±0.0168)	20.03	421.3 (±0.6)	13.20 (±0.83)	Very Strong	Poor
15	60.2 (±1.6)	0.7295 (±0.0086)	20.29	483.0 (±2.0)	18.96 (±0.30)	Very Strong	Adequate
25	54.6 (±1.1)	0.7052 (±0.0105)	20.21	559.0 (±2.0)	18.44 (±0.36)	Strong	Adequate
35	50.7 (±2.5)	0.5863 (±0.0089)	12.75	620.3 (±2.1)	19.01 (±0.56)	Strong	Adequate
45	63.4 (±1.8)	0.3739 (±0.0049)	9.676	702.0 (±2.0)	23.25 (±0.49)	Weak	Good
55	168.7 (±20.5)	0.1770 (±0.0012)	4.27	853 (±3.0)	51.01 (±0.91)	0	Excellent
65	343.8[a]	0.101 (±0.0009)	4.41	NM[c]	NM[c]	0	Excellent
75	468.8[a]	0.091 (±0.0009)	4.68	NM[c]	NM[c]	0	Excellent
85	625.2[a]	0.0765 (±0.0008)	1.20	NM[c]	NM[c]	0	Excellent
95	743.8[a]	0.0973 (±0.0014)	1.30	NM[c]	NM[c]	0	Excellent
105	789.7[a]	0.1041 (±0.0015)	1.45	NM[c]	NM[c]	0	Excellent

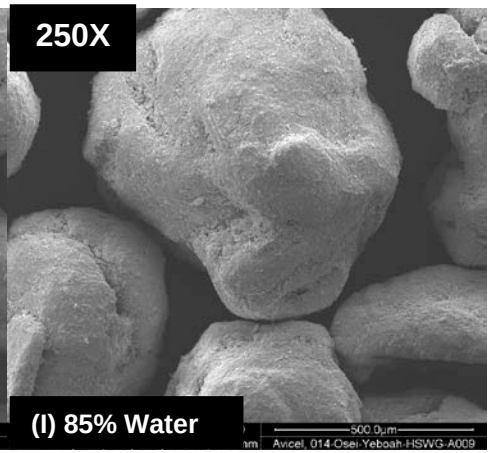
[a] Maximum Feret diameter obtained from SEM images
[b] Flow factor and bulk density of Avicel PH102 are 15.27 ± 0.23 and 403.3 ± 0.6 kg/m^3, respectively.
[c] Not measured due to overly large granule sizes

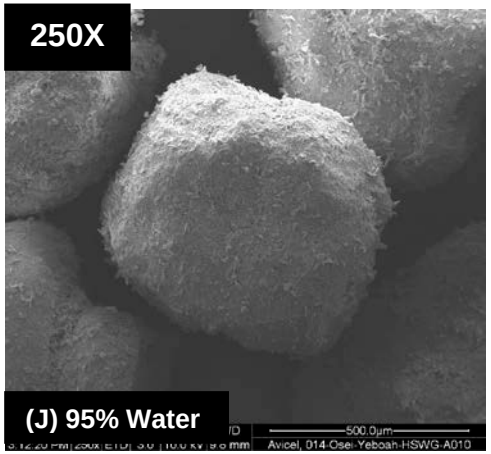
Figure 2.1 SEM images of physical mixture and granules at various granulating water levels




250X
(G) 65% Water
500.0µm
Avicel, 014-Osei-Yeboah-HSWG-A007


250X
(H) 75% Water
500.0µm
Avicel, 014-Osei-Yeboah-HSWG-A008


250X
(I) 85% Water
500.0µm
Avicel, 014-Osei-Yeboah-HSWG-A009


250X
(J) 95% Water
500.0µm
Avicel, 014-Osei-Yeboah-HSWG-A010

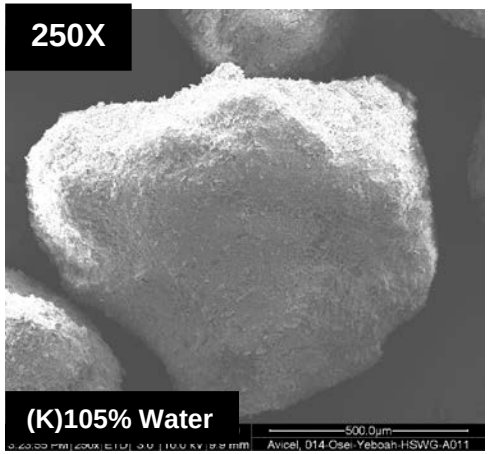

250X
(K)105% Water
500.0µm
Avicel, 014-Osei-Yeboah-HSWG-A011

Figure 2.2 Tabletability of MCC – PVP physical mixture and granules prepared with different amounts of water used for granulation

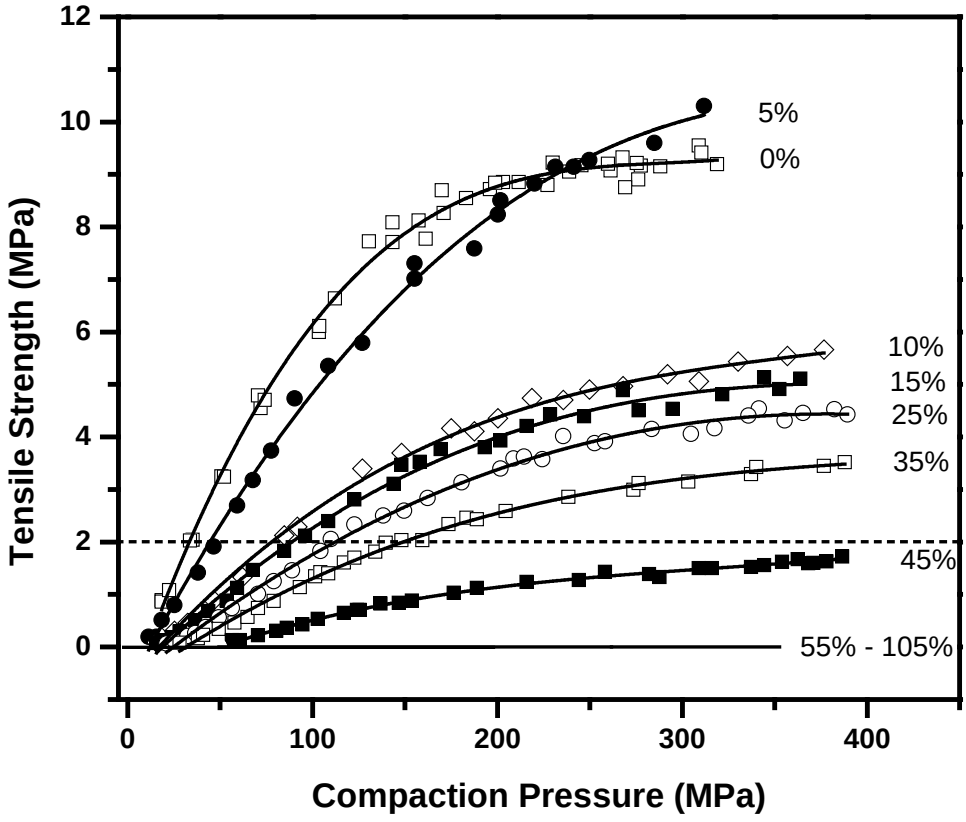


Figure 2.3 Compressibility of MCC – PVP physical mixture and granules prepared with different amounts of water

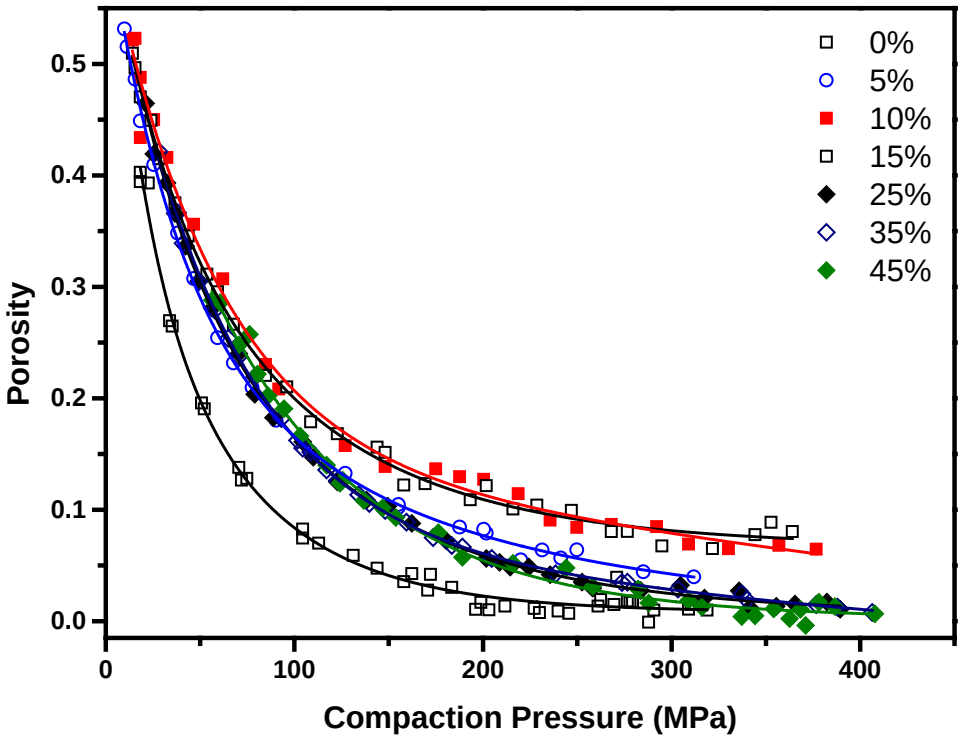


Figure 2.4 Compactibility of MCC – PVP physical mixture and granules prepared with different amounts of water

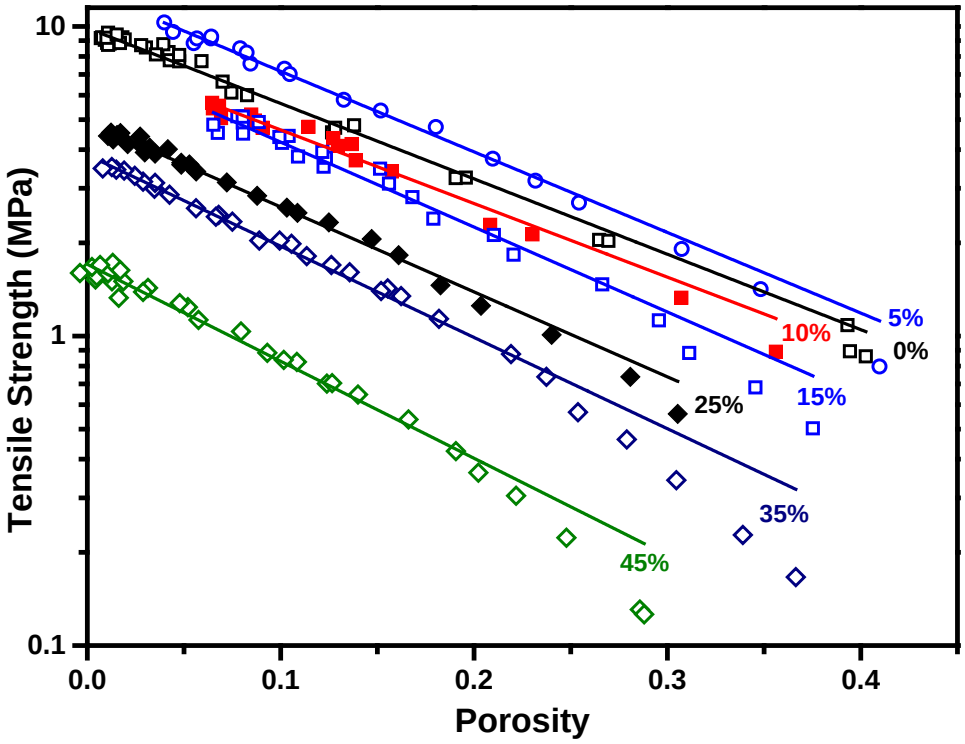


Figure 2.5 Effect of granulating water level on (A) tablet tensile strength at 300 MPa compaction pressure [open triangle] and tensile strength at 0 porosity [solid diamond] (B) the slope of the Ryshkewitch equation (change in tablet tensile strength with porosity) (C) tablet porosity at 300 MPa compaction pressure

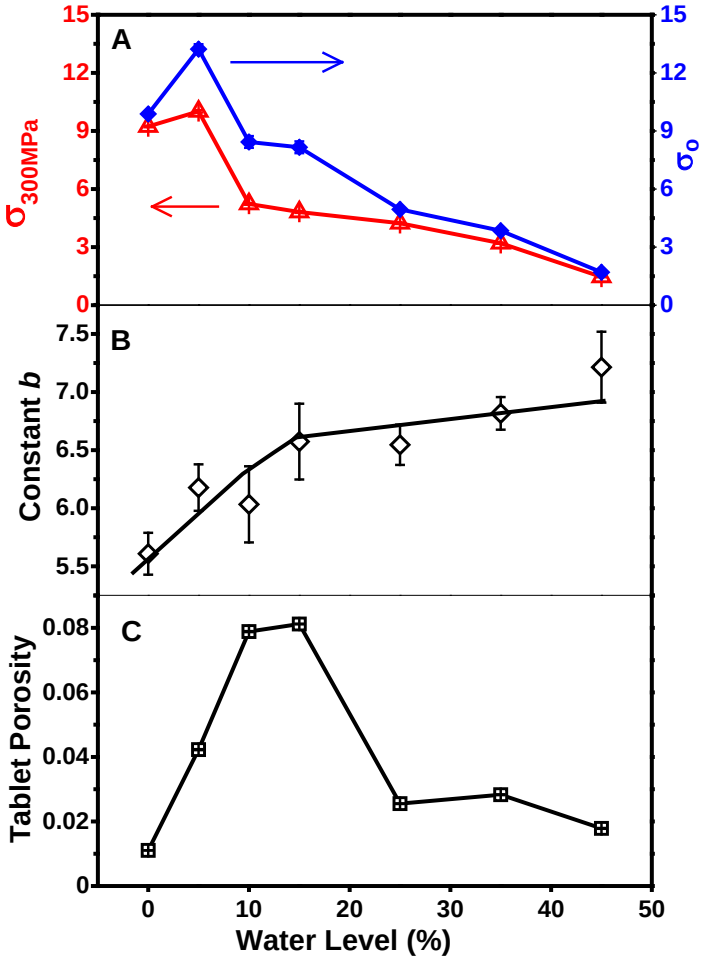


Figure 2.6 SEM images of the fracture surface of a tablet prepared from compressing an MCC granule with 45% water at 300 MPa

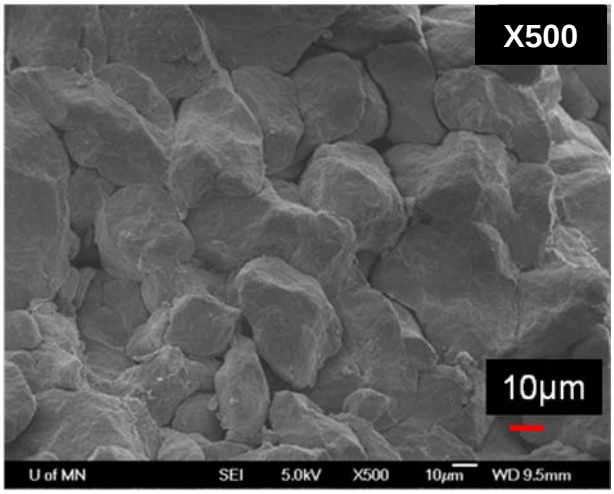


Figure 2.7 Effect of granulating water level on granules properties, (A) granule size (B) specific surface area, SSA (C) granule porosity and tablet tensile strength at 300 MPa compaction pressure

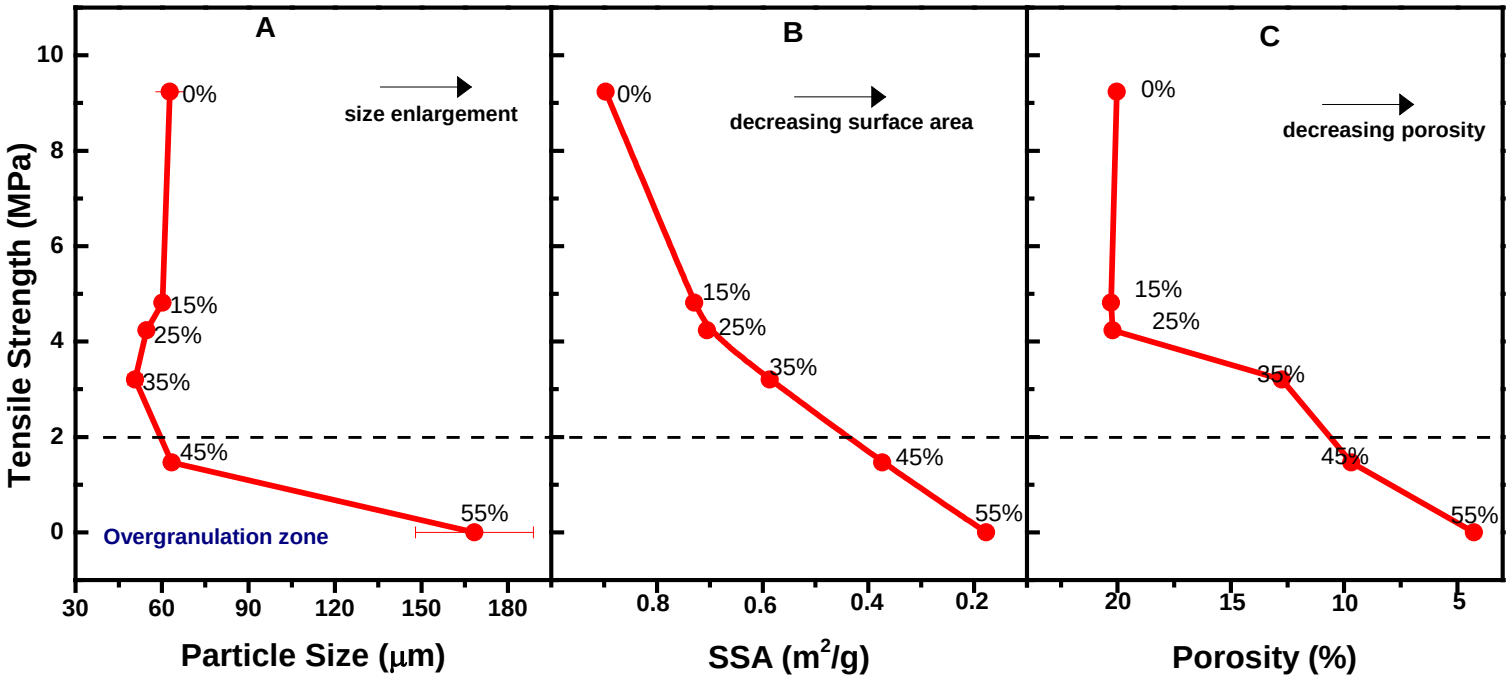
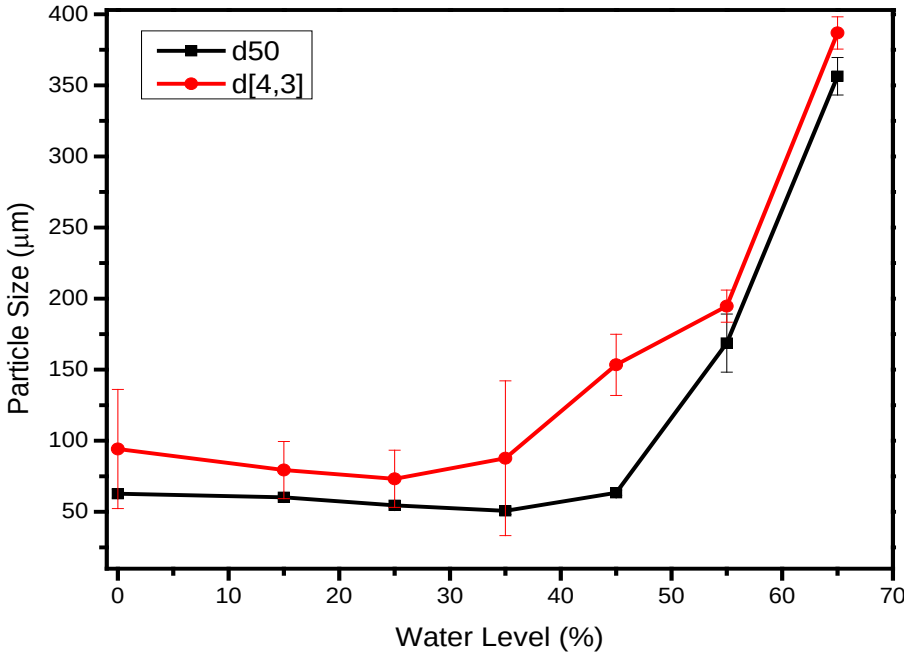


Figure 2.S. 1 Effect of water level on particle size, (A) d_{50} and $d_{[3,4]}$; and (B) size distribution of MCC-PVP granules measured by laser diffraction



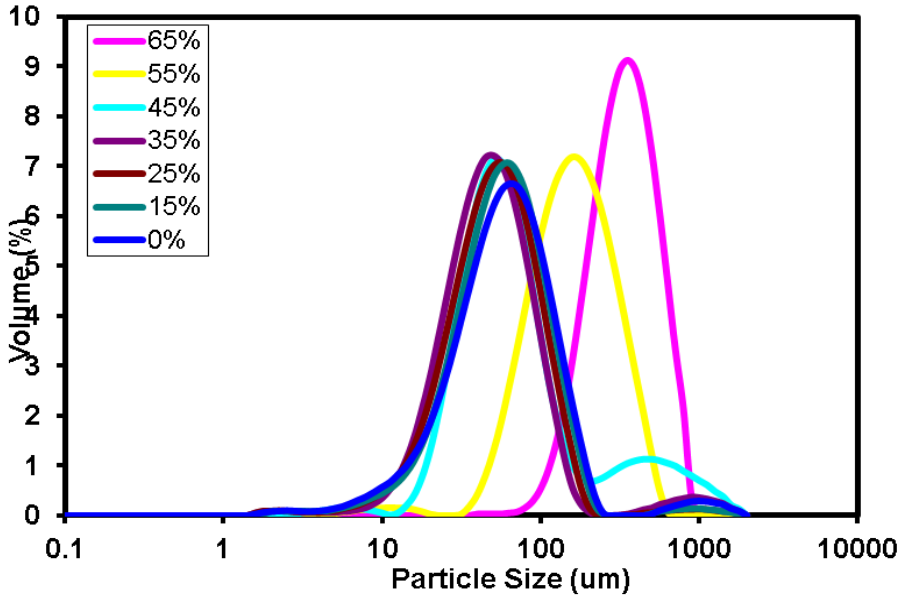
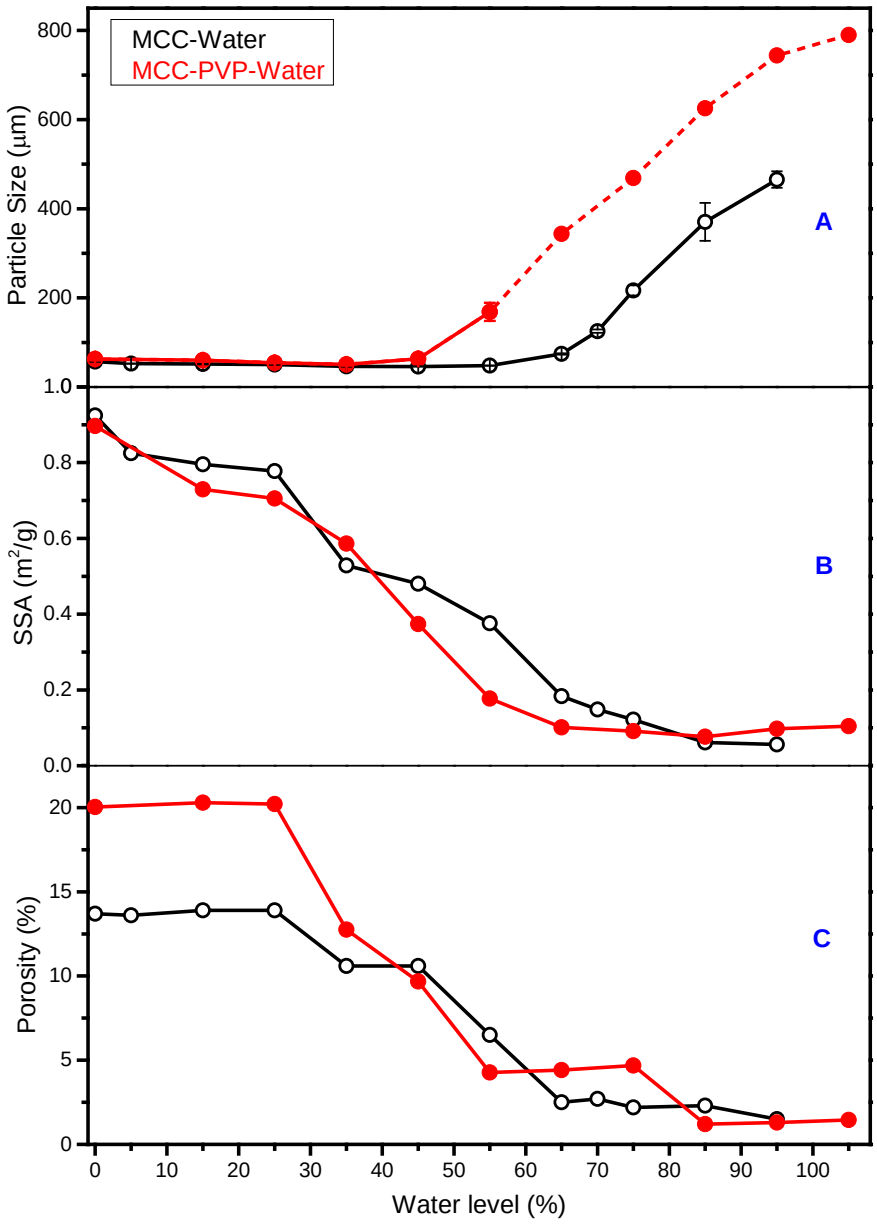


Figure 2.S. 2 Effect of PVP and prolonged massing time on granule properties, (A) d50 [solid line by laser diffraction, dotted line by SEM image analysis]; (B) specific surface area; and (C) intra-granular porosity



CHAPTER 3. A FORMULATION STRATEGY FOR SOLVING THE OVER-GRANULATION PROBLEM IN HIGH SHEAR WET GRANULATION

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Summary

Granules prepared by the high shear wet granulation (HSWG) process commonly exhibit the problem of over-granulation, a phenomenon characterized by a severe loss of the ability to form adequately strong tablet. We hypothesize that the incorporation of brittle excipients promotes brittle fracture of granules during compaction, thereby, improving tablet mechanical strength by increasing bonding area. On this basis, we have examined the effectiveness of incorporating a brittle excipient into a plastic matrix in addressing the over-granulation problem. A complete loss of tabletability is observed for plastic microcrystalline cellulose (MCC) when ≥55% of granulating water was used. The incorporation of a brittle excipient, either lactose or dibasic calcium phosphate (Dical), into the MCC matrix leads to improved tabletability in a concentration dependent manner, with higher amount of brittle excipient being more effective. For each mixture, tablet tensile strength goes through a minimum as the granulating water increases, e.g., 1.4 MPa for the mixture containing 80% of lactose and 2.1 MPa for the mixture containing 80% Dical. These results, along with SEM evidence, show that the addition of brittle excipients to an otherwise plastic powder is an effective formulation strategy to address the over-granulation problem in HSWG.

Introduction

The tabletability of wet granulated pharmaceutical powders is routinely observed to be reduced when compared with the virgin powder.[1-5] In extreme cases, a granulated powder does not form intact tablets[6], let alone forming tablets with adequate mechanical strength, in the pharmaceutically relevant compaction pressure range of 50 – 400 MPa. This phenomenon of severe loss of powder tabletability is known as over-granulation.[7] It has also been observed that drug release rate may be slowed down after wet granulation.[8] Consequently, the term "over-granulation" may also be used to describe the situation when the drug release rate is unacceptably low after granulation.

Recent work has shown that plastic microcrystalline cellulose (MCC) undergoes size enlargement, densification, shape rounding, and surface smoothing during high shear wet granulation.[5] These changes in particle properties limit the formation of sufficient inter-particulate bonding area, over which intermolecular attractive forces are significant.[9] For example, the over-granulated MCC granules are hard and resistant to deformation.[7] They likely undergo a significant degree of reversible elastic deformation during compression, a behavior observed in MCC pellets.[4] When it occurs, the extensive elastic recovery of granules during decompression decreases the total bonding area among granules. Consequently, the tablet is mechanically weak.[9]

Since high levels of plastic excipients, including MCC and other polymers, are routinely used in tablet formulations intended for wet granulation, it is reasonable to expect that the over-granulation problem of formulated powders during wet granulation has an origin similar to that observed in MCC, i.e., insufficient bonding area. If so, an effective strategy for overcoming the over-granulation problem would be to increase bonding area in a tablet. Consistent with this concept, size reduction by milling has been used to salvage over-granulated powders.[2,7] This size reduction strategy, although effective, is not ideal since it is merely reactive to a manufacturing crisis and it requires additional processing steps. An ideal strategy for solving this problem is to eliminate it by designing the formulation in such a way that the powder mixture is inherently resistant to over-granulation.

Insight for developing such a formulation strategy to address the over-granulation problem may be gained by considering parallel work in dry granulation that is also faced with a similar situation of loss of tabletability. It has been shown that, size enlargement in dry granulated powders deteriorates powder tabletability of plastic materials.[10] However, brittle materials exhibit little or no sensitivity to granule size enlargement.[11] These observations agree with the mechanism of reduced area of bonding in a tablet that leads to the lower tablet mechanical strength. Larger granules of plastic materials have smaller area that can form inter-particulate bonding in tablet because they do not fracture when compressed. This naturally leads to reduced tabletability. On the other hand,

brittle granules undergo extensive fragmentation when compressed to generate new lubricant free surfaces that are available for bonding. Therefore, the large original granule size exerts little negative impact on tablet strength of brittle materials.

Based on this understanding, we hypothesize that the incorporation of a brittle excipient into an otherwise plastic matrix for the HSWG process promotes fragmentation of large granules during compaction. The fragmentation subsequently minimizes the negative effect of large granule size on available bonding area to alleviate or even eliminate the over-granulation problem. We test this hypothesis using binary mixtures of MCC with each of the two brittle excipients, lactose and dibasic calcium phosphate. Although both lactose and Dical are brittle, they represent different types of materials because lactose is water soluble while Dical is not.[12] Some of the lactose is dissolved during the wet granulation process, which crystallizes out during subsequent water removal by drying. On the other hand, the solution mediated redistribution of brittle excipient during granulation process is not expected for Dical because of its extremely low solubility in water.[12] This may cause structural differences and affect fragmentation propensity of resultant granules.

Materials and Methods

Materials

Materials used in this study were provided by respective commercial suppliers as follows: microcrystalline cellulose (MCC, Avicel PH101, FMC Biopolymer, Philadelphia, PA), polyvinylpyrrollidone (PVP, Kollidon K30, BASF, Geismar, Germany), lactose monohydrate (Foremost Farms, Baraboo, WI), anhydrous dibasic calcium phosphate (Dical, Anhydrous Emcopress, JRS Pharma, Cedar Rapids, IA), and magnesium stearate, (Mallinckrodt, St Louis, MO). A fixed amount of PVP, 2.5% (wt%) of the powder mixtures, was dissolved in varying amounts of water to form polymer solutions, which were sprayed during the wet granulation process. For each mixture, the amount of water ranged from 5% to the maximum amount possible without forming a paste. Physical mixtures of MCC-PVP-lactose or MCC-PVP-Dical (0% granulating water) were prepared as a control.

The use of PVP as a binder during the granulation process and magnesium stearate as a lubricant prior to compaction make this work more relevant to the common HSWG process during pharmaceutical manufacturing. Hence, the knowledge derived from this work can be applied to solve overgranulation problems with more confidence.

Methods

Wet Granulation

Powder mixtures, 100 g per batch, at various ratios of MCC-lactose (20%, 40%, 50%, 60% and 80% lactose) and MCC-Dical (40%, 60% and 80% Dical) were first mixed in a laboratory-scale high-shear granulator (1.7 L bowl volume, modified KitchenAid food processor, two impellers, 1750 rpm) for 30 seconds before spraying an appropriate PVP binder solution at a rate of ~ 30 g/min through a nozzle placed approximately 5 – 8 cm above the moving powder. The materials were massed for 10 minutes after all binder solution has been added. The prolonged massing is intended to maximize the chance of overgranulation to challenge the effectiveness of the proposed formulation strategy. The wet granules were tray-dried for ~24 hours at 40 ^{o}C in an oven and then placed in a 32% relative humidity chamber for at least 48 hours prior to compaction. The physical mixtures were prepared by mixing MCC and lactose (or Dical) at predetermined ratios with 2.5 g PVP in the granulator for 30 seconds. Before compaction, all samples were mixed with 0.5% magnesium stearate for 10 minutes using a 1 quart (946 mL) twin shell blender (Patterson-Kelley, East Stroudsburg, PA) operated at 25 rpm.

Characterization of Tableting Properties

Powder compaction studies were conducted at room temperature and approximately 20% relative humidity. Granules were compressed on a compaction simulator (Presster, Metropolitan Computing Company, East Hanover, NJ) to simulate a 10-station Korsch XL100 tablet press using round flat-faced tooling (9.5 mm diameter). The dwell time was set at 20 ms, corresponding to a production speed of 61,600 tablets/hr. Tablet dimensions were measured immediately after ejection. Tablet diametral breaking force was determined using a texture analyzer (TA-XT2i, Texture Technologies Corporation, Scarsdale, NY) at a speed of 0.01 mm/s and 5 g trigger force. Tablet tensile strength was calculated from the breaking force and tablet dimensions.[13] Tabletability plot (tensile strength as a function of compaction pressure) was obtained.[14,15] All data fitting and statistical analyses were done using commercial software (Origin® 9.0, OriginLab Corp., Northampton, MA). Tabletability profiles were fitted to polynomial functions of appropriate order, from second to fifth, for the best fitting. Resultant functions were subsequently used to obtain the tablet tensile strengths at compaction pressures of 100, 200, and 300 MPa. Unless specified, tablet tensile strength reported in the following sections refers to tablet compressed at 300 MPa.

Tablet fracture surfaces after the diametral-compression test for breaking force were sputter-coated with platinum (~50 Å coating thickness) and examined with a Scanning Electron Microscope (SEM, JEOL 6500F, Tokyo, Japan) operated at 5 kV, to obtain

qualitative information on granule deformation behavior. Granules were also sputter-coated with platinum (~50 Å coating thickness) and observed with a Scanning Electron Microscope (SEM, Quanta 200F, FEI, USA) operated at 10 kV.

Results

Effect of Composition on Wet Granulation

Granule size generally increases with increasing level of granulating water or brittle excipient concentration.[6,16] To define the appropriate range of the granulating water, we first determine the water-holding capacity of each powder by recording the maximum amount of water that can be added to the powder while being granulated in the granulator without forming a paste or thick slurry (Figure 3.1). Water is added to the powder bed at 5% or 10% increments until the first sign of suspension formation is observed, at which point that water level is recorded as the paste-forming water level (red line in Figure 3.1). The water level immediately before the last water addition that leads to paste-formation is taken as the water holding capacity (black line in Figure 3.1). The formation of a thick slurry, which is essentially a dispersion of solid particles in the granulating liquid,[17] indicates that the maximum amount of liquid to produce agglomerates has been exceeded. The water holding capacity of powder without forming a slurry decreases in the order of MCC (135%) > Dical (45%) > lactose (15%). The water holding capacities

of the mixtures, range between those of the pure powders as expected. Similar observations have been made previously, where a higher MCC concentration in the starting powder required a higher amount of water to produce desired pellets or granules.[16,18,19]

Effect of Composition on Tableting Performance of Physical Mixtures

The effects of powder composition on tablet tensile strength of the MCC-lactose and MCC-Dical mixtures are shown in Figures 3.2A and 3.2B, respectively. When only the physical mixtures are considered, an increase in lactose or Dical concentration to 80% results in a drop in tablet tensile strength, by as much as 51% for lactose and by 64% for Dical. Similar to an earlier observation,[20] the tableting performance of MCC-lactose physical mixtures in this work is also better than the MCC-Dical mixtures at equivalent MCC concentrations.

Effect of Wet Granulation on Tableting Performance

The impact of wet granulation on the tableting performance of powder mixtures is demonstrated with plots of the tablet tensile strength as a function of water level for both lactose (Figure 3.2A) and Dical mixtures (Figure 3.2B). The tabetability of pure MCC

granules decreases rapidly with increased amounts of added water. MCC granules cannot be compressed into intact tablets at ≥55% granulating water level, i.e., they are completely overgranulated.[6] In contrast, the tablet tensile strength of granulated powders containing lactose or Dical initially decreases with increasing amounts of added water at a rate lower than that of MCC until it reaches a minimum at some granulating water level. Beyond this minimum, additional granulating water results in increased tablet tensile strength. The observed minimum tablet tensile strength is higher when the concentration of lactose or Dical is higher (Figures 3.2A and B).

Both the granulating water level corresponding to the minimum tabletability and the minimum tensile strength are related to powder composition. Mixtures with lower MCC concentration required less water to reach the respective minimum tensile strength. The value of the minimum tensile strength increases with increasing amount of brittle excipient for both lactose and Dical (Figure 3.3). When the amount of the brittle excipient is 40% or higher, the minimum tensile strength is no longer zero, marking a fundamental change in over-granulation behavior exhibited by MCC. The trend of the minimum tablet tensile strength value diverge when the concentration of the brittle excipients exceeds 40% (Figure 3.3). For MCC-lactose granules, there is about a 7-fold increase in the minimum value when the lactose concentration increases from 40% to 60% while that of the MCC-Dical granules is ~30-fold. At the same concentration, Dical appears to be more effective than lactose in terms of the minimum tensile strength. At

80% of the brittle excipients, the minimum tablet tensile strengths are 1.4 MPa for the mixture containing lactose and 2.1 MPa for the mixture containing Dical. Although both minima correspond to a granulating water level of 35%, the value of the minimum tensile strength of the MCC-Dical granules is about 50% higher than that of MCC-lactose granules. The higher efficiency of Dical in improving tablet tensile strength is likely because of its higher brittleness than lactose.[21]

To examine interplay among the compaction pressure, granulating water level, and composition, we compare tablet tensile strengths of MCC, MCC-lactose (80%) mixture, and MCC-Dical (80%) mixture at 100 MPa, 200 MPa and 300 MPa (Figures 3.4A–C). Tablet tensile strength improves with increasing compaction pressure for systems containing either brittle excipients at all granulating water levels. Consequently, the tabletability at the three compaction pressures do not converge. Tablet tensile strength of MCC granules approaches zero with increasing granulating water level (Figure 4A). Therefore, the three lines converge at ≥55%, the point at which the complete loss of tabletability takes place. While tabletability of MCC granules exhibit extreme sensitivity to granulating water level, the tabletability of the mixtures with 80% lactose or Dical does not. If we adopt the 2 MPa tensile strength threshold for overgranulation in typical pharmaceutical compaction pressure range (50 – 400 MPa)[7], the mixture containing 80% lactose recovers after granulating with 45% water (Figure 3.4B). However, the mixture

containing 80% Dical is free from the risk of over-granulation at any granulating water level (Figure 3.4C).

Effect of Composition on Tablet Structure

To assess the degree of brittle fracture versus plastic deformation of granule after compaction, morphologies of granules before and after compression at 100 MPa were compared by SEM (Figures 3.5A–C). These SEM images are for granules prepared with 25% water level and compressed into tablets at 100 MPa. The relatively low compaction pressure was selected to help identify granules that are more sensitive to stress induced fragmentation because only the brittle granules will show signs of fragmentation under low pressures. The fractured tablet surface from MCC granules shows defined outlines of the original granules although deformation is visible when compared to the uncompressed granules (Figure 3.5A). This lack of appreciable granule fragmentation is consistent with the known plasticity of MCC.[22] On the other hand, the fracture surfaces of MCC-lactose tablet (Figure 3.5B) and MCC-Dical tablet (Figure 3.5C) show clear signs of fragmentation when compared to the uncompressed granules. Within the areas examined, several pieces of granules are broken from the original granules, which suggests breakage of original granules into smaller fragments during compaction, hence minimizing the differences in initial size of the granules.

Discussion

Effective solutions to any pharmaceutical problem requires a mechanistic understanding of the inter-relationship among material structure, property of interest, and performance.[23] For granules prepared by HSWG, their structure, properties and tableting performance depend on both powder composition, i.e., formulation variables, and process parameters, such as massing time.[6-8] Properties that favor superior tableting performance include high intragranular porosity[24], and low granule mechanical strength[3]. These properties affect the degree of plastic deformation or fragmentation during compaction and, therefore, bonding area after compression. For large granules, plastic deformation alone is inadequate to develop sufficiently large bonding area required for strong tablet. When granule size cannot be reduced, fragmentation becomes an important deformation mechanism for enhancing bonding area and improving tabletability. Systematically studying the granulation performance of binary mixtures of plastic MCC with a brittle excipient offers an opportunity to assess the effectiveness of incorporating brittle excipients, on promoting fragmentation and reducing the over-granulation propensity of pharmaceutical powders. Brittleness of composite granules is expected to lie between those of pure components.

Relationship between Formulation Composition and Water-holding Capacity

Granulating liquid level is a key parameter of the wet granulation process. Water holding capacity of a powder may be affected by factors such as particle size, the powder wetability, powder bed porosity, hygroscopicity, and solubility in granulating fluid. The rank order of water holding capacity, MCC > Dical > lactose (Figure 3.1), in this work can be explained from their different hygroscopicity and aqueous solubility. MCC sorbs much more moisture than Dical and lactose. At the same granulating water level, less free water will be available for forming MCC agglomerates. To form a continuous liquid phase necessary for forming a paste, much more water is required for MCC. Although both Dical and lactose are non-hygroscopic, lactose is more soluble than Dical. At the same granulating water level, the relative amount of solid lactose is less and the volume of the liquid phase is larger than Dical because of the dissolution of a significant amount of lactose in water. Therefore, water holding capacity of lactose is lower than Dical. Consequently, the nucleation and growth kinetics is expected to follow the rank order of lactose > Dical >> MCC. This is consistent with the observations that a) more granulating liquid is required for successful wet granulation when more MCC is present in a mixture[18,19] and b) MCC-Dical mixtures generally take more granulating water than the corresponding MCC-lactose mixtures.[16] Regardless of the mechanisms that determine water holding capacity, the HSWG processing map (Figure 3.1) clearly assesses the ability of a powder to resist slurry formation. In our opinion, it should be

routinely determined for any HSWG formulation of interest since it sets a limit to the design space. A robust HSWG process should keep granulating water level away from the transition zone with a safe distance since it is a point of no return for the granulation process.

Relationship between Formulation Composition and Tableting Performance

Figure 3.2 shows that physical mixtures of MCC with either lactose or Dical exhibit lower tabletability than MCC; and a higher concentration of brittle excipient corresponds to lower tablet tensile strength. This is not surprising since MCC (Avicel PH101) exhibits much higher tabletability than both lactose and Dical.[25] For each granulated mixture, tablet tensile strength initially decreases with increasing water level. As shown for MCC,[5,6] this trend is likely caused by the surface smoothing, particle rounding, densification, and the elimination of primary MCC particles due to agglomeration. This explanation is consistent with the fact that a mixture containing more MCC tends to be more sensitive to the water addition, i.e., faster drop in tablet tensile strength with increasing granulating water (Figures 3.2A and B). However, unlike for pure MCC, tablet tensile strength increases with increasing granulating water level for these lactose or Dical mixtures when a critical water level is surpassed. This happens because higher water level leads to larger granules, which undergo more extensive fragmentation during

compaction to expose fresh unlubricated surfaces for bonding within a tablet. Consequently, tablets are stronger because the effect of magnesium stearate in reducing the inter-particulate forces of attraction becomes less.[26] MCC granules converge to a zero tablet tensile strength at 55% granulating water. This is expected if it does not undergo fragmentation under pressure because the hard, large, elastic granules resist deformation.[4] Such MCC granules may only crack under high stress instead of breaking into fragments.[27] However, brittle lactose granules of varying size, shape, and porosity produced using different methods exhibit equivalent tabletability to that of ungranulated lactose.[3] For a given system, higher amount of brittle excipient corresponds to lower sensitivity to the change in granulating water level. This means that the accessible granulating water range is narrower but the granulation process is more robust for a powder containing more brittle excipient. In this light, it should also be pointed out that higher concentration of brittle excipient, although effective in tackling the over-granulation problem, leaves less room for errors in the amount of water used during the granulation process.

The structures of dry granules likely differ between the lactose and Dical based granule where lactose is expected to mix with MCC more intimately than Dical because of the dissolution-crystallization process. Figure 3.3 suggests that the expected structural differences in the lactose and Dical based granules do not significantly affect the amount of brittle excipient required to have an impact on over-granulation. More than 40% of

brittle excipient is required for both. The higher minimum tablet tensile strength of Dical granules (Figure 3.3) implies that Dical is more effective than lactose in addressing the over-granulation problem. There are at least two possible explanations to this observation: a) Dical based granules are more brittle; and b) Dical has higher bonding strength than lactose. The first possibility is supported by literature evidences that suggest higher brittleness of Dical than lactose. For examples, Dical tablet strength increased at a higher tableting speed (higher punch velocity) but lactose did not[25] and Dical also exhibited higher degree of fragmentation than lactose when fracture tablet surfaces were examined.[28] The second possibility is speculated based on the higher thermal stability of the inorganic salt of Dical than the organic molecular crystal of lactose.[12]

Relationship between Formulation Composition and Tablet Structure

In addition to data discussed above, the proposed mechanism for the formulation strategy to solve the over-granulation problem is also supported by direct observation of granule fragmentation in tablet. At the fracture surface of an MCC tablet, each granule has a clear outline similar to that of individual granules prior to compression (Figure 3.5A). No fractured granules were present. This is consistent with the expected lack of brittle fracture of MCC granules. In MCC tablet, the intragranular strength is higher than

intergranular strength because granules are coated with a thin layer of magnesium stearate. Therefore, the separation occurs around particles instead of through them during the diametral-compression test. For granules containing 80% lactose or Dical, outlines of initial granules have been largely destroyed at the tablet fracture surface. Small fragments are scattered throughout the fracture surface, indicating the occurrence of extensive fragmentation of these granules. This supports the hypothesis that incorporation of brittle excipients renders granules brittle, which promotes size reduction during compaction, thereby, counters over-granulation problem during HSWG. Although a lab scale granulator under high shear was used in this study, this formulation strategy is expected to be valid for large scale wet granulation where shear is usually lower.

Conclusion

The incorporation of brittle excipients, lactose and dibasic calcium phosphate in this study, successfully solves the problem of over-granulation in plastic MCC. At the fixed compaction pressure of 300 MPa, the tablet tensile strength of MCC granules deteriorates rapidly with increasing granulating water. Intact tablet could not be made for MCC granules prepared with ≥55% of granulating water. When a brittle excipient is incorporated into the MCC matrix, a minimum tablet tensile strength exists over the entire range of granulating water level. The value of the minimum tensile strength is

higher when more brittle excipient is present. For mixtures containing a higher amount of brittle excipient, water addition generally leads to slower reduction in tabletability before the minimum is reached. Once the minimum is passed, tabletability of each mixture improves with increasing amount of granulating water due to the more extensive fragmentation of larger granules. The minimum tablet tensile strength of the mixture containing 80% of brittle excipient was 1.4 MPa for lactose and 2.1 MPa for dibasic calcium phosphate. These results along with SEM evidences show that the addition of brittle excipient to an otherwise plastic powder is effective in reducing, sometimes even eliminating, the over-granulation propensity of granules prepared by the high shear wet granulation process.

Figure 3.1 Effect of powder composition on the maximum granulating water capacity of powder mixture without forming paste. (A) MCC-Lactose and (B) MCC-Dical. Each point represents granulation water level used in preparing a batch of granules from the mixtures.

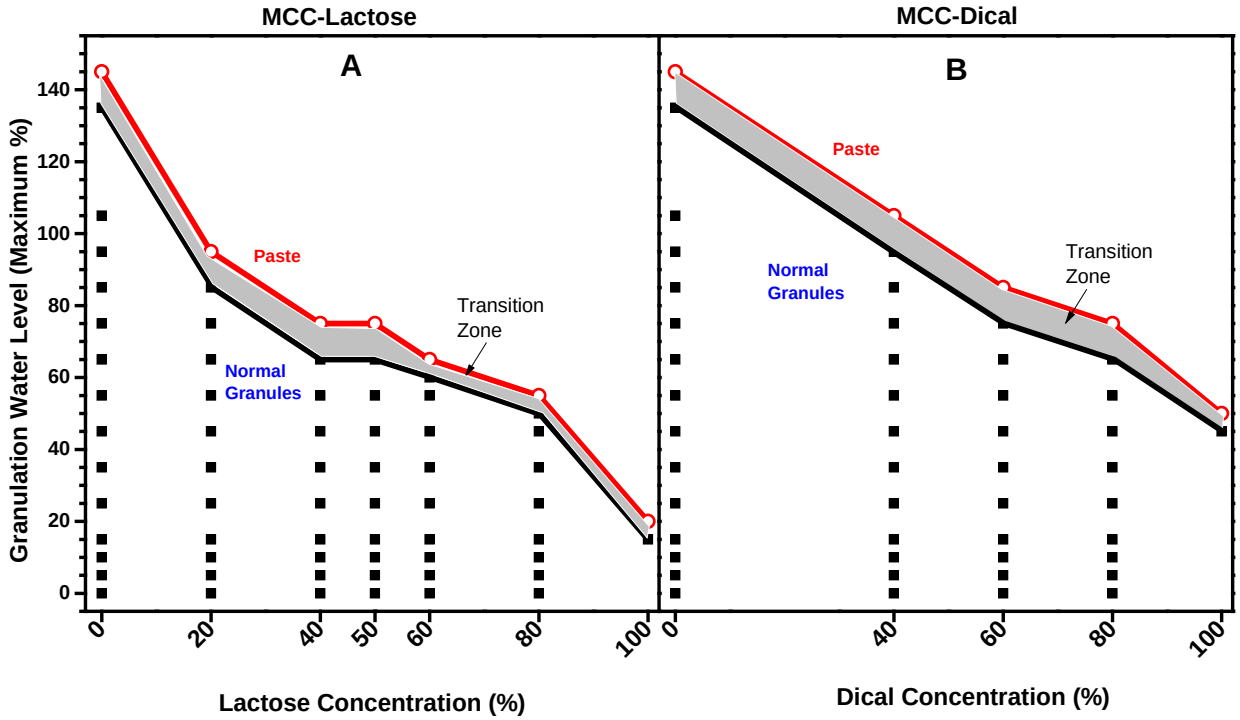


Figure 3.2 Effect of brittle excipient concentration (A) lactose, (B) Dical on tableting performance of MCC granules prepared at different water levels. The compaction pressure was 300 MPa

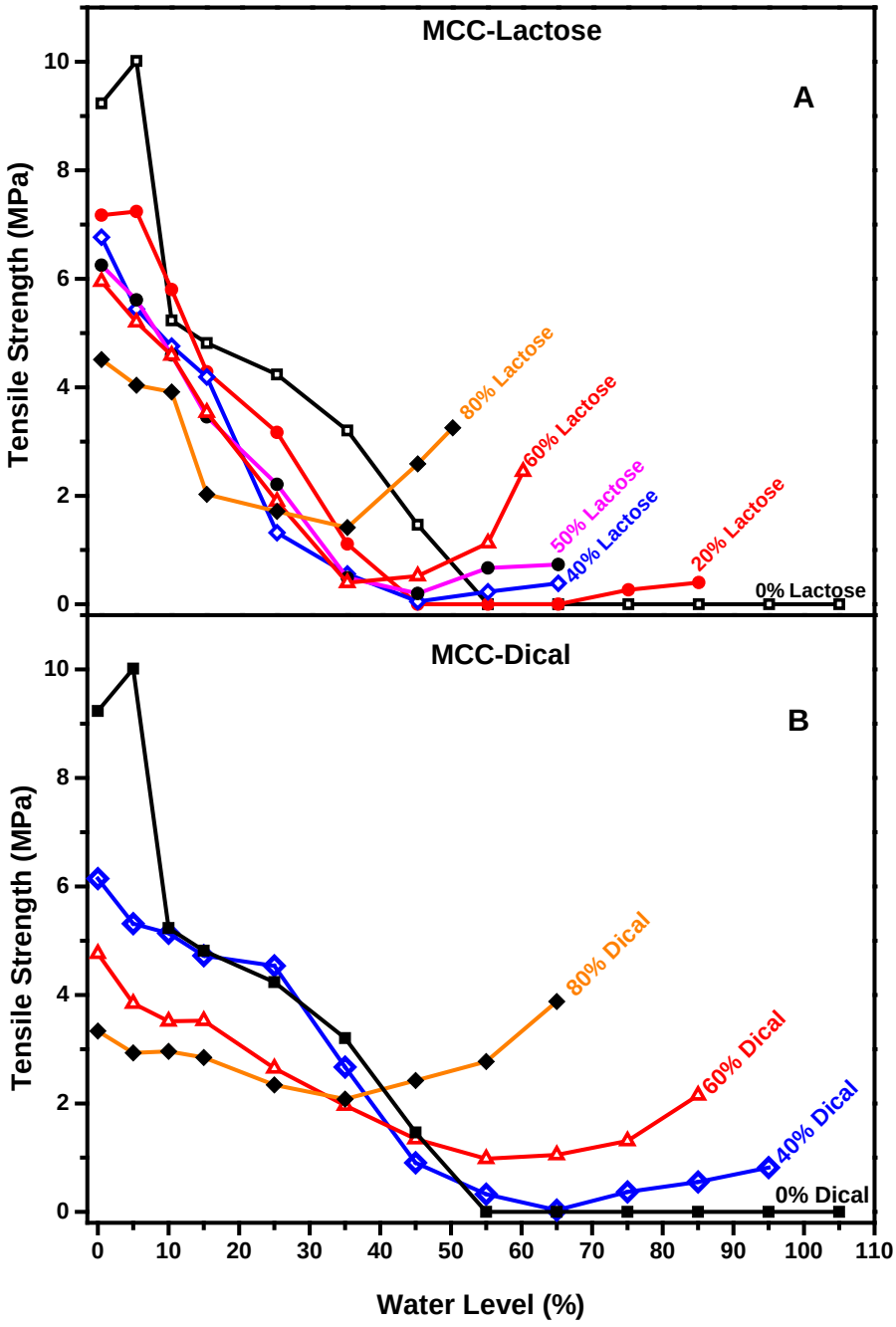


Figure 3.3 Comparison of lactose and Dical based powders at the minimum tablet tensile strength. Error bars denote 95% confidence interval for the tablet tensile strength at 300 MPa compaction pressure

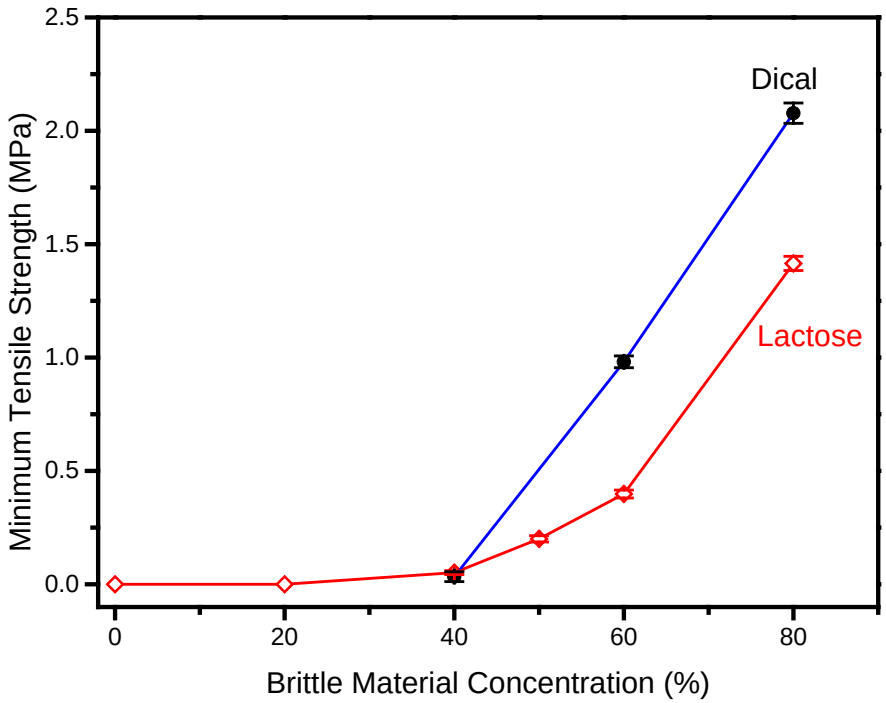


Figure 3.4 Comparison of lactose and Dical based powders at the minimum tablet tensile strength. Error bars denote 95% confidence interval for the tablet tensile strength at 300 MPa compaction pressure

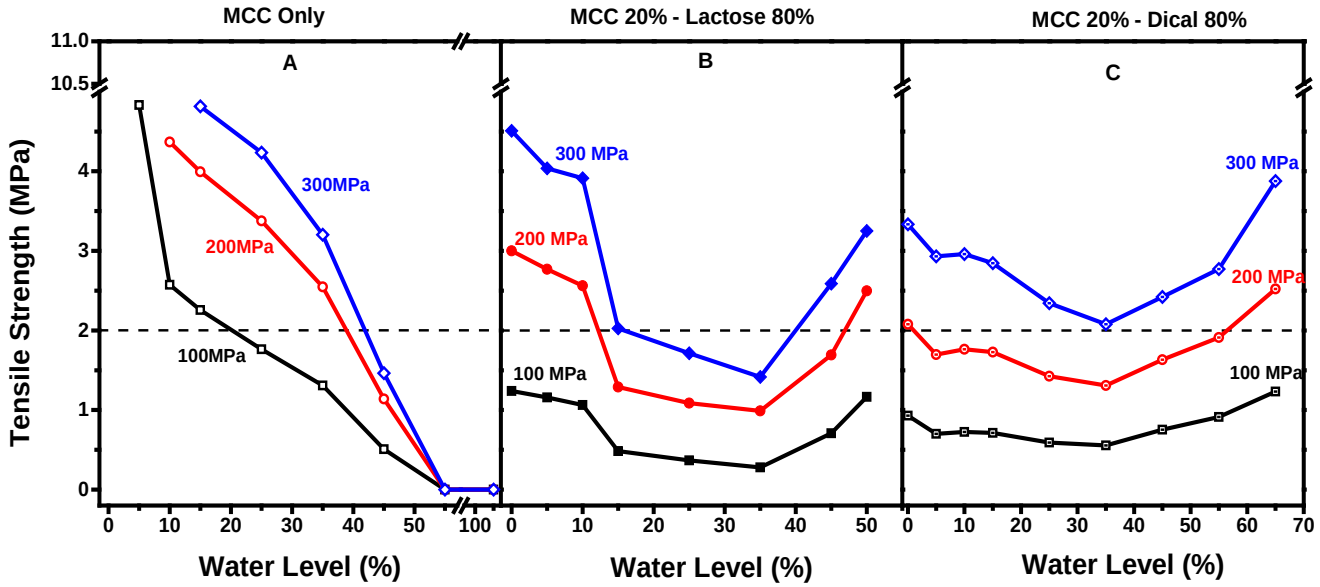
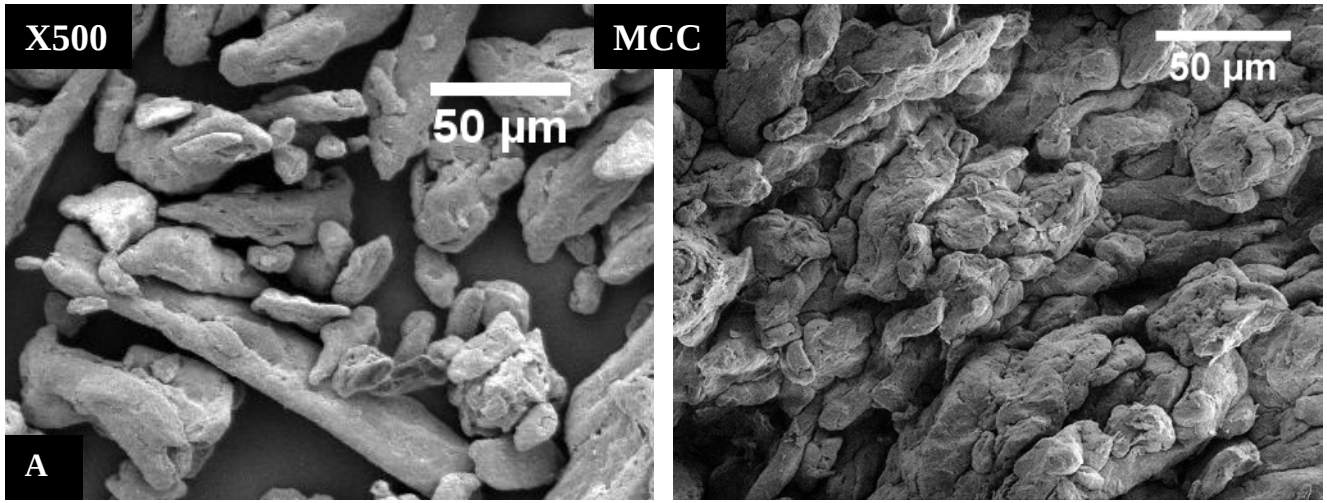
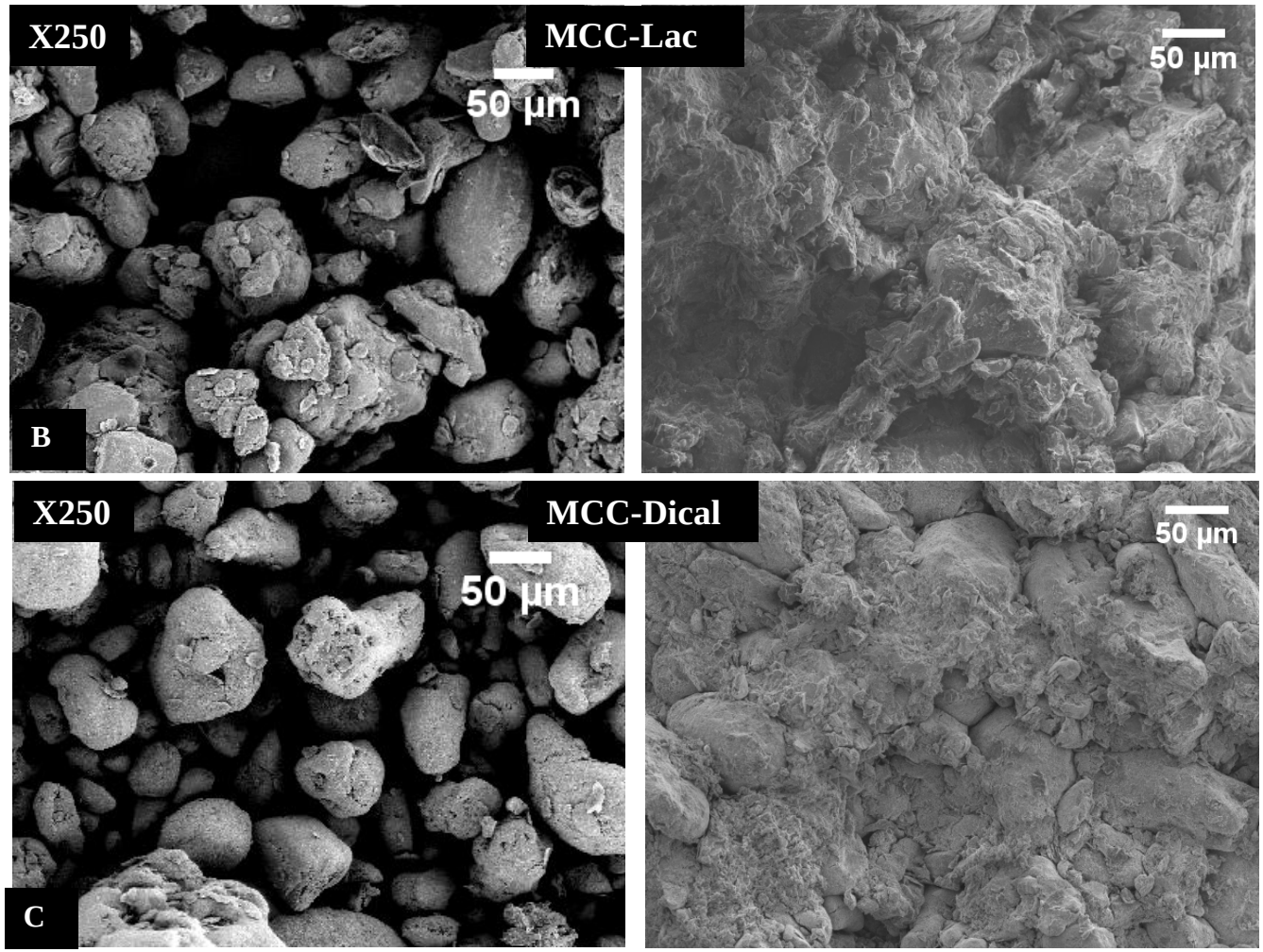


Figure 3.5 Scanning Electron Microscope images of granules (left panel) and corresponding tablet fracture surface (right panel) of (A) MCC (B) MCC 20% + lactose 80% (C) MCC 20% + Dical 80%. Granules were prepared at 25% water level and tablets were compressed at 100 MPa




X250
50 µm
B
MCC-Lac
50 µm
X250
50 µm
C
MCC-Dical
50 µm

CHAPTER 4. TABLETABILITY MODULATION THROUGH SURFACE ENGINEERING

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Summary

Poor powder tabletability is a common problem that challenges the successful development of high quality tablet products. Using non-compressible microcrystalline cellulose beads (spherical granules), we demonstrate that surface coating is an effective strategy for modulating tabletability, almost at will, through judicious selection of coating material. This strategy has broad applicability since tabletability of such particles is dictated by the properties of the outermost layer coat regardless of the nature of the core.

Introduction

Poor powder tabletability is a common problem that challenges the successful development of high quality tablet products. A symptom of this problem is that sufficient tablet mechanical strength cannot be attained within the accessible compaction pressure range (typically 50 – 350 MPa).[1] This problem occurs more frequently when a high dose of a poorly compressible drug must be delivered or when the powder is granulated, by an either dry or wet process, before compression.[2,3]

The problem of poor tabletability has been traditionally addressed during formulation development through the use of tablet excipients with superior tableting properties, such as microcrystalline cellulose (MCC).[4] In that case, a large amount of excipient is required to afford sufficient tablet mechanical strength. For example, in a mixture with non-compressible silica and a compressible polymer, 40% of the polymer is required to form intact, but weak (~0.25 MPa tensile strength), tablets and 60% of the polymer is required to form reasonably strong tablets (1.3 MPa tensile strength) at 250 MPa compaction pressure.[5,6] In another example, 40% of another highly compressible polymer is insufficient for forming an intact tablet with poorly compressible acetaminophen.[5,6] A tablet, however, cannot be too big (usually less than 1g) for easy swallowing and compliance by patients.[7] Consequently, this strategy of simply adding highly compressible excipients to a formulation is unfit for drugs that must be delivered in a high dose.

It has been shown previously that coating particles with a layer of highly bonding polymer is effective in improving powder tabletability of extremely poorly compressible powders.[5,6] When coated with a layer of plastic and highly bonding material, large bonding area can develop irrespective of the deformation mechanism of the original particles. Surface coating delivers highly bonding excipients where they are most needed in the tablet, i.e., at the particle-particle contact points as shown in the schematic Figure 4.1. Such coating controls the nature of particle-particle bonding, regardless of the mechanical properties of the core particles. Because coating is applied to all particles in the powder, a uniform three-dimensional bonding network is formed upon compression. Therefore, tabletability of the coated powder can be effectively controlled by judiciously selecting coating material. If the coating material is highly bonding, a strong tablet tensile strength develops even at a low compaction pressure. On the other hand, tabletability is expected to be poor when the bonding property of the coating layer is poor. The effectiveness of coating on tabletability is in contrast to the physical mixtures between a bonding excipient and a non-bonding drug, where a three-dimensional bonding network forms only when the amount of bonding excipient exceeds the critical threshold, as predicted by the percolation theory.[8,9] Therefore, a strong tablet cannot be obtained unless the three-dimensional strongly bonding network permeates the entire volume of the tablet, which requires the use of a large amount of bonding excipients. Otherwise, the tablet will fail at the weakest point.

Using 350 – 500 μm diameter MCC beads, we demonstrate the ability of modulating tabletability, almost at will, through judicious selection of surface coating materials.

Materials and Methods

MCC beads (Cellets 350, Glatt Air techniques Inc, Ramsey, NJ) were used as the core, polyvinylpyrrolidone (PVP, K30, BASF Geismar, Germany), poly(methacrylate-ethylacrylate) 1:1 co-polymer (Kollicoat® MAE 30DP BASF, Ludwigshafen, Germany), a 1:1 mixture of PVP and caffeine, and nano sized silica were used as coating materials in this study. Caffeine was used as a model drug to represent drug layering onto beads, a process commonly employed during the development of controlled release beads. Continuous film coating was achieved using a fluid bed (Unilab, Bosch, Germany). Discrete dry coating by silica was carried out in a twin shell blender (Patterson–Kelley, East Stroudsburg, PA). Cylindrical tablets (8 mm in diameter) were compressed on a Materials Testing Instrument (Zwick-Roell 1485, Ulm, Germany). Tablets were broken diametrically and tensile strength was calculated from the breaking force and tablet dimensions following the standard procedure.[10]

Results and Discussion

Figure 4.2 shows that the tablet tensile strength oscillates wildly as the beads are sequentially coated by bonding and non-bonding materials. The data show that the outermost layer dictates tableting performance of beads regardless of the structure of beads underneath. This deduction cannot be made by simply comparing tableting performance of beads individually coated with different materials. Figure 4.3 is a back scattered electrons (BSE) image of the cross-section of a bead obtained using a field emission scanning electron microscope (Sigma FE-SEM, Carl Zeiss, Oberkochen, Germany).

Nearly spherical MCC beads exhibit very poor tabletability. In fact, no intact tablet could be prepared by compaction up to 350 MPa. This is similar to dense MCC granules that are prepared by high shear wet granulation or dry granulation because they do not undergo sufficient amount of plastic deformation or fragment during compaction.[11] Consequently, a significant amount of elastic deformation is developed during compression. [12] The elastic recovery of particles upon the release of compaction pressure results in the survival of only a relatively small area of contact between adjacent particles (Figure 4.1A) and, therefore, low tablet tensile strength results.[13]

When exposed to 75% relative humidity (RH), the beads coated with 10% (wt% of beads) of caffeine-PVP (1:1) are visually free flowing and they form tablets with tensile

strength of 7.0 MPa at 300 MPa compaction pressure, which is significantly higher than 2 MPa, a tensile strength target for successful handling of tablets.[14] At lower RHs, tablet tensile strength improvement is marginal for the same beads (0.4 MPa and 1.0 MPa at 32% and 52% RH, respectively). This highlights the importance of plastic deformation of the outer layer on the tablet mechanical strength. Polymer equilibrated at a higher RH is more plastic because of the higher amount of moisture.[15,16] Hence, larger bonding area between particles is developed under identical compaction conditions as illustrated by Figure 4.1B.

When the beads further coated with a layer of Kollicoat (40%, wt%) are compressed, tablet tensile strength is significantly reduced to be nearly negligible regardless of the RH (Figure 4.2). The nearly complete loss of tabletability indicates that Kollicoat does not develop sufficient bonding area between adjacent beads, which is necessary for achieving a high tablet tensile strength.[17] Further top coating with 5-25% (wt%) PVP significantly restores the tabletability of beads. However, the highly plasticized PVP coating causes the problem of caking at 75% RH, which is the worst with 25% PVP coating. Beads form large and strong agglomerates over time due to the inter-diffusion of polymer chains at contact points.[18] This problem is solved by blending the PVP-coated beads with 1% (wt%) nano-sized silica to form a discrete coating layer of nano-particles, which serve as a physical barrier to prevent sticky PVP layers from coming to contact. With silica coating, beads coated with 25% PVP remain visually free flowing even after exposure to

75% RH for 6 days. The nano-coating is possible by a simple blending process because these free-flowing beads can come to frequent contact with silica to facilitate their spreading onto the beads.[19] For cohesive powders, successful coating by nano particles would require the application of external stresses to facilitate the interactions between host particles and nano sized guest particles.[20]

The silica coating layer significantly lowers the tablet tensile strength of PVP coated beads. This is not surprising because silica particles deposited on bead surface as agglomerates (Figure 4.3). Silica particles in the agglomerates do not bond to each other strongly. When they are present at the contact points, the total area of direct bonding between PVP layers on the beads is reduced, hence, tablet is weakened. Tablet tensile strength, however, gradually increases with longer exposure time at 75% RH. Tablet tensile strength has fully recovered after 8 days of exposure but caking also ensues. This suggests that non-bonding silica agglomerates have gradually "sinked" into the PVP layer, which leads to nearly complete recovery of PVP-PVP contact points similar to those observed in tablets without silica coating.[18] Figure 4.4 shows SEM images of free beads, top surface of compressed tablets, and fracture surface after tablet breaking. Tight inter-particular boding is evident from the tablet surface when the outer layer is either caffeine-PVP or PVP alone. Elongation and breakage of tightly bonded outer layers is evident at the tablet fracture surface, which explains their high tablet tensile strength (Figure 4.2). When the outer layer is Kollicoat, gaps between adjacent particles are

larger and the breakage plane moves along the bead surfaces instead of through the coating layer. This explains the lower tablet tensile strength of beads coated with Kollicoat. When silica is applied onto PVP coating, the gaps between beads are also larger and the elongation and breakage of the polymer layer is much less than that without silica coating. This is also consistent with the lower tablet tensile strength after silica coating (Figure 4.2).

Conclusion

Our results clearly show that tabletability of a powder can be effectively modulated through particle surface coating with materials of targeted bonding properties. Of all these surface-engineered samples, beads coated with 10% of the caffeine:PVP mixture exhibits the highest tensile strength as well as resistance to caking. This superior performance may lead to novel formulation strategies for overcoming tableting problems. Since coating is a well-established process in industrial manufacturing, innovative solutions to tableting problems based on this particle engineering strategy can be many. An immediate application is the preparation of tablets from usually non-bonding functionally coated beads, which have been generally delivered in capsules.[21]

Figure 4.1 Schematic of bonding between poorly compressible beads in a compressed tablet. (A) without coating, only a small bonding area is developed ; (B) with coating by a layer of highly bonding material, a large bonding area is developed. A thicker coating layer leads to larger bonding area.

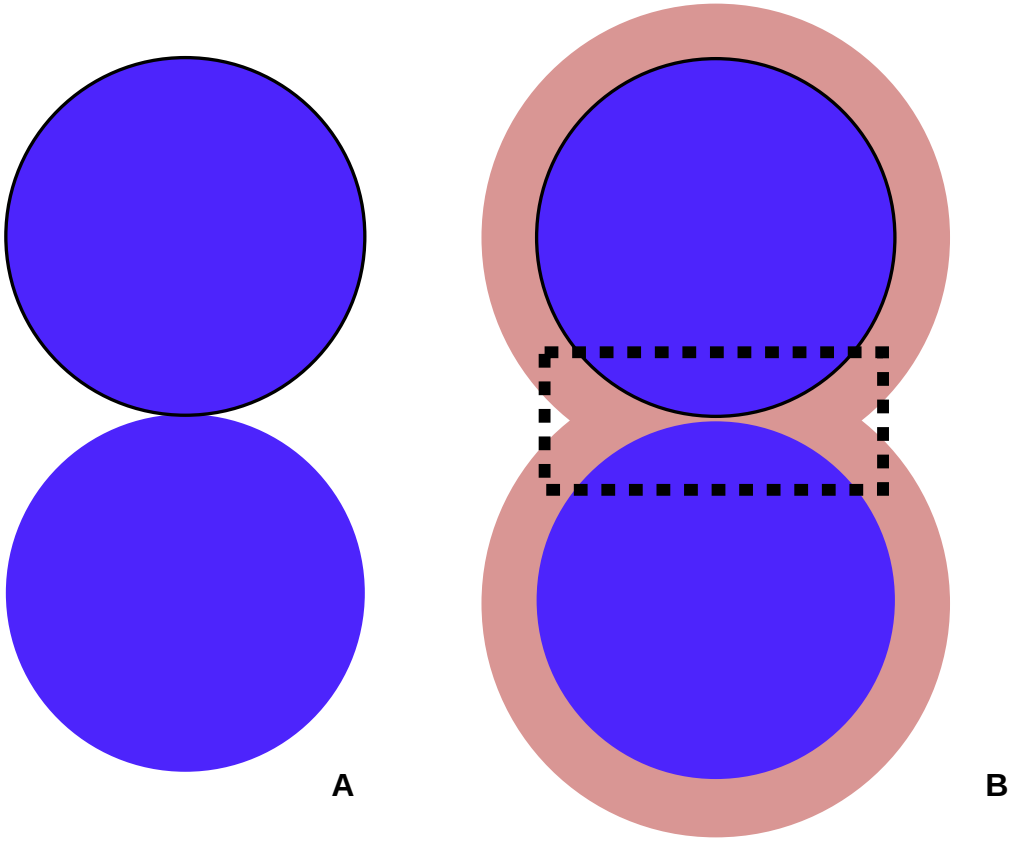


Figure 4.2 Effect of surface coating on tablet tensile strength of beads compressed at 150 MPa. Beads were exposed to 75% RH for 4 days. Layered structures of beads are illustrated. A. MCC core bead; B. bead A coated with caffeine : PVP (1:1); C. bead B coated with Kollicoat MAE; D. bead C coated with PVP; E. bead D coated with nano silica; F. bead E after 8 days of exposure to 75% RH. The broken line indicates the minimum tablet tensile strength that is desired for successful processing and handling of tablets.

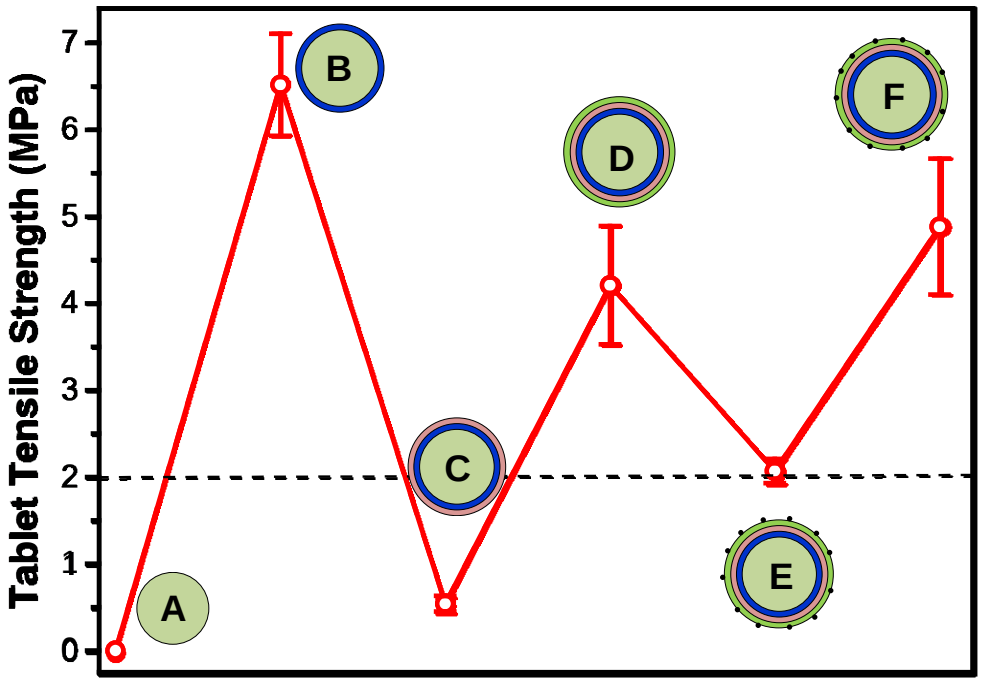


Figure 4.3 Back Scattered Electron SEM image of a cross-section of a coated bead showing core and various coating layers. A. MCC Core; B. 1:1 caffeine: PVP layer; C. Kollicoat MAE layer; D. PVP layer; E. Nano silica

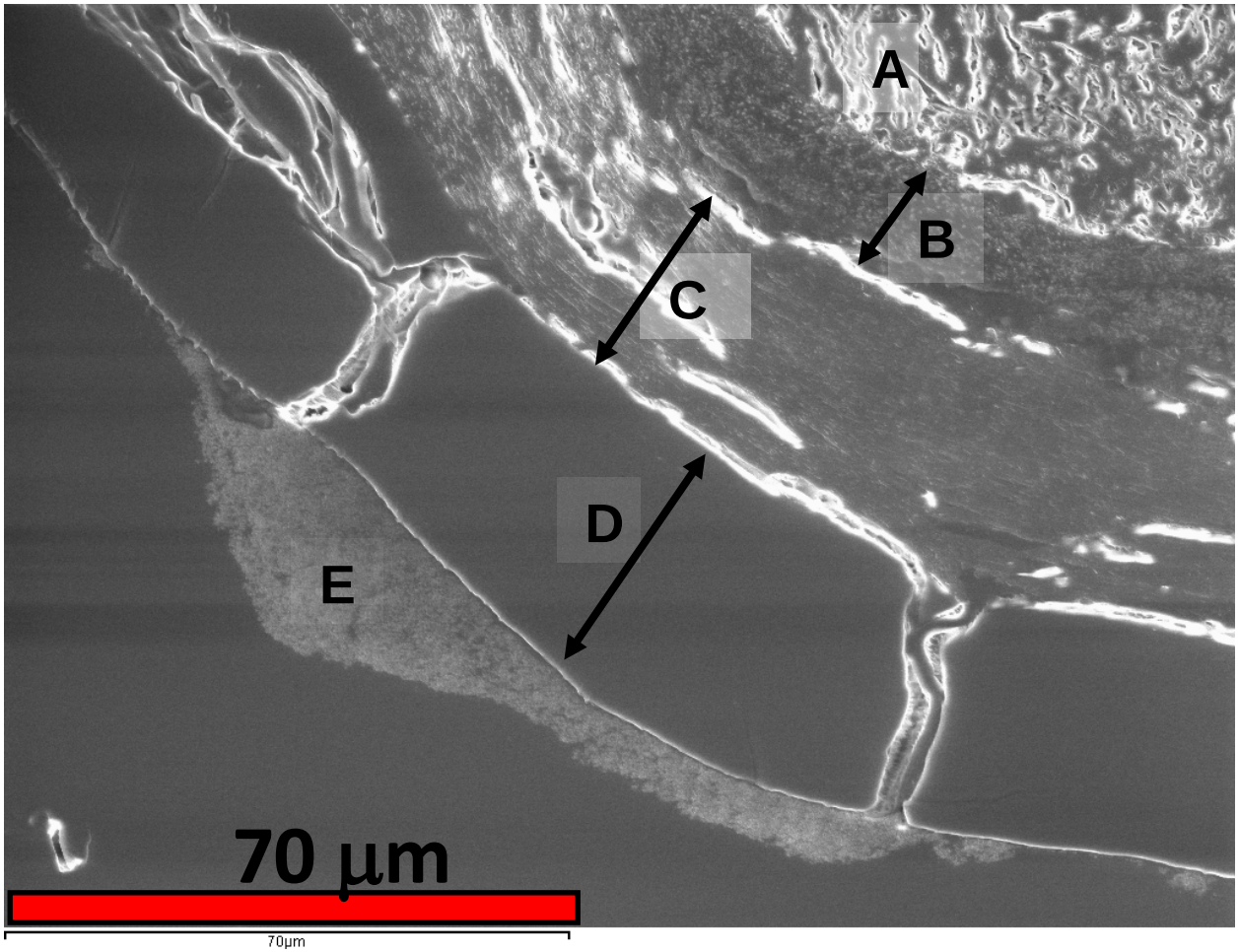
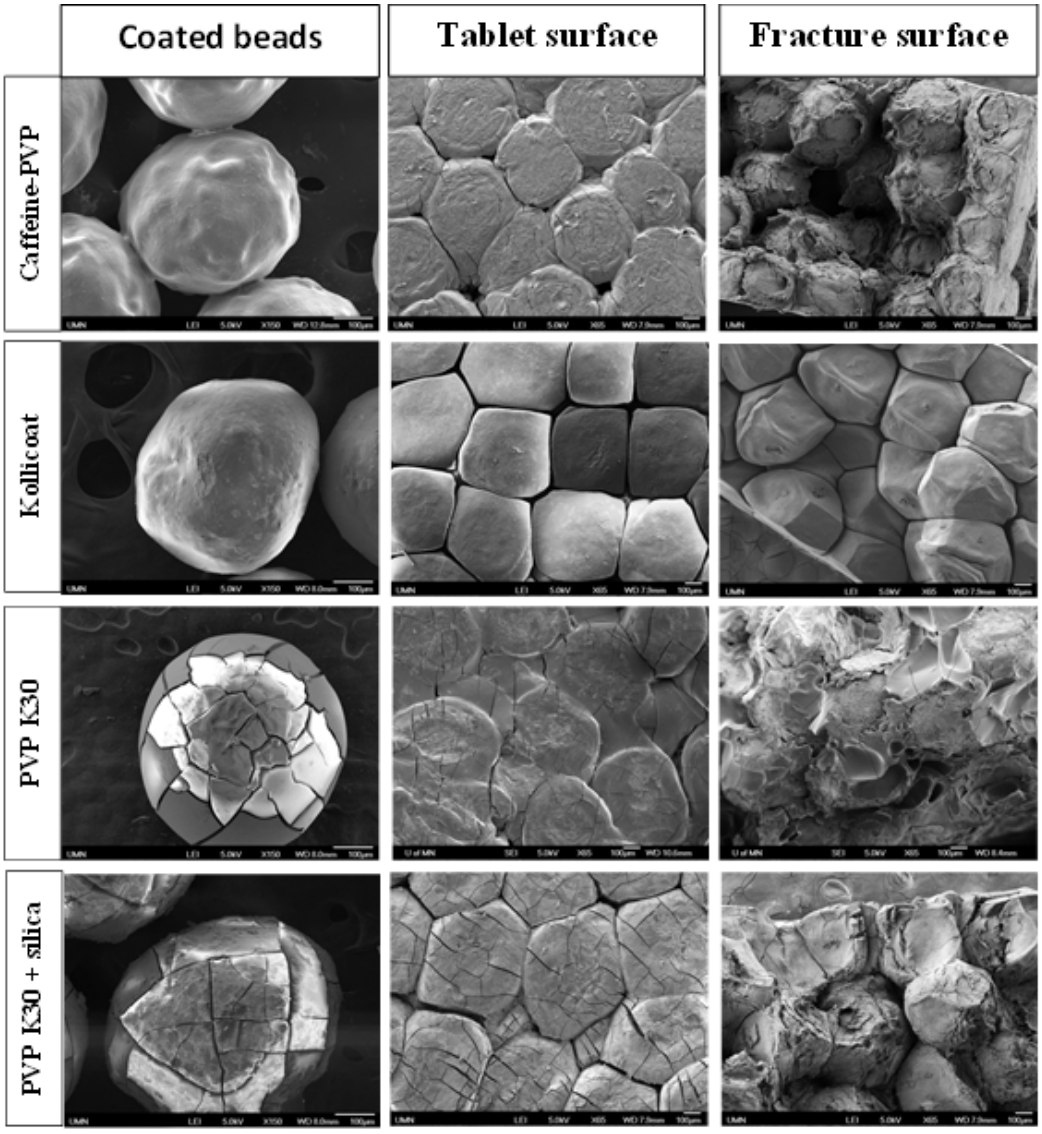


Figure 4.4 SEM images of coated Cellet beads with different top layer coating, top surface ofcompressed tablets, and tablet fracture surface after diametral breaking test. Beads were exposed to 75% RH for 4 days prior to compaction. Label at the left of each row of images indicates the outermost layer material. Cracks in the PVP coated beads (with and without silica) are caused by dehydration of PVP coating layer during sample preparation for SEM.



CHAPTER 5. A TOP COATING STRATEGY WITH HIGHLY BONDING POLYMERS TO ENABLE DIRECT TABLETING OF MULTIPLE UNIT PELLET SYSTEM (MUPS)

Summary

Multiple unit pellet system(s), MUPS, is one of the most commonly used means for achieving modified drug release through oral administration. MUPS is usually delivered as capsules that contain drug bearing beads coated with a release modulating functional layer. While highly desired, the routine manufacture of tablets of MUPS by direct compression is faced with the problem of poor tableting properties or altered drug release behavior due to the rupture of the functional coating layer. The use of a significant amount of cushion material alleviates these problems but is also challenged with the problem of segregation and reduced drug loading. We hypothesize that top-coating the beads with a layer of highly bonding polymer can enable direct tableting of beads without compromising the functional coating layer and without the segregation problem. Using functionally coated pyridoxine and caffeine beads, we confirmed that top coating with PVP sufficiently plasticized with water can enable the preparation of strong tablets at even low compaction pressures. Drug release profiles of tablets are comparable to those of uncompressed beads, indicating negligible amount of damage, if any, to the functional coating layer. Therefore, top polymer coating combined with silica coating is a promising universally applicable strategy for realizing the goal of delivering MUPS in the form of tablet.

Introduction

Drug-loaded beads/pellets, commonly referred to as multi-particulates or multiple unit pellet systems (MUPS) are increasingly being used for controlled drug delivery.[1-4] Individual drug-bearing beads are coated with polymeric functional layer(s) to modulate the drug release and essentially create mini drug depots.[2] Such systems offer advantages including: 1) reduced risk of dose-dumping; 2) lower tendency of localized gastric irritation from irritant drugs due to more even distribution of the drug in the gastrointestinal (GI) tract; 3) lower inter-subject variability in drug absorption into the bloodstream due to a more consistent transport of the beads in the GI tract; and 4) flexibility in developing products with unique drug release profiles through combining beads with different functional coating layers.[5-8]

For consistent administration, drug-bearing beads need to be placed into a capsule or compressed into a tablet.[6-9] The tablets are the preferred dosage form because tablets can be manufactured at a higher production speed, at a lower cost, and the tablet content cannot easily be tampered with.[10] Apart from the flexibility in shape and color, a tablet is also significantly smaller than a capsule for the same drug content. These are essential for developing an appealing and unique product with good patient compliance.

Tableting of MUPS, however, presents several challenges including inability to form tablets of adequate mechanical strength and pressure-induced destruction of the

functional coating layer when they do form.[11-16] These prevent tablet manufacturing from beads on a routine basis.

Several technologies have been investigated to improve tablet strength and preserve the functional layer.[3] A majority of the work in this field has focused on mitigating fracture of the functional coating by admixture of beads with soft cushioning excipients and/or compressible excipients to protect the coating layer against fracture during compaction and to improve tablet mechanical strength.[15-18] When excipients are mixed with beads, particle segregation is a major problem.[19] Layering of the top surface of beads with compressible excipients such as microcrystalline cellulose (MCC) to modify the mechanical properties of the beads is gaining more attention.[4,20,21] This approach, however, requires a large amount of the layering excipients and still with mixed results.[4] At present, the task of routinely tableting MUPS remains an unmet need in drug delivery. A simple and easy-to-implement solution to this problem is of great pharmaceutical importance.

We have shown that surface coating with a highly bonding polymer can be used to effectively modulate tabletability of powders.[22-24] This strategy is promising for enabling direct tableting of functionally coated beads without compromising functional coating layer. When adequately plasticized, the highly bonding top coated beads can easily deform and produce strong tablets even under a low pressure (e.g., 50MPa) because of 1) the presence of a three-dimensional bonding network in the tablet; and 2) the low hardness of the

top coated polymer layer permitting the easy development of a large bonding contact between adjacent beads upon compression (Figure 5.1). Consequently, stress on the functional coating is minimal, and the integrity of the functional coating layer can be preserved during tableting without risking drug content uniformity problems due to segregation. For this purpose, we have top-coated two kinds of drug-bearing beads with two kinds of modified release layer, and studied their tableting and drug release properties.

Materials and Methods

Materials

Two types of functionally coated beads were used in this study. The sustained release pyridoxine (vitamin B_6) beads, with 95% microcrystalline cellulose (MCC) + 5% povidone core prepared using an extrusion and spheronization process, and functionally coated with a dispersion of ethylcellulose (containing 5% Eudragit® L100-55, 4.5% triethyl citrate, and 3% talc), were received from Upsher Smith Laboratories (Maple Grove, MN). The caffeine beads had Cellet 350 (Glatt Air Tech. Inc., Ramsey, NJ) as the core and poly(methacrylate-ethylacrylate) 1:1 co-polymer-based enteric coating layer (Kollicoat® MAE 30DP, BASF, Ludwigshafen, Germany), which contained 4.5% triethyl citrate, and 3% talc. Polyvinylpyrrolidone (PVP) K30 and Vinyl Acetate, VA64

(BASF, Geismar, Germany) were used as highly bonding polymers for top coating. Fumed silica (Cab-O-Sil, M-5P, Carbot Corp., Billerica, MA) was used as an anti-adherent.

Methods

Bead coating

To coat pyridoxine beads with PVP K30, 40 g of beads were weighed and mixed with 10%, 15%, and 20% of PVP K30 using a spatula to obtain a uniform mixture before spraying ~3.2 g of an acidified water (pH ~2.4) unto the mixture under gentle mixing (low shear wet granulation). Coated beads were air dried at 25 ^{o}C and 7 % RH for 7 days.

Caffeine beads were prepared using a fluid bed coater (Unilab, Bosch, Germany, batch size was 2.5 kg). The caffeine layer was coated onto the core by spraying a suspension of 1:1 (w/w) PVP and caffeine in de-ionized water at 35^{o}C to attain ~5% (wt%) of total caffeine loading. Subsequently, 40% (wt%) Kollicoat MAE 30DP coating was applied. Finally, the outermost layer (5 – 25%, wt%) of bonding polymer, either PVP K30 or PVP VA64, was applied. The following coating parameters were kept throughout the coating process: inlet temperature 65 – 70 ^{o}C; fluidized bed air flow of 220 – 240 m^3/hr;

atomization pressure of 1 bar, nozzle sweeping air pressure of 0.2 bar, feed rate of ~15%, and 45 ^{o}C bed temperature for drying.

Lastly, where indicated, silica nanoparticles were deposited on the beads by mixing 1% (wt%) of fumed silica with 50 g of beads for 10 min in 1 quart (946 mL) twin shell dry blender (Patterson–Kelley, East Stroudsburg, PA) with the beads.

Tableting of beads

All beads were stored at 25^{o}C in different relative humidity (RH) chambers, containing saturated solutions of magnesium chloride (32% RH), magnesium nitrate (52% RH) or sodium chloride (75% RH).[25] Bead compression was carried out in the pressure range of 50 – 350 MPa using a universal Materials Testing Instrument (Zwick-Roell 1485, Ulm, Germany) using round and flat-faced tooling (8 mm diameter). For dissolution test, beads were also compressed using 13.5 x 8.5 mm oval convex punches and die. Tablet dimensions, and diametrical breaking force were measured within 2 hr post compression. Breaking force was determined using a texture analyzer (TA-XT2i, Texture Technologies Corp., Scarsdale, NY) at a speed of 0.01 mm/s with a 5 g trigger force. Tensile strength of cylindrical tablets was calculated from the breaking force and tablet dimensions using *Equation 5.1*.[26]

$$\sigma = \frac{2F}{DT} \qquad 5.1$$

where F is the breaking force, D is the tablet diameter, and T is the tablet thickness. Tabletability (tablet tensile strength as a function of compaction pressure) has been used to describe the tableting properties of various beads.[27]

Morphology of free beads and tablets

The physical appearance of beads before and after compression was captured by a digital microscope (Dino-Lite, AnMo Electronics Corp., Taiwan), and a scanning electron microscope (SEM, JEOL6700, Tokyo, Japan). Samples for SEM were sputter-coated with platinum (100 Å thickness) using ion beam sputter (IBS/TM200S, VCR Group Inc., CA, USA). SEM images were collected at 3 or 5 kV accelerating voltage.

Drug release from beads

Drug release from ethyl cellulose-coated pyridoxine beads was determined after compression at 150 MPa for beads without PVP K30 (no intact tablet was formed without the PVP coating) and at 300 MPa for 10 – 20% PVP-coated beads. The dissolution test was carried out in 700 mL of aqueous HCl solution (pH 2.4) using a 900 mL beaker and

agitated briskly with an overhead stirrer (1750 rpm, Lightnin Model L mixer, Rochester, NY) at 25^{o}C. Samples (3 mL) withdrawn at 1 and 2 hr time points were analyzed for pyridoxine concentration using UV-vis spectrophotometry at 240 nm wavelength (DU530 Beckman Coulter UV-vis spectrophotometer, Fullerton, CA). The rapid mixing facilitated tablet disintegration in less than 1 hr. Caffeine release from Kollicoat coated beads was tested in 750 mL of 0.1 N HCl, using a type II USP apparatus (Varian 705 DS Dissolution Apparatus, Walnut Creek, CA) at 100 rpm and 37^{o}C. Samples (3 mL) withdrawn at various time points were analyzed for caffeine using UV-vis spectrophotometry at 275 nm wavelength. Amount of each active chemical released was determined from the corresponding concentration - UV absorbance standard curves.

To compare the equivalence of dissolution profiles, the similarity factor, f_2 (*Equation 5.2*) was adopted taking uncompressed beads as reference and the compressed beads as test.[28,29]

$$f_2 = 50 \times \log\left\{\left[1 + \frac{1}{n}\sum_{j=1}^{n} w_j \left|R_j - T_j\right|^2\right]^{-0.5} \times 100\right\} \qquad 5.2$$

where R_j and T_j represent amount of drug released from reference sample and test sample, respectively, at each time point j; n is the number of time points in the profile; and w_j is a weight factor, which is kept at unity in this work. With f_2 being the logarithmic transformation of sum-squared error of differences in dissolution, a value of greater than 50 represents less than 10% difference in the dissolution behavior in general.

Results

Comparing different top-coating processes

The different coating process leads to very different final appearance of coated beads. During the modified low shear granulation process (gentle mixing under wetting) of the pyridoxine beads, PVP dissolves on contact with the sprayed water and the polymer solution spreads on bead surface. This process is simple and suitable for coating a small batch of beads in laboratory but is faced with the problem of agglomeration of coated beads, which is more severe as the PVP concentration increases (Figures 5.S1A - C). This problem is inevitable for this particular procedure because sufficiently plasticized PVP on the beads is sticky and fuse when they come in contact.[30]

In contrast, free flowing individual beads can be prepared using the fluid bed coating process. Here, a polymer solution sprayed onto beads is immediately dried by hot air that fluidizes the beads before they come in contact with each other to form agglomerates.

This process generally produces beads with good uniformity of the different coating layers (Figure 5.S1E), and is suitable for industrial production of MUPS.

Tableting and drug release performance of beads

Pyridoxine beads

Although the beads top coating by the low shear coating process is unfit for commercial manufacturing due to the agglomeration, it is suitable for investigating the feasibility of the top coating strategy to improve the tableting properties of the beads. When beads with 20% PVP K30 coating equilibrated at 32% RH are compressed in the 50 – 350 MPa range, tablet tensile strength is lower than 0.75 MPa (Figure 5.2A). This indicates only a small area of contact is created for bonding upon compression due to insufficient amount of plastic deformation.[31] Therefore, at 32% RH, the water content in PVP K30, ~3%, does not achieve sufficient plasticization. One strategy to address this problem is to further plasticize PVP K30 by elevating the equilibration RH because moisture content in PVP increases rapidly with increasing RH (Figure 5.S2).[32] The tabletability of beads equilibrated at 52% RH (~10% water in PVP K30) slightly improves (Figure 5.2A). At 75%, the tablet tensile strength is considerably improved, ranging from 3 to 7 MPa for beads coated with 20% PVP (Figure 5.2A). With 20% PVP coating, tensile strength higher than 2 MPa can be obtained even at the low pressure of 50 MPa. The formation of

strong tablets under “soft compression” conditions favors the preservation of the functional coating layer.

Coated beads equilibrated at 75% RH exhibited over-compression behavior at 10% PVP K30 coating level when the compaction pressure was above 250 MPa. That is, tablet tensile strength begins to decrease with increasing pressure after passing a critical value.[23] Beyond the critical pressure, bonding contacts between particles gained by the pressure increase is less than that lost due to the elastic recovery during the decompression phase. Consequently, there is a net reduction in forces holding particles together. The higher the compaction pressure, the greater the degree of over-compression because the release of more stored elastic energy leads to more breakage of initially formed bonds. The over-compression is not observed in the 15 and 20% PVP K30 coated beads indicating the corresponding coating layers are sufficiently thick to either minimize stored elastic energy during compression or provide adequate plastic deformation to mitigate detrimental effect by elastic recovery during decompression, or both.

The release profiles of compressed pyridoxine beads, with and without PVP coating (0 – 20%), are compared to evaluate the effectiveness of PVP coating in protecting the ethyl cellulose based functional layer. Beads without PVP coating do not form an intact tablet, and pyridoxine is released within the 2 hr time period, indicating appreciable amount of damage to the functional coating layer (Figure 5.2B). On the other hand, 10% - 20% PVP coated beads form strong tablets without release of pyridoxine even when the

compaction pressure was as high as 300 MPa (Figure 5.2B). All tablets disintegrate in less than 1 hour.

Caffeine beads

PVP top-coated caffeine beads in a fluid bed coater are free from agglomerates (Figure 5.S1E), suggesting the effectiveness of the coating process and the feasibility for industrial implementation of this top coating strategy.

As observed earlier with the pyridoxine beads, moisture activation of PVP bonding was also observed for caffeine beads. Tablet tensile strength of 2 MPa can be obtained at 50 MPa pressure for 5-25% PVP top coating (Figure 5.3A). In contrast, tabletability of beads with Kollicoat as the outermost layer is low and does not change with equilibrating RH. Since tablet tensile strength remains relatively low at 52% RH but jumps to very high tensile strength at 75% RH for PVP top-coated beads, the critical RH that activates superior tabletability must lie between 52% and 75% RH. This again shows that adequate plasticity of the PVP layer is critical to the tabletability of coated bead.

At this point, we have shown that the top coating strategy is feasible for preparing compressible beads that may be used to manufacture MUPS tablets. To enable successful adoption of this strategy, it is useful to identify additional suitable polymers for the same application. We therefore, select a second polymer, PVP VA64, to coat caffeine beads by

the same fluid bed coating process. Similar to PVP K30, tabletability of PVP VA64 coated beads is low at 32% RH, but improves with increasing RH and becomes excellent at 75% RH (Figure 5.3B). With 10% or 20% PVP VA64 top coating, tablets with tensile strength higher than 2 MPa can be obtained at 100 MPa pressures at 75% RH. The results show that PVP VA64 is also a suitable polymer for preparing compressible beads through beads top coating.

Mitigating Caking Tendency for PVP K30 top-coated beads

Although moisture activation profoundly improves tabletability, polymer (PVP K30 or PVP VA64) coated beads have the tendency of caking when equilibrated at 75% RH (Figure 5.S3). Essentially, the PVP layer becomes so plasticized that the polymer chains gain sufficient mobility to fuse beads on contact without applying any external pressure.[33] Similar phenomenon was also observed in some other film forming polymers used for functional coating.[30] This problem was, however, not observed for Kollicoat MAE 30DP coated beads within the period (4 days) of equilibration.

To address this caking problem, 1% (by wt. of beads) of nano-sized silica is surface coated on the beads before their exposure to 75% RH to provide physical barrier to reduce caking tendency. With 1% silica coating, 25% PVP K30 coated beads (~40 g) remain free flowing for at least 6 days when stored at 75% RH. The silica coated beads,

however, exhibit ~30% reduction in tabletability (Figure 5.4). Despite the reduction in tabletability, sufficiently strong tablets (> 2 MPa tensile strength) can still be formed at as low as 150 MPa compaction pressure. Moreover, on prolonged equilibration for 8 days or longer, the tabletability is restored (Figure 5.4) while the caking also ensues.

Drug Release from PVP K30 top-coated beads

In addition to the improved tabletability, another critical criterion for the success of the top-coating strategy is the preservation of functional coating layer after compaction. Both 250 mg cylindrical and 500 mg oval convex tablets were prepared and their dissolution profiles were compared with uncompressed PVP K30 coated beads. For the dissolution test, the cylindrical tablets were compressed at 150 MPa, which produced tablets of 2 MPa tensile strength. Oval convex tablets, compressed at 4 kN, had acceptable mechanical strength (breaking force of 142 ± 19 N) as confirmed by the low (0.79%) tablet friability.

Without the Kollicoat layer, the drug goes into solution immediately as expected (Figure 5.5). The drug release from the cylindrical tablets of PVP K30 coated beads is more variable (large error bars) than those of uncompressed beads (Figure 5.5). This is partly caused by the failure of cylindrical tablets to disintegrate into individual beads due to its high tablet mechanical strength. After dissolution, the tablets are loose plugs staying at

the bottom of the vessel and crumbled with the slightest touch. On the other hand, the large-sized oval convex tablets completely disintegrated into individual beads in the dissolution medium within 55 minutes. At the 100 rpm paddle speed, the current in the dissolution medium was able to move the larger oval convex tablet but not the smaller cylindrical tablets. Lack of tablet movement during dissolution may have contributed to the long disintegration time of the cylindrical tablets. However, this is not expected to be a problem in vivo because mechanical stress exerted by the GI track is stronger than that during dissolution.

The similarity factor of the caffeine layered beads was 6.4, which confirms the visually observed difference in the dissolution profiles (Figure 5.5) is indeed significant. The initial drug release is observed from the two types of tablet but not from the reference beads (Figure 5.5). The possible reason is that functional coating on beads near the edge of the tablet, are still damaged despite the presence of PVP layer. The initial differences in drug release between compressed and uncompressed beads diminish continuously and become almost the same after 6 hours for reference beads and both tablets. Overall dissolution profiles are similar as shown by the similarity factor, $f_2 > 50$ (Table 5.1).[29] In addition, the amount of drug released is essentially the same at 6 hr time point.

Discussion

MUPS have become a prominent system for oral drug delivery. However, the problems of poor tableting performance and pressure-induced rupture of the functional coating layer significantly limit routine production of MUPS-based tablet.[11,15] The poor tabletability of functionally coated beads is caused by the lack of sufficient plastic deformation of the functional layer. Compaction-induced fracture of the coating layer may be caused by either excessive compressive stress at contact points between two hard beads or excessive tensile stress at points away from the contact due to the large extent of deformation of beads.[34]

Hard and dense MCC spheres are among the most commonly used cores for MUPS.[11] Their mechanical properties are such that they do not undergo easy plastic deformation nor fragmentation during compression.[31,35] Under low compaction pressures, limited degree of permanent deformation takes place by these beads. Under high compaction pressures, these beads' surface rupture at points of maximum strain without fragmentating into smaller particles (Figure 5.5A). Because of the large size of MCC beads, from hundreds of micrometers to several millimeters, and their resistance to fragmentation, the contact area among beads (bonding area) remains small after compaction and ejection. Hence, they exhibit extremely poor tabletability.[36]

To form sufficiently strong tablets, adequate interparticulate contact area after compression is required. The approach of increasing the bonding area through surface coating with plastic polymers (Figure 5.1) is expected to be effective.[22] When compressed, the easily deformable top-coating layer forms a 3D network, even at a low pressure, to afford appreciable mechanical strength to the tablet.[36] The ability to form strong tablets at low pressures makes this approach attractive to the development of directly compressible MUPS tablets. Top surface coating strategies reported so far require the use of complex multiple layers.[4,20] A single layer top-coating strategy to enable the production of MUPS has many advantages in comparison.

The significant improvement of tabletability of both pyridoxine and caffeine beads after PVP coating is encouraging. The further activation of tabletability by water (at high RH) is consistent with the dependence of tablet mechanical strength on bonding area. More plasticized PVP layer can naturally form larger bonding areas under identical compression conditions. Thicker PVP coating also favors the formation of strong tablets. The difficulty in separating beads is evident by the SEM images of tablet fracture face as demonstrated in our previous work.[24] For Kollicoat layered beads, surfaces are smooth after tablet breaking. Consequently, the tablet mechanical strength is low because of the small bonding area between such beads. In contrast, the top coating by plasticized polymers enhances both bonding area and bonding strength.[36]

The increased mobility of polymeric chains in the top coating layer, although makes it easier to form intimate bonding between adjacent beads, also causes the caking problem. The introduction of an anti-adherent, silica, on the surface solves the problem but with the sacrifice of lower tablet tensile strength (Figure 5.4). However, the tabletability remains sufficient for forming strong tablets and the loss in tablet tensile strength is recovered after prolonged exposure to the 75% RH. There is an appreciable window of equilibration time where beads are both highly compressible and free-flowing.

For the top coating strategy to be successful, it is critical that the integrity of the functional coating layer is preserved after compaction. When coated with 10% - 20% PVP K30, the ethylcellolose functional coating layer on pyridoxine beads remains intact even after a high compaction pressure (Figure 5.2B). When coated with 25% PVP K30, adequate protection of the Kollicoat functional coating layer is achieved as shown by the similar dissolution profiles of the beads and compressed tablets (Figure 5.6). Therefore, satisfactory protection of the functional coating layer has been attained in both systems studied.

The demonstrated success of the top coating strategy on two types of functional coating with two different polymers suggests the possible universal applicability of this strategy. If further systematic investigations confirm this, it forms a basis for developing a much more efficient manufacturing process than other existing approaches (e.g., onion ring, etc.).[20]

Conclusion

Top coating with highly bonding polymer is an effective and potentially universal strategy for enabling the manufacture of MUPS tablets. Fluid bed coating is a reasonable process for producing agglomerate-free top-coated beads. A combined moisture activation and silica coating of polymer top coated beads can be used to successfully prepare MUPS tablets with high mechanical strength and desired dissolution profile. The success with two top coating polymers, PVP K30 and PVP VA64, and two most commonly used functional coatings suggest this strategy may find broad applications in the controlled oral delivery of drugs.

Table 5.1 Comparison of drug release profile to that of caffeine beads top-coated with 25% PVP K30

Type of beads	**Similarity Factor (f_2)**
Caffeine layered beads	5.9
Kollicoat layered beads	62
PVP K30 + Silica coated, Cylindrical Tablet (250mg)	73.8
PVP K30 + Silica coated - Oval Convex Tablet (500mg)	54.7

Figure 5.1 Schematic of the development of a large interparticulate contact area between beads coated with a layer of highly bonding polymer

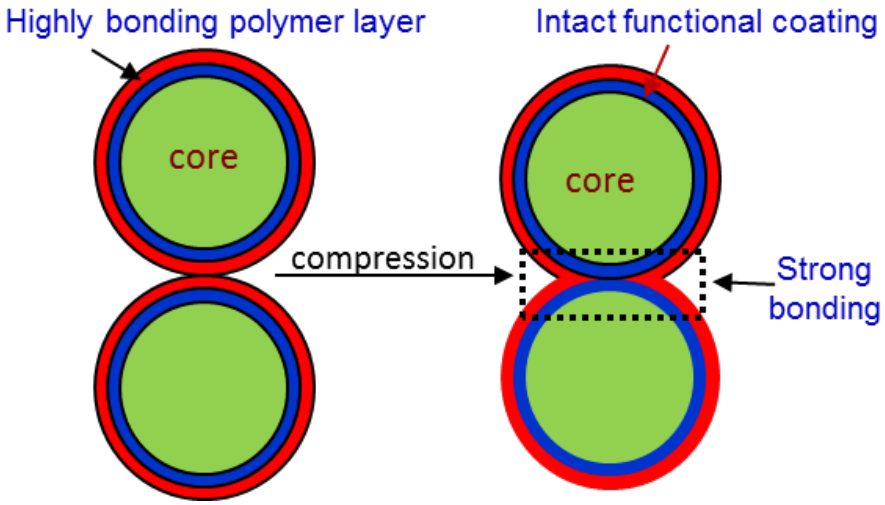
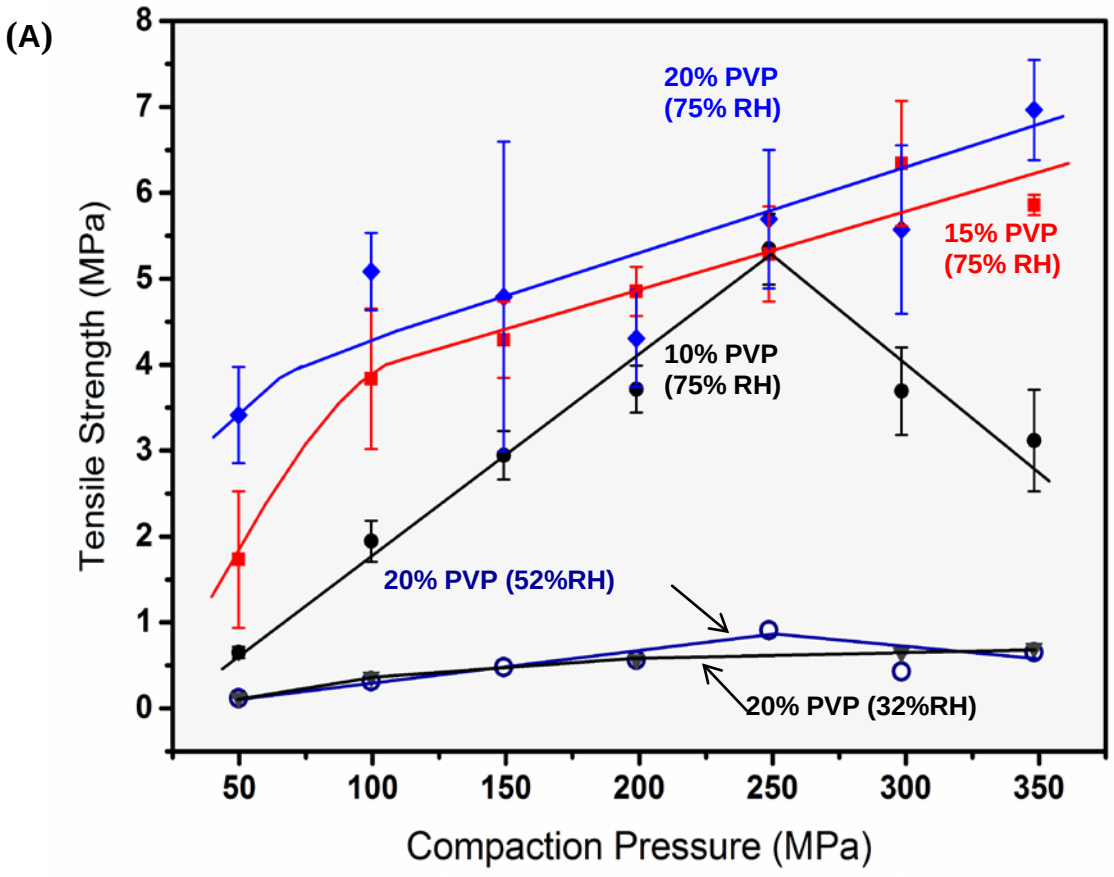


Figure 5.2 Performance of 10 – 20% PVP top-coated pyridoxine beads: (A) Effect of RH on the tabletability (B) Pyridoxine release profile from compressed tablets in comparison to beads without PVP top coating. Beads were equilibrated at 75% RH before compression. Tablets disintegrated completely within 1 hour.



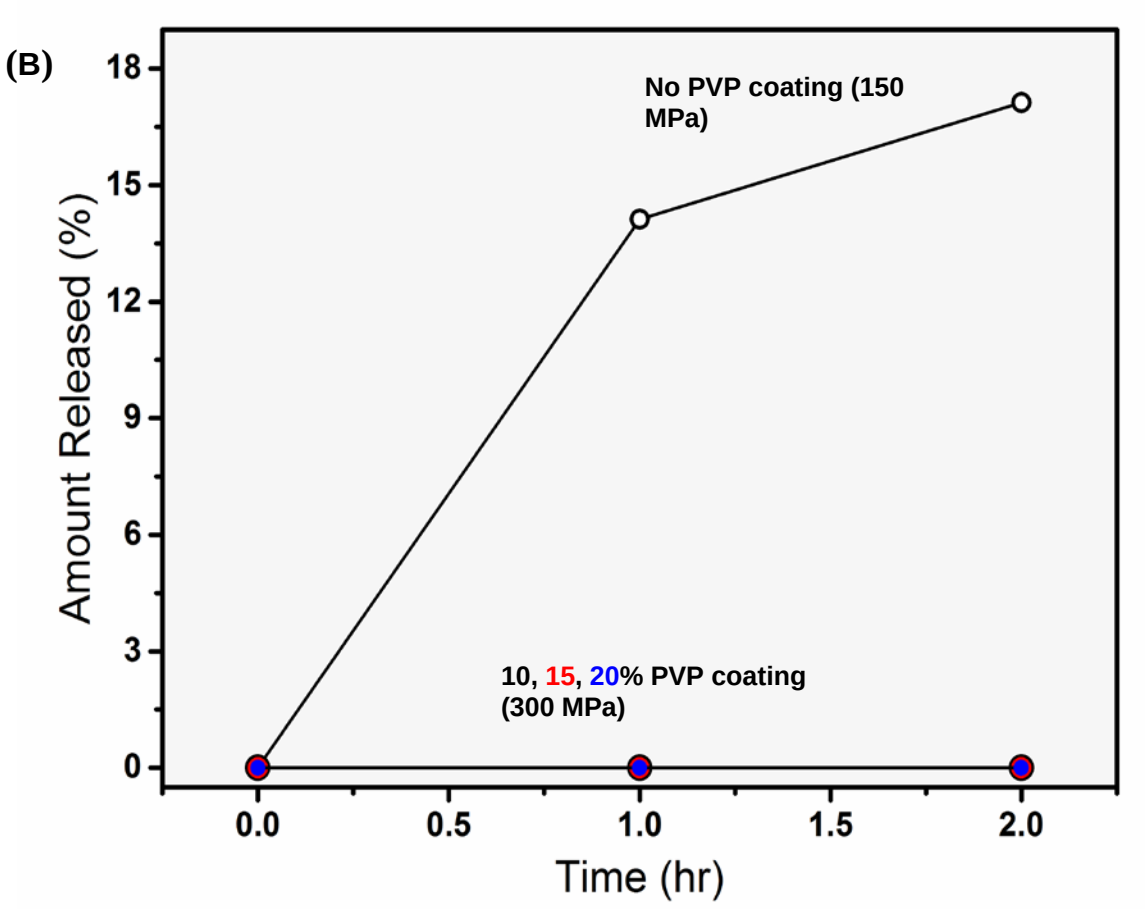
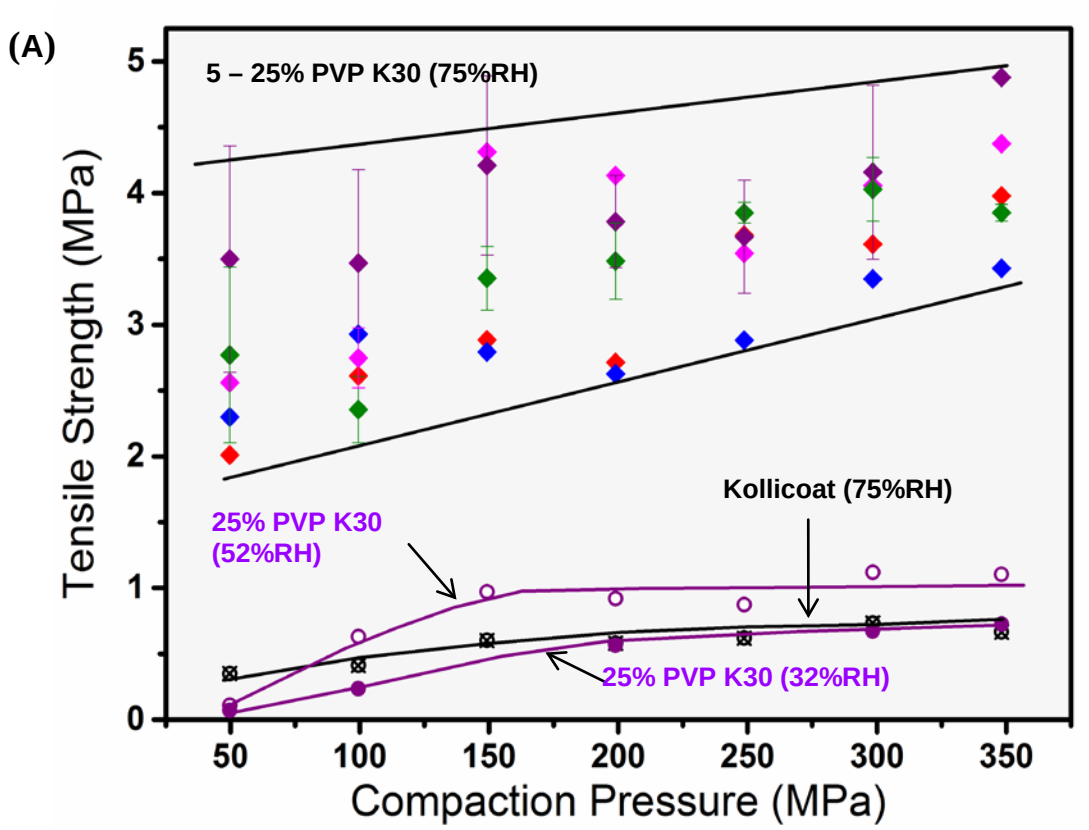

(B)
Amount Released (%)
Time (hr)
No PVP coating (150 MPa)
10, 15, 20% PVP coating (300 MPa)
0
3
6
9
12
15
18
0.0
0.5
1.0
1.5
2.0

Figure 5.3 Effect of RH on the tabletability of beads coated with a Kollicoat layer top-coated with (A) PVP K30 and (B) PVP VA64 With 10% or 20% PVP VA64 top coating, tablets with tensile strength higher than 2 MPa can be obtained at 100 MPa pressures at 75% RH.



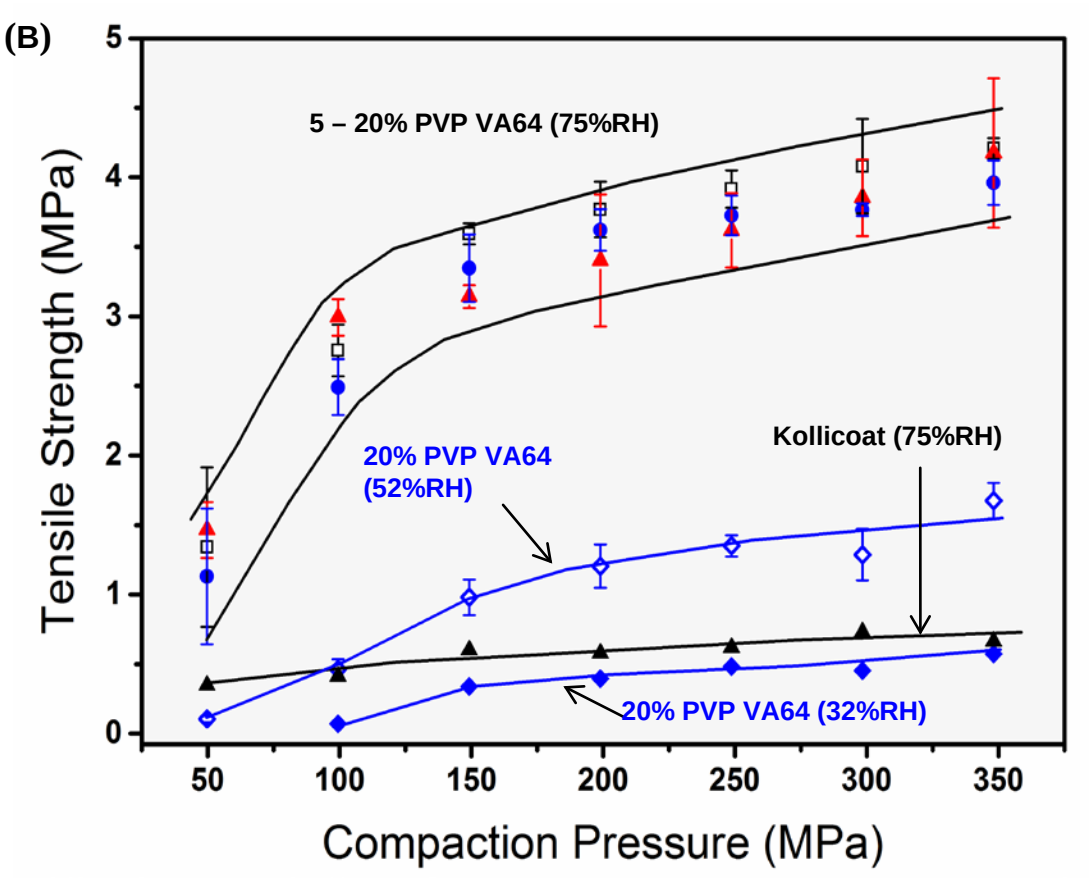

(B)
Tensile Strength (MPa)
Compaction Pressure (MPa)
5 – 20% PVP VA64 (75%RH)
20% PVP VA64
(52%RH)
Kollicoat (75%RH)
20% PVP VA64 (32%RH)
0
1
2
3
4
5
50
100
150
200
250
300
350

Figure 5.4 Effect of outermost coating layer on tabletability of caffeine-bearing beads conditioned at 75% RH; A) Kollicoat MAE 30DP, B) PVP K30, C) PVP K30 + Silica (equilibrated for 4 days), D) PVP K30 + Silica (equilibrated for 8 days)

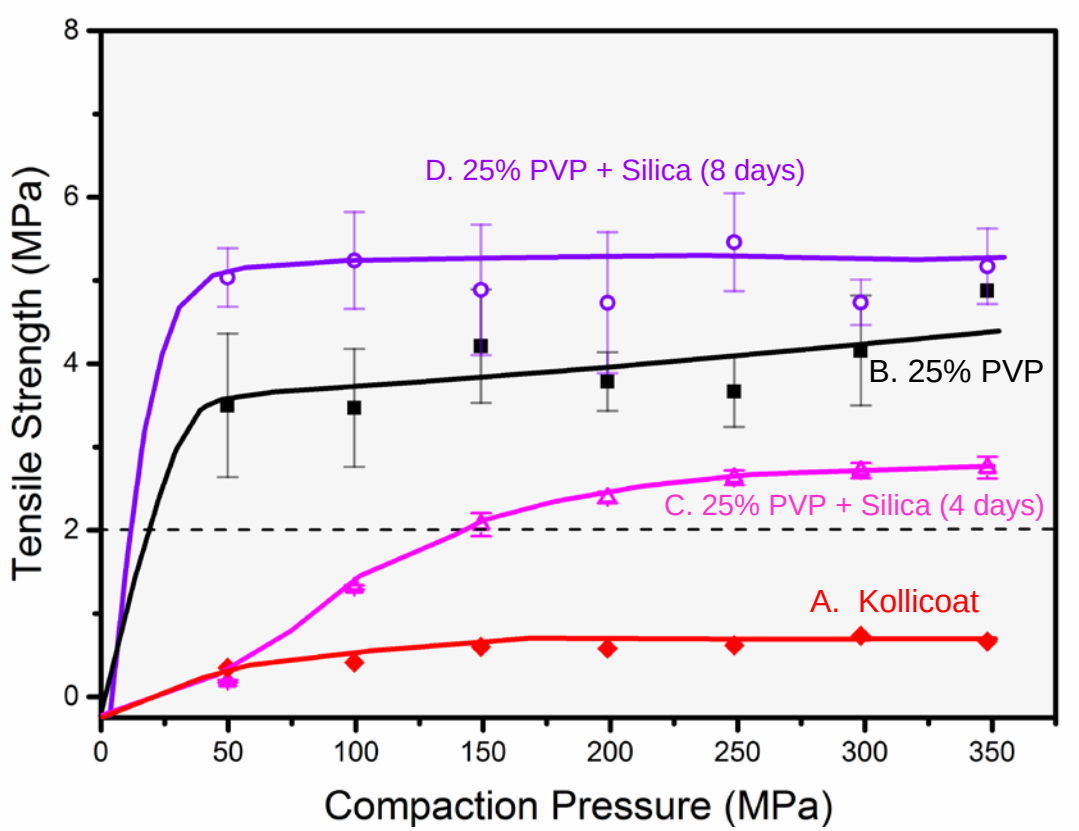


Figure 5.5 Release profiles of beads with the outermost layer: (A) caffeine, (B)) PVP K30 (free beads), (C) PVP K30 with silica (cylindrical tablets, 8 mm diameter, 150 MPa compaction pressure), (D) PVP K30 with silica (oval convex tablets 13.5 x 8.5 mm, 4kN compression force).

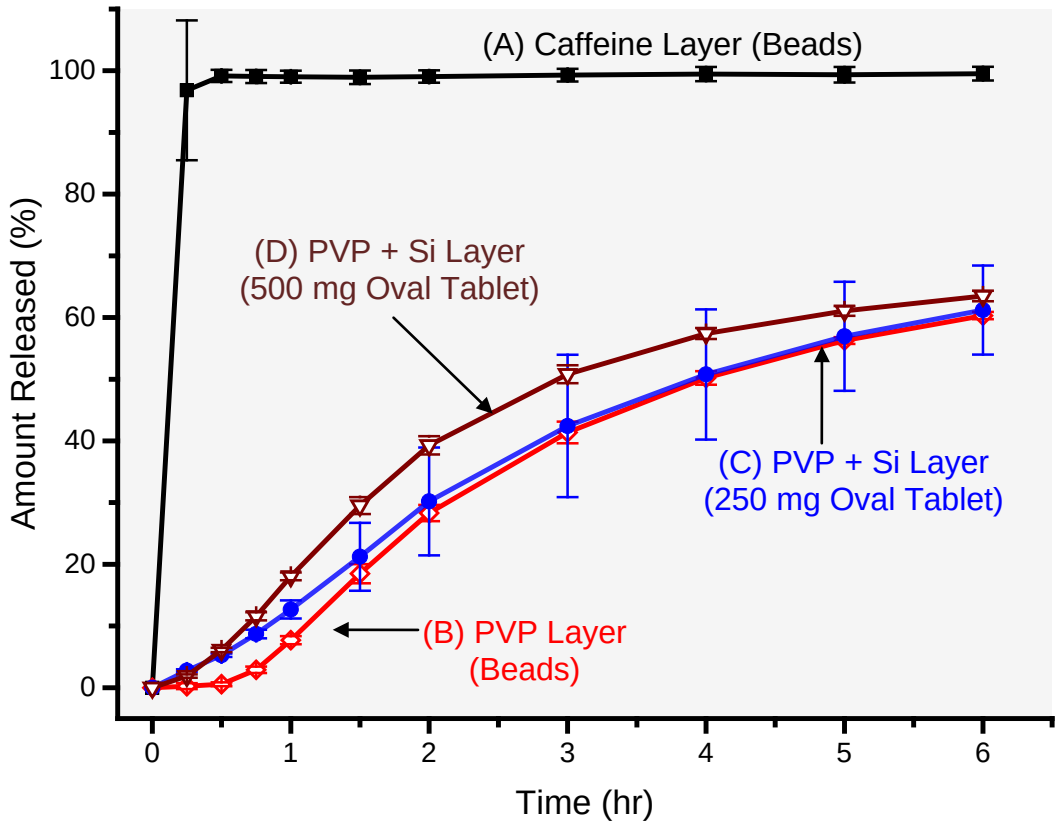


Figure 5.S 1 PVP K30 top coating on pyridoxine – layered beads (A – C) and on caffeine – layered beads (D) Intact Beads (E) Cross-sectioned bead showing individual layers.

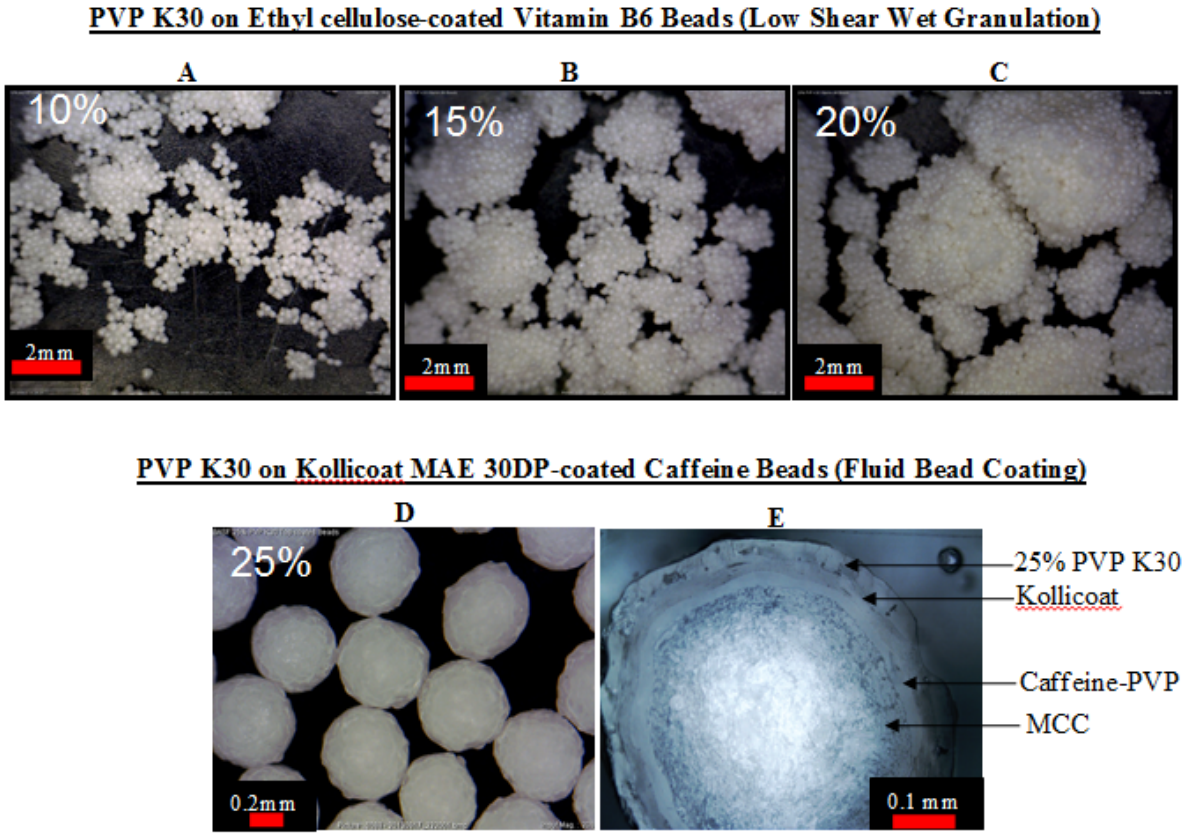


Figure 5.S 2 Moisture sorption/desorption isotherm of polymers used as protective coating, PVP K30 and PVPVA 64. At the same RH PVP K30 takes up moisture much more than PVPVA 64

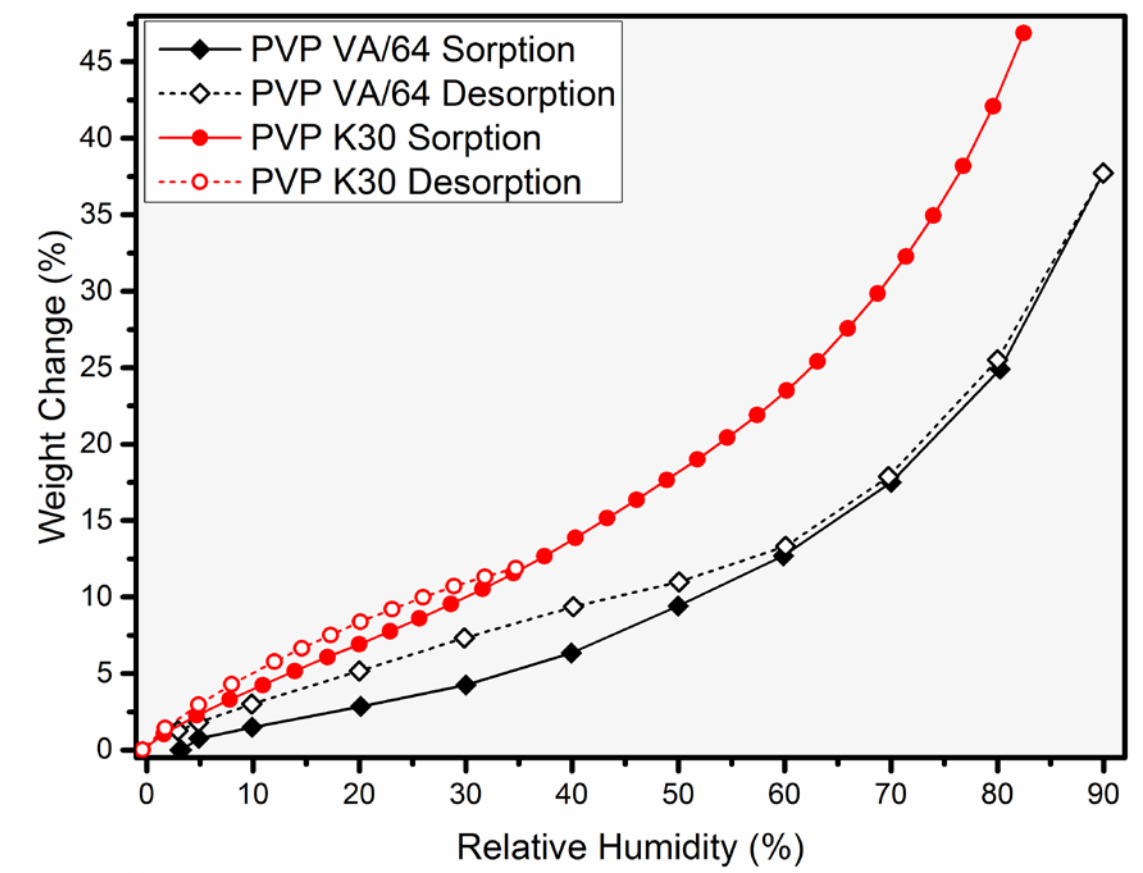
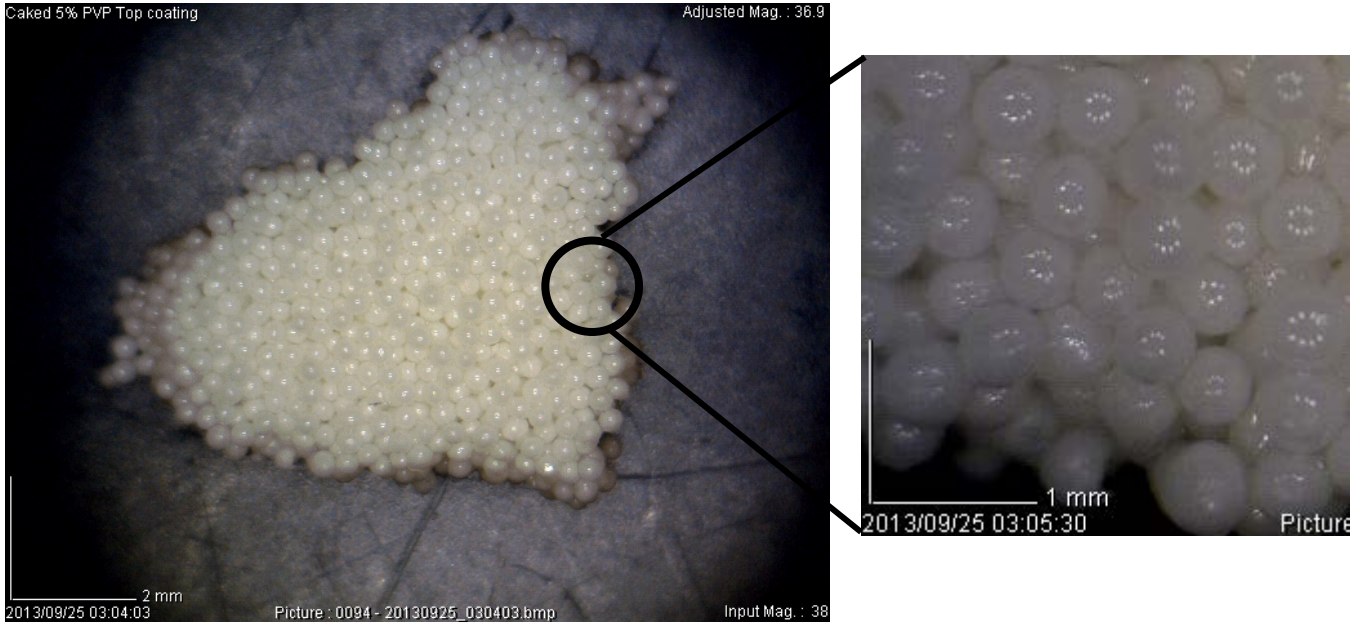


Figure 5.S 3 Images of caked beads after PVP K30 beads are equilibrated at 75% RH



CHAPTER 6. MECHANICAL PROPERTIES AND TABLETING PERFORMANCE OF CELECOXIB–PVP VA64 AMORPHOUS SOLID DISPERSIONS STUDIED BY NANOINDENTATION AND POWDER COMPRESSION

Summary

The amorphous solid dispersion (ASD) is an important class of materials widely used for delivering poorly soluble drugs through the tablet dosage form. The dependence of mechanical properties and tableting performance of ASDs on compositions, e.g., drug loading and water content, is expected but not yet systematically characterized. In this work, we have quantified mechanical properties, i.e., Hardness, *H*, and Elastic Modulus, *E*, of PVP VA64 - Celecoxib ASDs as a function of relative humidity (RH) and drug loading by nanoindentation. With increasing celecoxib loading, *E* only slightly changes but *H* rises to a maximum at ~60% drug loading before gradually decreasing to approach that of the pure celecoxib. An increase in RH from 15% to 32% slightly lowers *E* and *H* but a further increase to 61% significantly lowers both. Fine ASD powders (0 – 40% celecoxib) (<75 μm) with comparable size distributions showed complex tableting performance with changing drug loading and RH. During compaction, ASDs with a lower *H* can deform more easily to develop a larger bonding area between adjacent particles. However, their bonding strength is also lower. Based on the consideration of effects of mechanical properties on bonding area and bonding strength, complex dependence of tabletability on these factors could be clearly explained. Understanding the impact of RH and drug loading on tabletability is useful to the design of ASD tablet formulation with robust manufacturability.

Introduction

The amorphous solid dispersion (ASD) technology plays an important role in developing oral dosage forms of poorly soluble drug candidates.[1-3] A suitably formulated ASD is able to increase dissolution rate and improve oral bioavailability of drugs exhibiting solubility-limited absorption.[4,5] In ASDs, drug molecules are molecularly dispersed in an amorphous carrier, typically a hydrophilic polymer.[2,6] Plasticizers and surfactants may also be included in ASDs to facilitate processing and to improve wetting.[7,8] Concentration of polymer(s) and/or the other additives in these drug composites are known to vary widely from one ASD formulation to another, depending on the dose and physical stability.[5,9] To maintain the advantages of increased apparent solubility and dissolution rate, a successful ASD product must keep drug(s) in the amorphous state throughout its shelf life. Due to the stability consideration, drug loading in ASDs is usually not very high, usually 10 – 20% (wt%). Therefore, even a relatively low dose drug, say 20 mg, requires 100 – 200 mg of the ASD in each tablet, which corresponds to 20 – 40% loading for a 500 mg tablet. At this loading, mechanical properties and tableting behaviors of the ASD are expected to play an important role in the tableting performance of the formulation, which is critical to successful commercial manufacturing.

However, in contrast to the large number of studies that are focused on physical stability, e.g., crystallization inhibition during storage and dissolution, of ASDs[10-12] literature on

mechanical properties and tableting behaviors of ASD is scarce.[13,14] There is a clear need of systematic investigations of this important but under-studied topic. Mechanical properties of ASDs are expected to depend on the drug loading and formulation compositions.[13] Variations in moisture content, when exposed to different environment relative humidity (RH) during processing and manufacturing of a tablet product, influences ASD's mechanical properties. Hence, the effects of RH on tableting performance should also be investigated. This has practical importance for developing any tablet product, which must assume adequate mechanical strength among other requirements.[15]

For ASDs, studies that highlight the impact of processing parameters such as compaction pressure or formulation variables on product performance are limited.[5,16,17] In the absence of such fundamental understanding, formulation of an ASD-based tablet remains empirical and may lead to formulation problems. For example, incorporation of a plastic excipient into a formulation of an already plastic ASD powder could intensify disintegration problems with the resulting tablet product.[18] A clear understanding of the relationships between compositions, mechanical properties, and tableting performance will be critical for achieving the ability to efficiently optimize ASD compression properties through formulation or particle engineering.[19]

Nanoindentation is a depth-sensing technique for evaluating material mechanical properties, i.e., Hardness, *H,* and Elastic Modulus, *E,* under well controlled experimental

conditions (rate and magnitude of force and displacement).[20] It has been used to characterize mechanical properties of a range of materials, including organic crystals.[21,22] We adopt this well-established technique to characterize mechanical properties of ASDs in this work.[13]

We aim to systematically examine the influence of composition (drug loading and moisture content) on the mechanical properties and to link that to tableting performance of ASD powders. Based on a clear understanding between mechanical properties and powder tabletability, our ultimate goal is to integrate nanoindentation as one of material-sparing tools to guide the the ASD tablet formulation development.

Materials and Methods

Materials

Polyvinylpyrrolidone Vinyl Acetate, Kollidon® VA64 (BASF, Geismar, Germany) and Celecoxib (Aarti Drugs Ltd., Maharashtra, India) were used as the model compounds in this study. Methanol (Sigma Aldrich, St. Louis, MO) used was of analytical grade. All materials were used as received.

Methods

Preparation of ASD Films

Amorphous solids containing 0 – 100% celecoxib were prepared by dissolving appropriate mixtures of PVP VA64 and Celecoxib (1 g total powder weight) in 10 mL of methanol. The solutions were filtered using a 0.45 µm membrane filter. Three drops (~0.1 mL) of the filtered solution were placed on a ~10 x 10 mm cut glass slides using a 3 mL syringe. Samples were first allowed to air-dry at 25 ^{o}C. Samples were then placed in a pre-heated oven (Binder GmbH, Germany) at 175 ^{o}C for 5 – 10 min and quickly transferred onto a chilled steel block. Film thickness is 200 -400 um. Shortly before the glassy films were studied by nanoindentation, they were inspected under a polarized light microscopy (Eclipse e200, Nikon, Tokyo Japan) for detecting any sign of the presence of crystalline domains. In all cases, no birefringence was detected.

Mechanical Properties by Nanoindentation

The glass slides, which supported ASD films, were fixed unto aluminum plucks with the aid of super glue and tested for their mechanical properties using a nanoindenter (NanoXP, MTS-Nano Instruments, Oakridge, TN) at 20 ± 1 ^{o}C. We did not have complete control of RH due to instrument limitations. However, careful design of

experiment in combination of continuous RH monitoring ensured relatively constant RH (± 1%) during the course of measurement for each seires of samples.

The samples were equilibrated at each selected RH for at least 24 hours before testing. An indenter probe with a Berkovich diamond tip was used to indent the films. Area function of the tip was previously established as a function of penetration depth into a standard fused silica. The experiments were conducted in the continuous stiffness measurement mode, making 3 x 3 indents, 50 μm apart on each sample to a maximum penetration depth of 1000 nm at a rate of 10 nm/s. Once target penetration depth was reached, the indenter was held at constant at the maximum load for 10 s before unloading. Before and after indenting each film, a fused silica standard with a nominal elastic modulus of 72 GPa was indented to a depth of 2000 nm to ensure instrument was in good working conditions. Another purpose of indenting fused silica was to clean the tip in case unwanted contamination to the tip occurred during the measurement of the previous sample.

The mechanical properties i.e., the elastic modulus, *E*, and hardness, *H*, were extracted from the raw data following the standard Oliver and Phar method.[23] The indentation data between 600 – 900 nm penetration depth were used for the calculation of *E* and *H*. A Poisson's ratio, υ of 0.3 was used in calculating E for all samples.

$$E_r = \frac{1}{\beta}\frac{\sqrt{\pi}}{2}\frac{S}{\sqrt{A}} \qquad \textit{Equation 6.1}$$

$$\frac{1}{E_r} = \frac{(1-\upsilon^2)}{E} + \frac{(1-\upsilon_i^2)}{E_i} \qquad \textit{Equation 6.2}$$

$$H = \frac{P_{\max}}{A} \qquad \textit{Equation 6.3}$$

where E_r is the reduced elastic modulus, E_i is the indenter elastic modulus, S is the stiffness and calculated as the slope of the load displacement curve of the initial segment of the unloading curve and β is a correction factor of the value 1.034.

Preparation of ASD Powders

Drug and polymer solutions were prepared by dissolving in 100 mL of methanol a total of 50 g powder mixtures of PVP VA64 and Celecoxib , containing 0 - 40% celecoxib. ASD films were obtained by casting in aluminium boats. The solutions (~12 g) were dried at 70 ^{o}C for ~12 hrs. The ASD films were pulverized in a high shear blender (Ninja Warrior, NJ200 30) using the Ninja® 4-blade running at 3600 rpm, followed by cryomilling (6800 Freezer/Mill, SPEX CertiPrep Inc., Mutechen, NJ). Powders were filled into a 190 mL polycarbonate tube stoppered by two steel end plugs with a steel rod-

shaped impactor in the tube. Powders was pre-cooled for 15 mins and milled at an impact frequency of 10 Hz for 3 mins per milling cycle for a total of 5 cycles with 1 min cooling between cycles. The intense milling under liquid nitrogen effectively reduced the particle size significantly.[24] The powders were equilibrated at room temperature over drierite for at least 24 hrs. Sieving was used to further ensure that the size range was narrowed to <75 µm.

Particle Size Analysis

Particle size distributions, PSDs, of the powders were measured by a laser diffraction particle size analyzer (Sympatec GmbH, Clausthal-Zellerfeld, Germany) using the wet dispersion method in a 50 mL cuvette and HELOS (H2060, 0.5/0.9 - 175µm) sensor. For each sample, ~10 mg of powder was dispersed in about 1 mL of cyclohexane in a 1.5 mL vial and sonicated for about 50 seconds. The dispersion was then introduced drop-wise into the cuvette containing cyclohexane agitated by means of a magnetic stirrer (1000 rpm) to 20 - 25% optical density. The optical density was maintained between 15 and 25% during the measurements. For each powder, two samples were studied and 3 readings were taken per sample. The measurement time was 10 seconds with a 5-second pause time for repeated measurements for each powder.

Moisture Sorption

Water sorption isotherms of ASD powders were obtained at 25^{o}C using a dynamic vapor sorption apparatus (DVS 1000, Surface Measurement Systems, Alperton, Middlesex, UK). The nitrogen flow rate was kept at 15 mL/min. The samples were equilibrated at a desired RH for 8 hours before changing to the next target RH. The water vapor sorption isotherm of PVP VA64 was obtained on SGA-100 (VTI Inc., Hialeah, FL), where the sample was equilibrated at a desired RH with equilibrium criteria of < 0.0001%/m or maximum 120 mins before moving to the next target RH.

Powder X-ray Diffraction

Powder X-ray diffraction (PXRD) pattern was obtained on a wide-angle diffractometer (D5005, Bruker AXS) operated at 45 kV and 40 mA using Cu Kα radiation. The measurement was performed with a step size of 0.02^{o} in the 2θ range of 5 – 35^{o} and a dwell time of 0.5s. The PXRD data analyses were conducted using JADE software (Materials Data Inc., Livermore, CA)

Tableting Properties

Powders were conditioned at 25 ^{o}C in chambers containing saturated salts of lithium chloride (11% RH), potassium carbonate (43% RH) and cupric chloride (67% RH) for ~24 hrs before tableting. Powder compression was carried out in the pressure range of 50 – 300 MPa using a universal Materials Testing Instrument (Zwick-Roell 1485, Ulm, Germany) using round and flat-faced tooling (6 mm diameter). Tablet dimensions, and diametrical breaking force were measured immediately after ejection. Breaking force was then determined using a texture analyzer (TA-XT2i, Texture Technologies Corp., Scarsdale, NY) at a speed of 0.01 mm/s with a 5 g trigger force. During powder compression, environment RH was ~10% RH for the 11% RH conditioned powder and ~50% for the 43% and 67% RH conditioned powders. Tensile strength of tablets was calculated from the breaking force and tablet dimensions using a standard methods.[25] Tableting properties of various ASD powders has been characterized by tabletability (compaction pressure as a function of tablet tensile strength).[26] The PXRD of a 40% drug loading ASD equilibrated at 67% RH was collected at the end of the compaction study to verify its physical stability. Other powders are assumed to be more stable than this powder because this powder contained the highest level of celecoxib and its storage RH was the highest.

Statistical Analysis and Data Modeling

Origin statistical software (OriginPro® 2015, OriginLab Corp., Northampton, MA) was used for all data fitting and statistical analysis. Design Expert®, (v8.0.6, Stat-Ease Inc. Minneapolis, MN) was used for data modeling. In the model, compaction pressure (CP), drug loading (DL) and percentage RH were the main independent variables while tablet tensile strength (TS) was the dependent variable. Transformation was used where necessary to ensure data normality and random residuals. During initial regression, both the main factors (DL, RH, and CP) and all possible interactions were included. Insignificant terms (p-value > 0.05) were then removed after performing ANOVA.

Results

Figure 6.1 shows typical load displacement curves obtained by nanoindentation on the ASD films. The maximum load and the displacement at the maximum load are clearly different for ASD films with different compositions, e.g., the 0% to 40% drug loadings. From these raw data, *E* and *H* were obtained.[23] Qualitatively, both the higher *Pmax* together with lesser penetration depth during the holding period under *Pmax*, i.e. lesser creep[20], suggest increased stiffness and reduced plasticity of the composite films as drug loading increases from 0% to 40%. In contrast to nanoindentation raw data of crystals,

both loading and unloading curves of these samples are smooth, which is consistent with the isotropic nature of amorphous solids.[27]

At 61% RH, both *E* and *H* initially increase with drug loading to a maximum at ~60% drug loading and then decrease with further increased drug loading (Figure 6.2). A similar trend was observed with voriconazole - PVP VA64 ASDs.[13] In the range between 15% and 32% RH, *E* and *H* only slightly varies. In fact, *H* is almost identical at these two RHs. However, increase in RH from 32% to 61% results in a dramatic decrease in both *E* and *H* at all drug loadings. At high RH, films sorb more moisture (Figure 6.S1). The change in mechanical properties as a result of RH (moisture) from 15% to 61%, is larger in the polymer-rich region (lower drug loading) than in the drug-rich region. This correlates with the higher level of sorbed moisture by ASDs containing more polymer, a phenomenon also observed in other systems.[8,13] For example, the average *H* reduction, in the 0% - 20% drug loading range is ~37% while that at 80% – 100% drug is ~10% (Table 6.1). The position of the maximum for both the *E* and *H* profiles lies in the drug rich region, i.e. ~60% drug. Compared to *E*, *H* is more sensitive to the changes in composition at a given RH (Figure 6.2). When RH increases from 15% to 61%, the percent change in *H* is 3 – 56% while that in *E* is 5 – 31% (Table 6.1). To summarize, small impact of RH on mechanical properties was observed in the low RH range. However, at high RH, all ASDs significantly soften. Moreover, impact of RH on mechanical properties is coupled to drug loading. ASDs, containing more of the

hydrophobic celecoxib sorbs less water. Correspondingly, the impact of RH change on mechanical properties is also less as drug loading increases (Table 6.1).

All powders in this study are of comparable size (Fig. 6.S2). The d_{10}, d_{50} and d_{90} all five powders varied within a narrow range, 1.9 – 3.0 μm; 8.6 – 14.2 μm; and 32.8 – 40.2 μm, respectively (Figure 6.3). The powder obtained from the 10% drug loading has slightly less fines and more larger particles (Figure 6.2S). While it is impossible to attain identical PSD among different powders, the overall PSD are satisfactory for the intended purpose of minimizing the effect of particle size on powder tabletability.[28,29]

Tabletability of PVP VA64 (0% drug loading) and 40% drug loading ASD at 11%, 43% and 67% RHs is shown in Figure 6.4. The tableting performance of PVP VA64 undergoes complex change with RH. Below 200 MPa, tablet tensile strength at 67% RH is superior to those at both 43% RH and 11% RH. With further increase in pressure, the tabletability line at 67% RH crosses those of 43% RH and 11% RH at 200 MPa and 250 MPa, respectively. At 11% and 43% RHs, tablet tensile strength increases continuously with increasing pressure. At 67% RH, tablet tensile strength initially rises quickly with pressure then levels off at ≥150 MPa before slightly trending down at >200 MPa. At the relatively low compaction pressure of 50 MPa, tablet tensile strength at 67% RH exceeds 2 MPa, a tensile strength generally regarded as adequate for tablets to sustain stresses during handling.[30] At 40% drug loading, higher RH leads to higher tablet tensile strength throughout the compaction range studied, 50 – 300 MPa. However, the crossover might

occur eventually at a higher compaction pressure if the converging trend continues beyond 300 MPa (Figure 6.4B). This is, however, of less relevance to pharmaceutical tablet manufacturing, where higher than 350 MPa pressure is rarely used. A common feature between the tabletability profiles of the polymer and 40% drug loaded ASD is that both gradually become more curved with increasing RH (Figure 6.4), although the change is more profound for the pure polymer. At 11% RH, the tabletability profiles of both powders are almost linear. Unlike the polymer at 67% RH, tablet tensile strength of this kind of powders can effectively be improved by increasing compaction pressure. Tabletability of other ASDs, containing different amounts of celecoxib, is shown in Figure 6.S3. The general feature follows those noted in 0% and 40% drug loaded ASD.

Figure 6.5 gives a succinct summary of the tableting performance of these powders at different RHs and two extreme compaction pressures, 50 and 300 MPa, employed in this work. Regardless of the drug loading and RH, tablet tensile strength exceeds 2 MPa at 300 MPa. This suggests that PVP VA64-based ASDs with a wide range of compositions can still exhibit adequate tabletability. From the 50 to 300 MPa compaction pressure, the average increase in tensile strength for all drug containing ASD powers is about 10-, 8- and 4-fold for the powders conditioned at 11% RH, 43% RH, and 67% RH, respectively. The change is however slightly different for the PVP VA64 powder; showing from 8- , 6- to just 2-fold increase at 11%, 43% and 67% respectively. The change in tensile strength with drug loading at 50 MPa is quite similar at the 11% and 43% RHs. At 67% RH, there

is a monotonic decrease in the tablet strength except at 20% drug loading which exhibits the minimum strength. This trend is roughly opposite to the trend of *H* and *E* in this drug loading range (0 – 40%) (Figure 6.2). This hints to the possible role of mechanical properties on tablet tensile strength predicted based on the bonding area bonding strength model. Powder tableting behavior is generally more sensitive to their mechanical properties at lower compaction pressure. More plastic materials tend to deform more under the same pressure and, therefore, larger bonding area. The correspondence between *H* and tensile strength for the polymer at 67% RH indicates that the bonding area dominates the bonding area – bonding strength interplay in a way similar to the role of water on tableting performance of MCC.[31] At 300 MPa, especially at 11% and 43% RHs, the trend appears to be biphasic where an initial drop in tablet mechanical strength to 20% drug loading before trending up at higher drug loading is observed. At 67% RH the effect is less obvious partly because of the higher variability in tablet mechanical strength.

To quantitatively describe the dependence of tablet mechanical strength on RH, drug loading, and compaction pressure, a quadratic model (Eqn. 1) was obtained from regression analyses of data. This model can then be used to predict the performance of an ASD powder of similar particle size as powders in this work at any celecoxib loading and RH.

$$TS^{1/2} = 0.42 + 0.015CP + 0.0079RH - 0.019DL - 0.00001CP*RH - 0.00002CP^2 + 0.0004DL^2$$

Equation 6.4

The p-*value* of the interaction (CP * RH) term is 0.04, while that of all other terms is < 0.005. Therefore, all included factors in Eqn. 1 can significantly influence tablet tensile strength. CP and DL has the most impact because they have the highest coefficients. R^2 of this model was 0.9623 and the adjusted R^2 was 0.9603. The negligible change in the adjusted R^2 suggests that the model is not over-specified with unnecessary predictors. Furthermore, it suggests that this model accounts for ~96% of all the variations in the data set. Figure 6.6 shows the surface plot for the ASD containing 40% celecoxib to visualize such effects.

Discussion

Understanding the impact of composition on the structure and particle deformation behaviors is of primary importance to controlling tableting performance and achieving adequate tablet mechanical strength. This is because these material characteristics influence the area of contact between particles in tablets (bonding area) and the forces of attraction between the particles (bonding strength).[32]

Mechanical properties of particles affect tableting performance.[22,33] These mechanical properties can be modulated by moisture[13,34], crystal structure[21,35] etc. The nanoindentation data shown in Figure 6.2 demonstrate the effects of both drug loading and moisture on mechanical properties (Figures. 6.1 & 6.2). *E* is a measure of material stiffness and *H* is a measure of the ability of a material to resist permanent plastic deformation by an external stress.[36] In the context of tableting, materials with a lower *H* undergo more extensive plastic deformation, which corresponds to increased bonding area between compressed particles. Lower *E* corresponds to larger elastic recovery, which negatively impact bonding between particles especially when compression pressure is high. The greater sensitivity of *H* to change in composition than *E* (Figure 6.2) implies that fundamentally different molecular processes are responsible to these two mechanical properties. During indentation, a load is applied by the indenter to increase both stress and strain. It is conceiveable that the same load can result in more permanent deformation when it is applied for a longer time. However, *E* is not affected. In this ASD system, *E* of pure polymer and drug is comparable. This indicates comparable intermolecular interactions in these two materials. When they are molecularly mixed, the interaction strength within the composite does not change significantly, which is reflected as comparable E across the composition range of the ASDs. The incorporation of celecoxib initially increases *H* of ASD and then decreases with the maximum attained at ~60% celecoxib loading at all three RHs. Therefore, celecoxib antiplasticizes the polymer in the 0 – 60% celecoxib loading range Although the decreasing effect at more

than 60% celecoxib loading can be interpretated as plasticization effect, a more appropriate analysis should be based on the effect of polymer on mechanical properties of celecoxib glass, which is the more abundant components in these ASDs. When a small amount of polymer is molecularly dispersed in the celecoxib matrix, the long chain polymer molecules likely extend over a large area of celecoxib glass. This would strengthen the glassy celecoxib matrix by distributing stress over a larger area similar to the straw–in–brick structure, where the presence of the straw strengthens the brick by impeding deformation.[37] Some examples from the every day life include wired window glass and nano carbon tubes reinforced sports wares. From either direction, polymer rich and drug-rich, the effect is maximized at some drug composition which is dependent on the intrinsic property of the pure substances, polymer and drug. As such, a maximum is observed when the *H* is plotted against composition as shown in Figure 6.2. If this analysis is valid, a maximum may be expected in all ASD systems. This will need to be further tested. In the case of PVP VA64 – Celecoxib ASDs, the maximum roughly corresponds to 60% celecoxib (Figure 6.2).

The change in PVP VA64 water content when RH is changed from 15% to 32% (2.6% changes in water content from moisture sorption isotherm in Figure 6.S1) does not cause noticeable change in *E* but slightly reduces *H* (Figure 6.3). Therefore, the small amount of additional water can fit in spaces in the ASD without significantly modifying molecular properties of its constituents. The much more water at 67% RH, plasticizes the

molecules (both drug and polymer) so that they are more mobile, which results in a less rigid ASD. [38] Consequently, both *H* and *E* are significantly reduced. Although antiplasticization effect by water is possible[7,31], it likely occurs in an RH range below 15% RH. The essentially negligible effect of RH between 15% and 32% suggest that this RH range may be the where the transition from antiplasticization to plasticization occurs. Antiplasticization occurs when the free volume associated with the polymer structure is reduced when a small amount of small molecules, including water, bind to the polymer chains.[39] At such a small amount, even very effective plasticizers do not increase mobility of polymer chain. Of course, the transition concentration from antiplasticization to plasticization effects depends on the properties of the small molecule additive. The different effects on *E* and *H* clearly demonstrate that water transitions polymer to the plasticization zone much earlier than celecoxib

The changes in *E* and *H* of ASDs are expected to have an impact on powder tabletability. The tabletability profile of PVP VA/64 powder equilibrated at 67% RH is typical of highly plastic materials, where tablet tensile strength rises quickly and plateaus shortly afterward with increasing pressure.[31] Above the plateau region, further increase in compaction pressure only introduces more stored elastic energy without further increasing bonding area which has already reached the maximum (thus the pleatau). The more extensive elastic recovery can then break some of the bonding sites and lead to over-compression, which is shown as a drop in tensile strength when compaction

pressure increases above a certain limit.[40] The nearly linear tabletability profiles at 11% RH for both polymer and drug loaded powders are typical of powders that exhibit limited plastic deformation, such as calcium phosphates.[41] This is consistent with the higher *H* and *E* values at 11% RH over those at 61% RH, especially for the pure polymer (Figure 6.2). Although *H* and *E* data at the exact RH used during tableting studies are not available due to our limited ability in precisely controlling environment in these experiments, it is reasonable to expect that at 67% RH, *H* would be much lower than that at 11% RH (Figure 6.2). This is consistent with the more curved tabletability profiles at 67% RH (Figure 6.4). It is also useful to mention that the maximum tablet tensile strength of the highly plasticized PVP VA/64 powder at 67% RH is significantly lower than what can be achieved by the the same powder but at lower RHs (Figure 6.4), which have not reached the state of saturated bonding sites at 300 MPa due to the high hardness. This suggests that the higher amount of moisture at 67% RH, although favors tablet formation by promoting plastic deformation, also reduces bonding strength. Hence, the maximum tablet tensile strength is much lower at 67% RH, which is consistent with the lower *E* and *H* (Figure 6.2).

The antiplasticization effect by celecoxib molecules is expected to have two countering effects on the tablet tensile strength: 1) reducing bonding area due to lesser ability to undergo plastic deformation under stress, and 2) increasing bonding strength, arising from the increased intermolecular forces of attraction between particles for the same

reason as the increased *E* and *H*. This bonding area-bonding strength interplay explains the complex effects of drug loading and compaction pressure on the tableting performance (Figure 6.5). In the low compaction pressure region, e.g. 50 MPa, bonding area effect is dominant when drug loading is below 20%. Therefore, higher drug loading leads to more loss in bonding area in table tensile strength than gain due to higher bonding strength. Tensile strength decreases with increasing drug loading up to 20% (Figure 6.5). Above 20% drug loading, the reverse trend is observed, indicating the favorable effect of drug loading on bonding strength exceeds the negative effect on bonding area. This trend is observed in all cases, except at 67% RH and 300 MPa. Bonding area is near saturation in all cases because of the high plasticity due to the high RH and high pressue. Therefore, difference in bonding area between powders is small. Ideally, the trend in tensile strength should continue to rise with increasing drug loading. However, the relatively large errors in measurements for two powders (10% and 30% celecoxib) make such an assessment impossible. In addition, differences in particle size will also have an impact on the total available bonding area among these powders. The slightly larger particles in 10% celecoxib ASD powder, should lead to lower tensile strength if particle size effect plays a major role because they have smaller surface area available for bonding and extensive fragmentation of these particles is unlikely. However, this is not the case according to Figure 6.5. Therefore, the efforts to minimize possible effects of particle size on tableting performance is effective in this study.

When developing ASD based tablet formulations, ASD powders may be prepared using a number of processes, such as spray-drying and hot melt extrusion.[9] Impact of different particulate properties, such as size, shape, on tabletability should also be considered.[33,42] All powders in this study are fine, which likely exhibit poor flowability. Size enlargement by granulation or hot melt extrusion is expected to improve powder flowability[43] but may also impact tabletability. The net effect of particle size on tabletability depends on mechanical properties. Highly plastic particles likely exhibit reduced tabletability[44,45] but highly brittle particle do not.[46,47] In absence of extensive fragmentation during compaction, larger particles result in reduced tablet tensile strength because of the smaller number of contact points in the tablet and the lower total bonding area. Putting aside such factors, results from this work suggest that tabletability of all PVP VA64-based ASDs is adequate for forming sufficiently strong tablets (by the 2 MPa criterion). Therefore, tabletability of celecoxib-PVP VA64 ASDs should not present a insurmountable barrier in its formulation and manufacture into tablets.

The usefulness of tableting data of PVP VA64-celecoxib ASDs is further enhanced by constructing a multi-variate model, which may be used to predict the tableting performance under different conditions of drug loading, pressure, and RH. Figure 6.6 shows the surface plot for ASD containing 40% drug loading to visualize the model. Lastly, it is important that ASDs remained physical stable within the time frame of

experiments. This is verified by PXRD, which established the absence of of crysalline domains of celecoxib in the sample containign 40% celecoxib at 67% RH (Figure 6.S3).

Conclusion

Particle composition, e.g., drug loading and moisture content, influence both the mechanical properties and tableting performance of ASDs. Within the RH range studied, higher moisture level reduces both *H* and *E* of pure PVP VA64 and Celecoxib ASDs due to plasticization effect of water. Drug loading also impact *H* and *E* and tabletability. Effects of moisture and drug loading on tableting performance can be explained by simultaneously considering their impact on bonding area and bonding strength . The knowledge derived from this study is useful to the design of ASD-based formulation with superior tabletability.

Table 6.1 Percentage change in E and H when RH increases from 15% to 61%

% Drug	Δ E (%)	Δ H (%)
0	31	56
10	16	36
20	26	31
30	19	32
40	6	8
60	12	12
80	11	7
90	12	3
100	5	11

Figure 6.1 Typical load – displacement curves showing indents on 0%, 20% and 40% drug loading

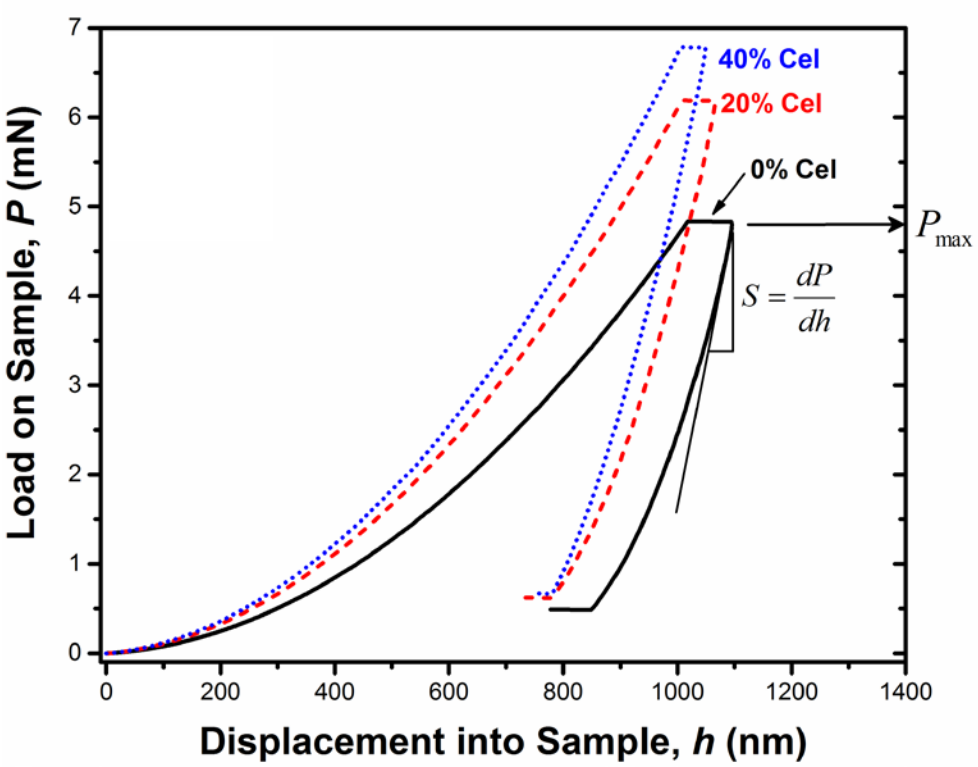


Figure 6.2 Effect of relative humidity condition on (A) Elastic Modulus, E and (B) Hardness, H of Celecoxib – PVP VA64 ASD films

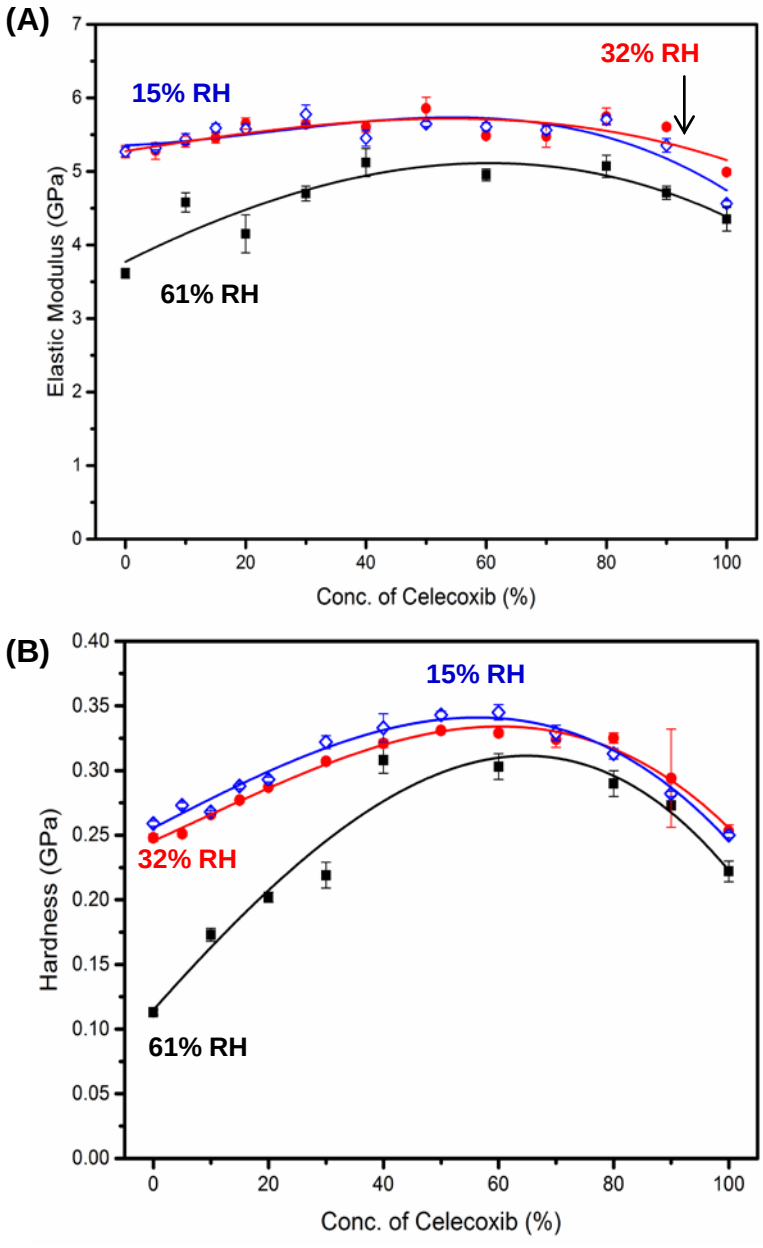


Figure 6.3 Characteristic particle sizes (d_{10}, d_{50} and d_{90}) of Celecoxib – PVP VA64 ASD powders, 0 – 40% drug loading

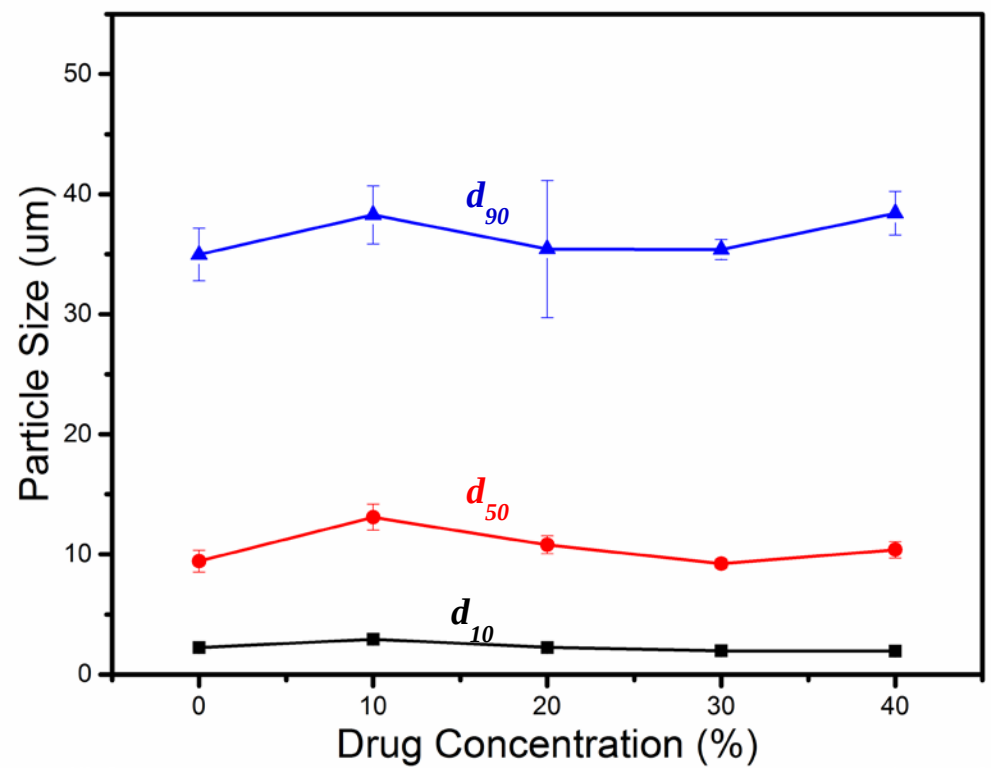
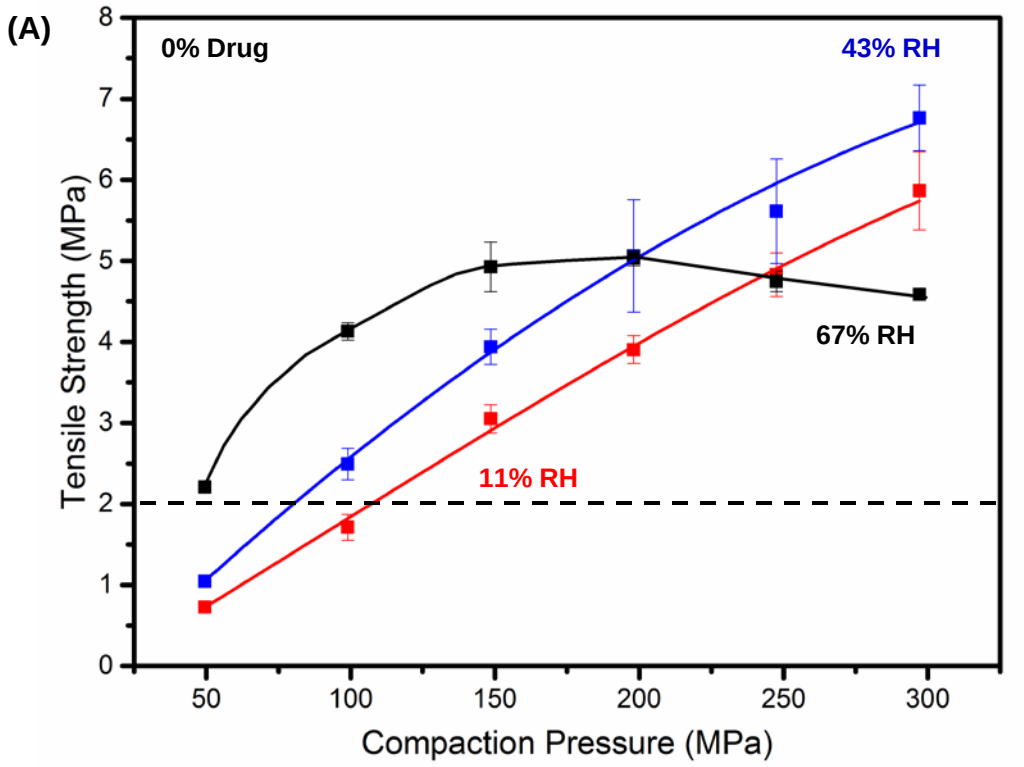


Figure 6.4 Effect of relative humidity condition on the tabletability of Celecoxib – PVP VA64 ASD, (A) 0% and (B) 40% drug loading with 2 MPa representing adequate mechanical strength



(B)

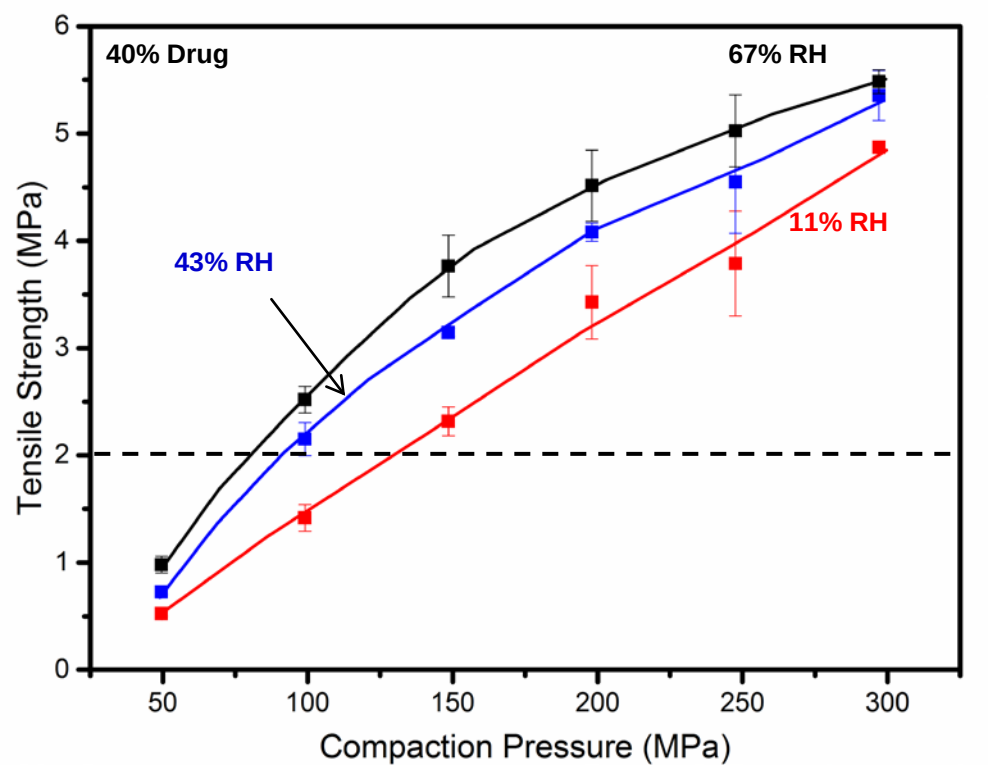

40% Drug
67% RH
43% RH
11% RH
Tensile Strength (MPa)
Compaction Pressure (MPa)
0
1
2
3
4
5
6
50
100
150
200
250
300

Figure 6.5 Relationship between drug loading and tableting performance (A) 11% RH (B) 43% RH and (C) 67% RH at low and high compaction pressure, with 2 MPa representing adequate tablet mechanical strength

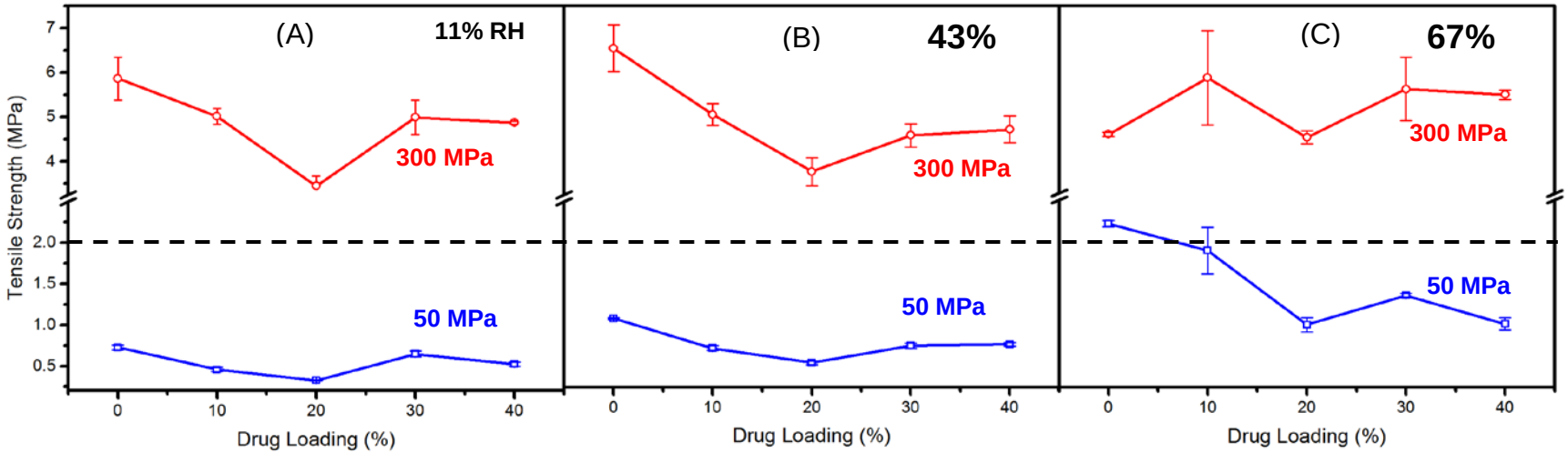


Figure 6.6 Surface plot of the multi-variate regression model showing the effect of RH and compaction pressure on tableting performance for 40% Celecoxib ASD

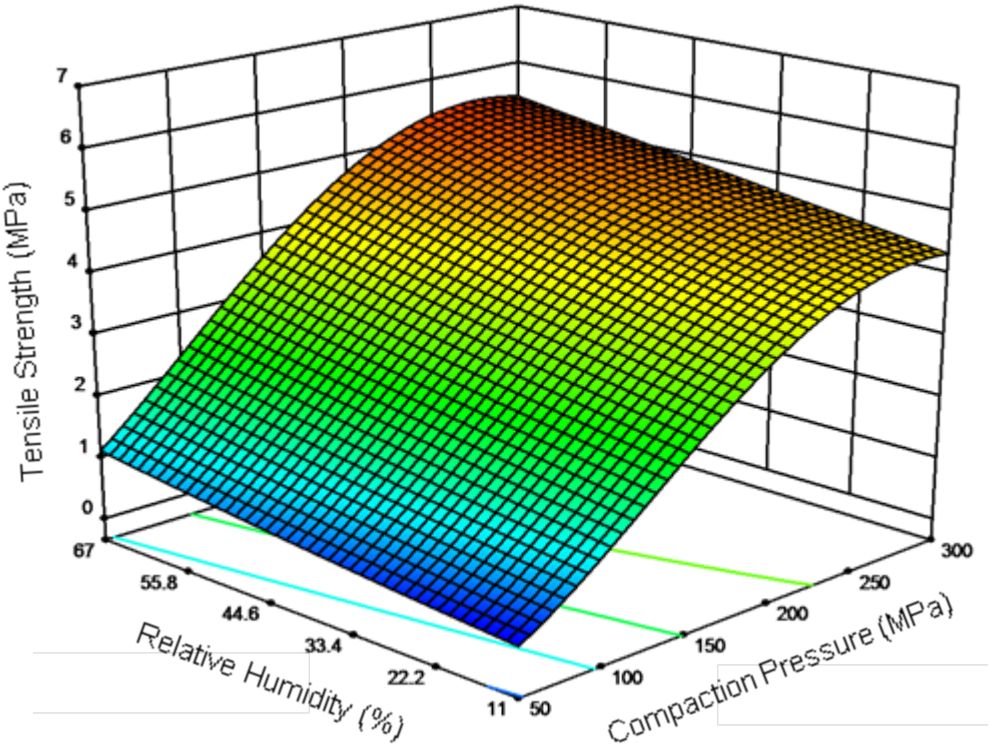


Figure 6.S 1 Effect of celecoxib loading on moisture sorption of ASDs. Moisture level progressively decreases with increasing loading of celecoxib, which is hydrophobic

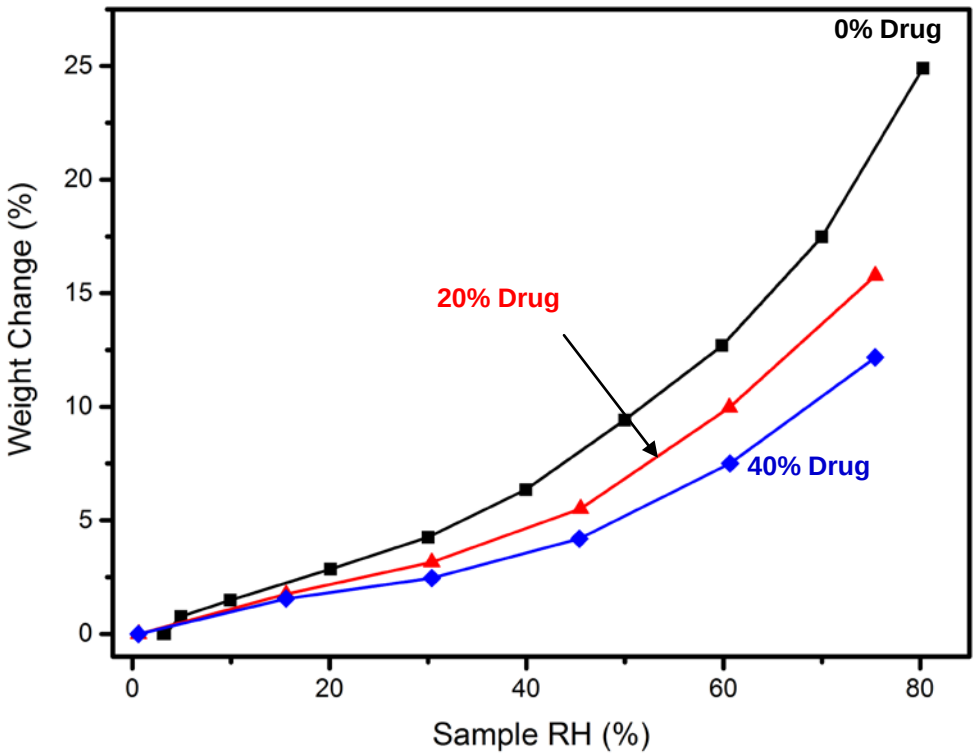


Figure 6.S 2 Particle size distribution of ASDs at (A) 0% ; (B) 10% ; (C) 20% ; (D) 30%; (E) 40% Drug Loading

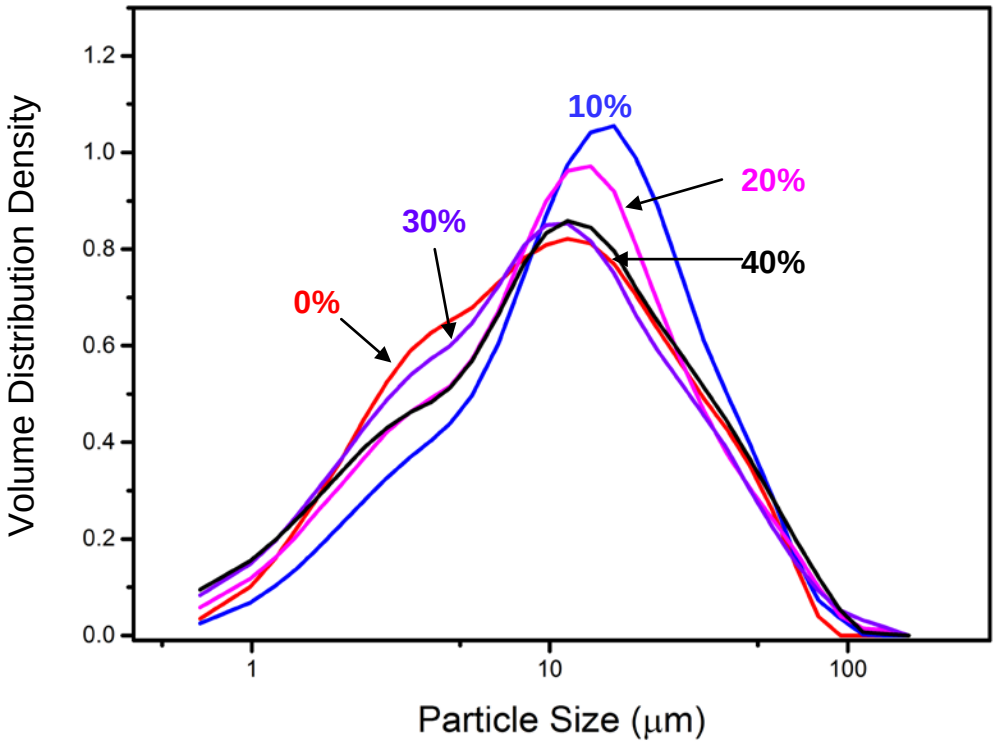
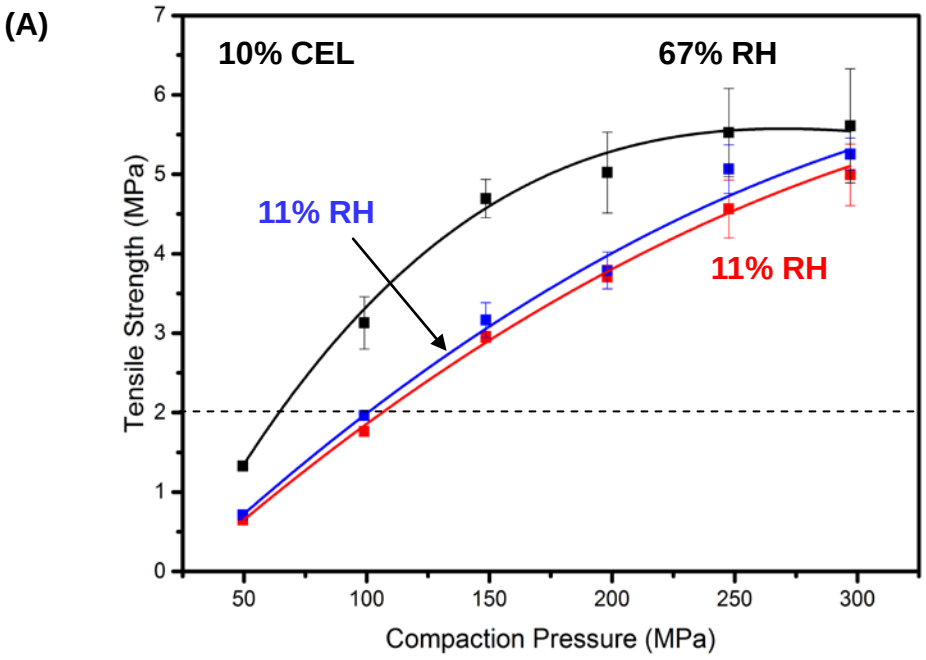
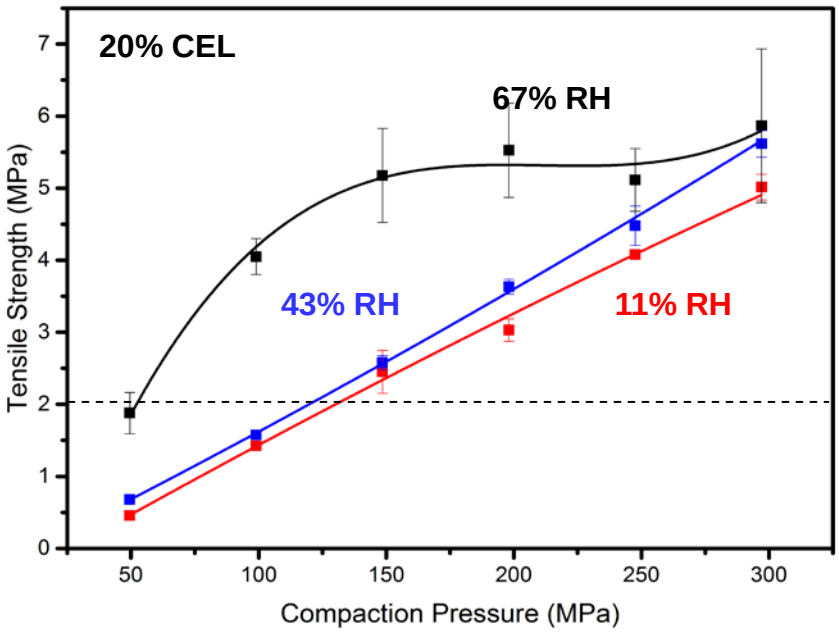


Figure 6.S 3 Effect of relative humidity condition on the tabletability of Celecoxib – PVP VA64 ASD, (A) 10% (B) 20% and (C) 30% drug loading. Tensile strength of 2 MPa is indicated for easier identification of pressure required for forming adequately strong tablet



(B)


20% CEL
67% RH
43% RH
11% RH
Tensile Strength (MPa)
Compaction Pressure (MPa)
0
1
2
3
4
5
6
7
50
100
150
200
250
300

(C)

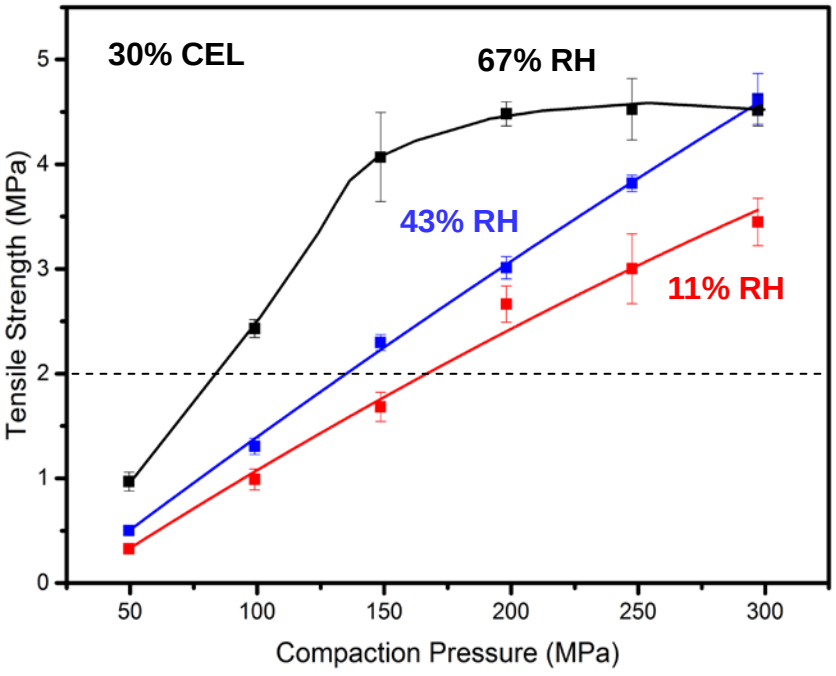
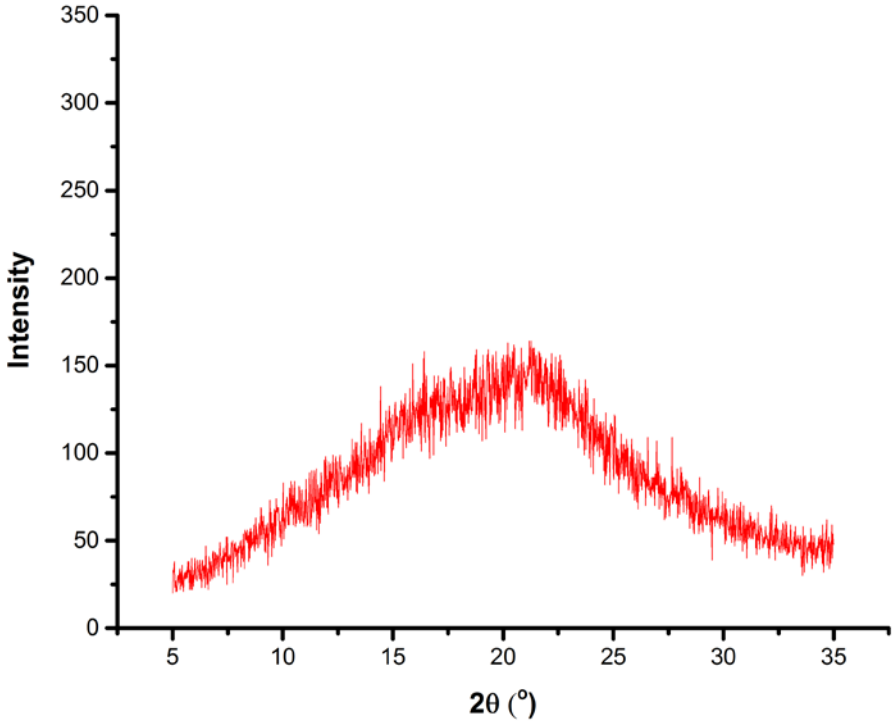

30% CEL
67% RH
43% RH
11% RH
Tensile Strength (MPa)
Compaction Pressure (MPa)
0
1
2
3
4
5
50
100
150
200
250
300

Figure 6.S 4 Powder X-ray diffraction pattern of 40% Celecoxib ASD after equilibration and compaction at 67% RH



CHAPTER 7. A CRITICAL EXAMINATION OF THE PHENOMENON OF BONDING AREA - BONDING STRENGTH INTERPLAY IN POWDER TABLETING

Summary

The bonding area (BA) and bonding strength (BS) interplay has been used to explain complex tableting behaviors but it has never been proven. This study is aimed to unambiguously demonstrate such interplay. Soluplus® was used as a model powder. To individually modulate BA, the powder was compressed into tablets at different temperatures but tablets were broken at 25 ^{o}C. To modulate BS, identical tablets were broken at different temperatures. To simultaneously modulate BA and BS, both powder compression and tablet breaking test were carried out at different temperatures. Lower tablet tensile strength is observed when the powder was compressed at a lower temperature while breaking at 25 ^{o}C, which is consistent with the polymer's less ability to deform at lower temperatures. When equilibrated at different temperatures, tensile strength of the same tablets increases with decreasing storage temperature, proving that BS is higher at lower temperature. When powder compression and tablet breaking are carried out at the same temperature, the BA-BS interplay leads to a profile with a maximum tensile strength at 4 ^{o}C. By systematically varying temperature during tablet compression and breaking, we have clearly demonstrated the phenomenon of BA - BS interplay in tableting.

Introduction

The forming of compact by compression is a process critical to many industries, including energy (coal, petroleum, and nuclear), foods, automobiles, metallurgy, pharmaceuticals, and ceramics.[1-4] Although many compression equations have been proposed to describe the density – pressure relationship[4-7] , there are only very limited attempts in quantitatively describing the relationship between tablet tensile strength and compaction pressure, which is sometimes known as tabletability.[8,9]

The difficulty in quantitative description of tabletability arises from the challenges in quantifying the areas of contacts between particles in a compact[10] and summarizing the intermolecular forces over these areas to arrive at a final strength value. Further complications are caused by the particle size and shape, surface structures at atomic level, the orientation of contact planes in the compact.[11] While tensile strength – pressure data can be fitted with equations, e.g., Leuenberger's equation[8], the ability to predict tabletability based on material mechanical properties and particulate properties is the ultimate goal.[10]

The qualitative bonding area-bonding strength (BABS) model is a useful tool for moving closer to that goal by allowing clear explanation of complex powder tableting behaviors[12]. The BABS model treats tensile strength as an outcome of the bonding area

between adjacent particles and the strength of interactions over that area. A harder material develops smaller bonding area because it does not deform easily under pressure. However, harder materials usually also have higher interaction strength over the bonding area that is formed.[13] The interplay between bonding area (BA) and bonding strength (BS) can lead to complex tableting behavior of materials, depending on pressure, temperature, composition, and particulate properties (e.g., size and shape).[14-17]

To effectively solve tabletability problems, the identification of the cause of poor tabletability is critical.[18] Although BABS model is conceptually sound, its direct demonstration is difficult due to the challenge in completely separating the contributions from BA and BS. For example, obtaining two powders with identical particle size, particle surface roughness, morphology is impossible for materials prepared using two separate procedures, such as crystallization. This problem of different particle size and shape was partially addressed by comparing tableting properties of an anhydrate - hydrate pair.[19] Anhydrate – hydrate phase change can be achieved through a vapor mediated process without eliciting changes in particulate properties. However, the different mechanical properties between the hydrate and anhydrate (or hydrates with different degrees of hydration) can still lead to simultaneous changes in BA and BS.[20] In other words, BA can be very different for two materials with different plasticity even if the particulate properties are the same. A better tabletability of a hydrate may be caused either by its superior plasticity, which leads to larger bonding area, or by its higher

bonding strength, or both. Thus, the coupling between BA and BS for systems involving different solid forms makes it impossible to unambiguously demonstrate contributions from BA and BS.

Decoupling contributions from BA and BS requires the use of the same solid phase. Therefore, we need to use a material with the ability to have its plasticity and BS modulated by external stimuli, such as temperature and pressure. To this end, organic glasses are promising as long as their glass transition temperature, T_g, is not too far away from temperatures suitable for carrying out powder compression and tablet strength experiments.[21] Using such materials, we can change BA by changing the temperature at which the powder is equilibrated and compressed. For example, the higher plasticity of the same glass at a higher temperature will favor the development of larger BA. Mechanical strength and the strength of intermolecular interactions (or BS) of glassy materials also depend on temperature. Once the tablet is formed, we can control BS by equilibrating the tablet at different temperatures. Usually, higher temperature corresponds to lower BS because of increase thermal motion of molecules.[22] For a given material under constant environmental conditions, pressure impacts BA but not BS.

Materials and Methods

Materials

We selected Soluplus®, a polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer, as a model material in this study. Dry Soluplus has a T_g ~70 ^{o}C, ~45 ^{o}C when equilibrated at 52% RH, 36 ^{o}C at 67% RH, and below 25 ^{o}C at 75% RH. In the vicinity of T_g, it is possible to change particle plasticity while keeping particle size, shape, and surface properties unchanged. Soluplus powder was obtained by milling dried films (solvent evaporation method) under liquid nitrogen and sieving through 75 um mesh. The powder, equilibrated at 67% RH at 25 ^{o}C over cupric chloride saturated salt solution[23] was used in this study.

Methods

All compression was carried out on a universal material testing machine (Model 1485, Zwick, Ulm, Germany) at a speed of 10 mm/min using round (8 mm diameter) flat-faced tooling. Two custom-made rigid PVC blocks were used to align the punches and die to allow successful compression. Tablet dimensions were measured using a digital caliper and tablet density was calculated from tablet weight and volume just before tablet breaking force determination. The tablet diametrical breaking force was determined

using a texture analyzer (Texture Technologies Corp., Scarsdale, NY/Stable Micro Systems, Godalming, Surrey, UK), at a speed of 0.01 mm/s with a 5 g trigger force.

Modulating BA by compressing powders at different temperatures

Capped plastic vials that contain Soluplus powders were wrapped with paraffin film and aluminum foil were equilibrated at 25 ^{o}C, 4 ^{o}C, and -20 ^{o}C rooms for at least 48 hours. The water content in Soluplus was stable during storage as suggested by TGA shortly before powder compression. Each powder was compressed at three compaction pressures, 50, 100, & 400 MPa. Pre-conditioned tooling was assembled in the block and powder was filled at the desired temperature (in either a refrigerator or a freezer). The temperature inside the refrigerator or freezer was monitored to within 2 ^{o}C of desired temperature during die filling. The whole assembly was then quickly moved to the materials testing machine for compression at 25 ^{o}C. The cold compressed tablets were quickly wrapped in paraffin film and equilibrated at 25 ^{o}C in sealed vials to avoid condensation of water vapor on tablets and frost formation. The chilled tooling and holding block served as temperature buffer that minimizes gross deviation of the powder bed temperature from the target temperature during the course of compression, which lasted < 1 min at 25 ^{o}C. Under these conditions, differences in tablet mechanical strength are due to different bonding areas formed during compression. Particles at lower

temperature are harder. Therefore, smaller bonding area is developed during compression. Relative difference in bonding area is expected to be higher at lower pressure. However, when pressure is sufficiently high to induce extensive deformation of even harder particles, the relative difference in bonding area is expected to be reduced. The tablets compressed at 4 and -20^{o}C were allowed to equilibrate to 25 ^{o}C in sealed containers before exposing all three sets of tablets to 68% RH.

Modulating BS by changing tablet equilibration temperature

We prepared a set of tablets at 400 MPa at 25 ^{o}C. Tablets, sealed in individual 1.5 mL vials, were equilibrated under specified temperatures (-20 ^{o}C, 4 C, and 25 ^{o}C) for at least 24 hours before breaking force determination. Tablet breaking experiments at 25 ^{o}C and 4 ^{o}C were performed at respective temperatures. Due to equipment limitations, tablets equilibrated at -20 ^{o}C were broken at a 4 ^{o}C environment immediately after they were taken out of the freezer, one at a time. The total time of exposure to the 4 ^{o}C environments was less than 60s for all tablets to limit the influence of tablet "warming" during the course of breaking test.

We assume that bonding area remains unchanged in a tablet during equilibration at a different temperature. However, bonding strength is a function of equilibration temperature. Therefore, differences in breaking strength are due to differences in

bonding strength not to bonding area. At the temperature closer to T_g, bonding strength is expected to be lower. Therefore, breaking force is expected to be lower at higher temperature. The use of a relatively high compaction pressure, 400 MPa, is to assure bonding area is large so that a change in bonding strength can be detected with more sensitivity.

Modulating coupled effects by BA and BS

Powders were equilibrated and compressed at -20 ^{o}C, 4 ^{o}C, and 25 ^{o}C. Tablets were also stored and broken at the same temperature as compression, without the exception of -20 ^{o}C tablets quickly broken at 4 ^{o}C. In this design, bonding area is expected to be lower at a lower temperature because the glassy material is harder (more rigid).[21] The higher material hardness also means that bonding strength is higher when the tablets are equilibrated and broken at the lower temperature. The net effect on tablet tensile strength depends on the interplay between the negative effect on bonding area and positive effect on bonding strength. In addition, we also varied compaction pressure, 50, 100, & 400 MPa, to further change bonding area. The impact of different material plasticity on relative bonding area is more when pressure is lower, e.g. 50 MPa. When compaction pressure is sufficiently high, even materials not so plastic can also form fully

consolidated tablets. Therefore, difference in bonding area is less affected by difference in particle plasticity.

In the entire study, a total of five tablets were prepared under each condition.

Results and Discussion

Soluplus sorbs 8% water at 67% and 25 ^{o}C. Excellent agreement was reached between the equilibration water content in a static relative humidity chamber (cupric chloride saturated salt solution) and a dynamic moisture sorption balance (Figure 7.1A). With this water content, T_g of soluplus is 36 ^{o}C (Figure 7.1B).

Figure 7.2A is the results of powder equilibrated and compressed at different temperatures. A powder that is equilibrated and compressed at a lower temperature exhibits lower tabletability. Since tablets were equilibrated back to 25 ^{o}C before conducting the breaking force test, bonding strength is the same for the same material. The difference in tabletability is therefore attributed to the different bonding area. At a lower temperature, particles are harder and are expected to be more resistant to plastic deformation.[17,24,25] As a result, the area of contact reduces with temperature for the same powder.

Figure 7.2B shows that tensile strength of otherwise identical tablets decreases with increasing equilibration temperature. Since the contact areas in these tablets are the same, the difference in tablet mechanical strength is due to the energy required to separate the particles. This is consistent with the expectation that the glassy material is harder at a lower temperature below T_g.[21]

When tablets were formed and broken at the same temperature, a change in temperature impacts both bonding area and bonding strength. As shown in Figure 7.2C, tabletability at 4 ^{o}C is the highest. This may be explained by considering the interplay between bonding area and bonding strength. At a lower temperature, smaller bonding area is developed (Figure 7.2A) but larger bonding strength is also expected at the same compaction pressure (Figure 7.2B). Comparing the case where tablets are warmed to 25 ^{o}C before being broken, tablets formed and broken at 4 ^{o}C and -20 ^{o}C is higher. This is again a result of the higher bonding strength at lower temperature. The data suggest that at -20 ^{o}C, the negative effect of lower bonding area on tensile strength overpowers the positive contribution due to higher bonding strength. Therefore, lower tablet tensile strength is observed. However, the higher bonding strength dominates the BABS interplay at 4 ^{o}C. Hence, tablet tensile strength is the highest.

For harder particles, the consolidation by compaction is less effective. Therefore, tablet density should be lower when compressed at the same pressure.[24] This is exactly what is observed in Figure 7.3A. When tablets are equilibrated at a higher temperature, tablet

density is slightly lower (Figure 7.3B), possibly due to the thermal expansion of solids. The interplay gives an expected density trend except for the 400 MPa frozen which appears to be similar to 4^{o}C tablets (Figure 7.3C). The data is consistent with the concept that harder particles are more difficult to deform, therefore, lower tablet density. At 25 ^{o}C, tablet density is lower at 400 MPa than at 100 MPa. This is not observed when compression was carried out at 4 ^{o}C and -20 ^{o}C. We attribute this to the fact that Soluplus is much more plastic at 25 ^{o}C because it is close to T_g. Therefore, some material is squeezed into the gap between punch and die which is usually referred to us flashing.[26] Such flashing on tablets could not be completely removed even with very careful handling. Hence, it introduces positive errors in tablet thickness measurement, which leads to lower tablet density. At 4 ^{o}C and -20 ^{o}C, the plasticity of Soluplus is not too high to cause gross errors in tablet thickness measurements. Figure 7.3D shows the effect of tablet equilibration temperature on density. For tablets compressed at -20 ^{o}C, tablet density is noticeably higher at -20 ^{o}C storage temperature than 25 ^{o}C, which may be again attributed to the thermal expansion effect. This thermal expansion effect is less significant when tablet storage temperatures of 4 ^{o}C and 25 ^{o}C are compared.

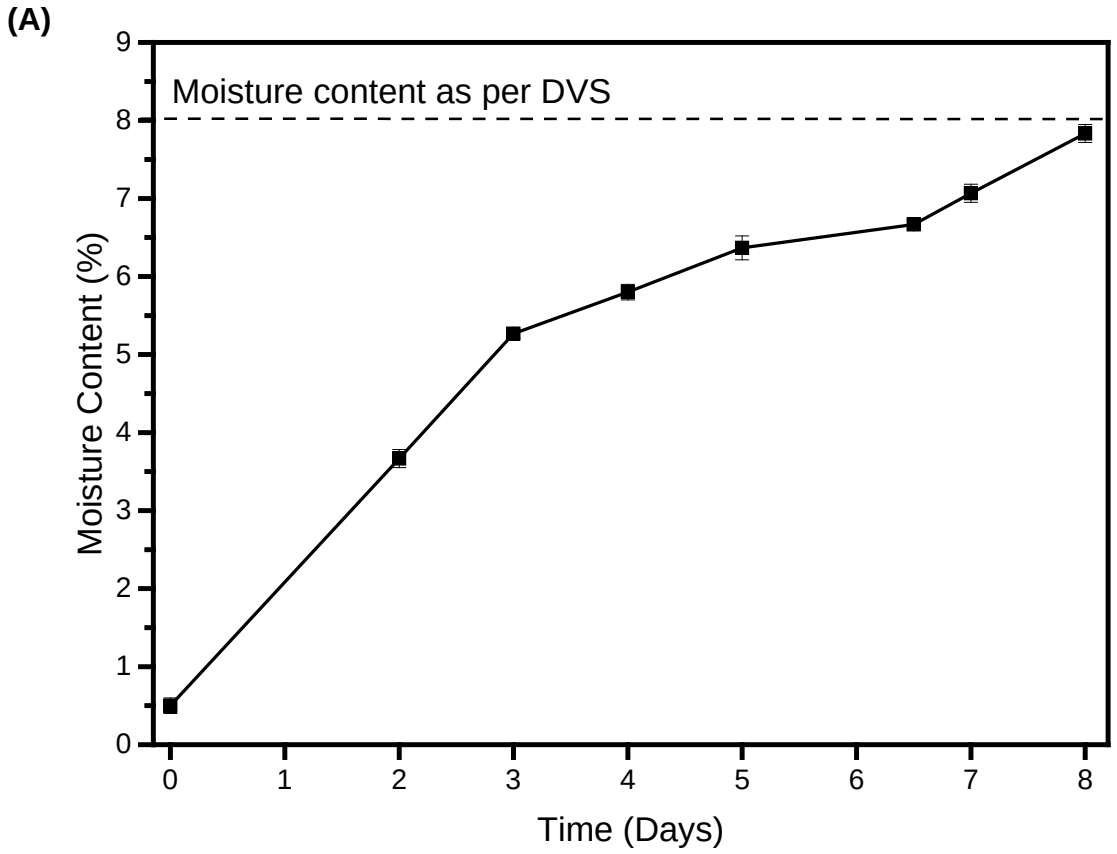
Figure 7.4 shows the impact of the BABS interplay on tablet mechanical strength. Tablets are weaker when compression is carried out at a lower temperature but re-equilibrated at 25 ^{o}C. This is explained by lower BA because Soluplus particles undergo less extensive plastic deformation at lower temperature. The same tablet becomes

stronger when equilibrated and broken at a lower temperature because material is farther below its T_g, which makes it harder. Hence, BS is higher. The profile of tablet tensile strength under the situation of compressing and breaking tablets at the same temperature is interesting. As discussed earlier, lower temperature can lead to both smaller BA and higher BS. At 4 ^{o}C, tablet tensile strength is highest because the positive effect of higher BS overpowers the negative effect of smaller BA. Had the study been conducted at only 25 and -20 ^{o}C, one would have observed no significant effect on tableting performance by temperature because of the cancellation of two opposing effects.

Conclusion

Through systematic control of temperature during tablet compression and breaking using an amorphous polymer, we have separately demonstrated the contributions of bonding area and bonding strength to tablet tensile strength as well as the interplay between bonding area and bonding strength. Thus, the results in this study support the validity of the BABS mode, which can be used to decipher the diverse powder tableting behaviors.

Figure 7.1 (A) Moisture sorption kinetics at 67% RH and 25 ^{o}C and (B) DSC thermogram of Soluplus



(B)

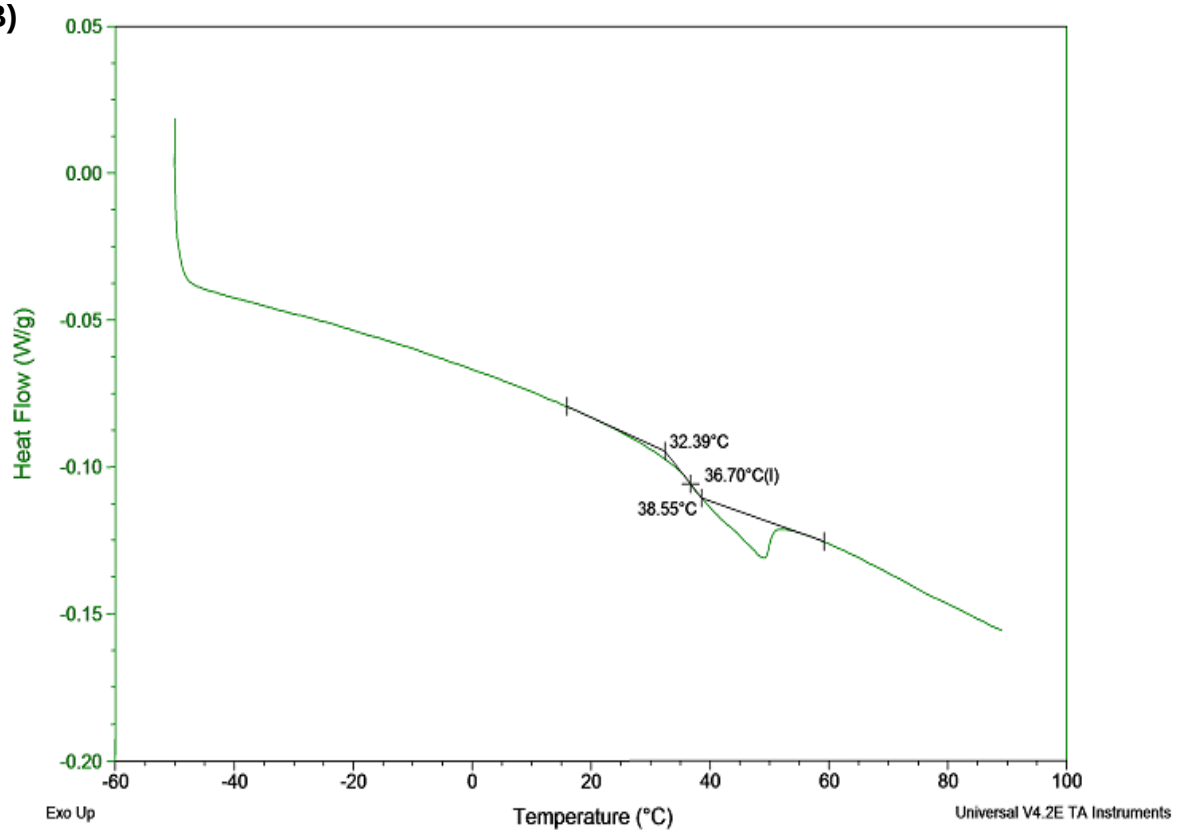
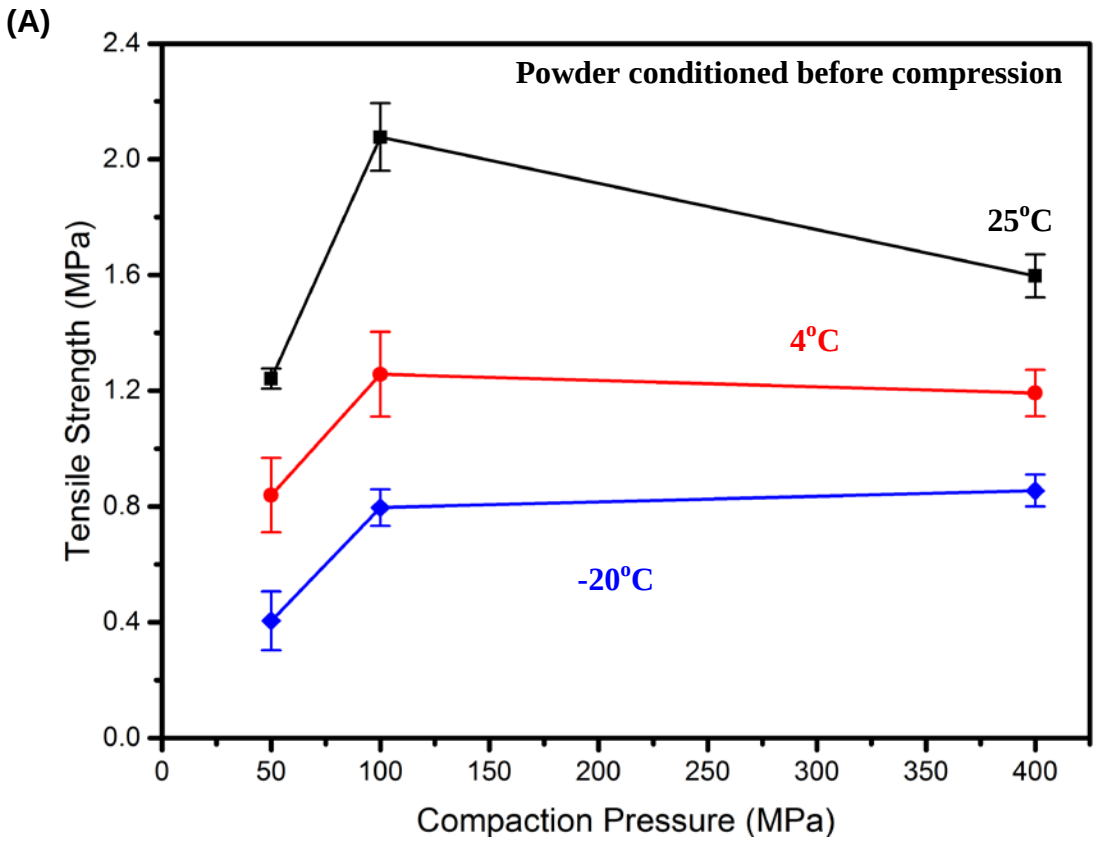
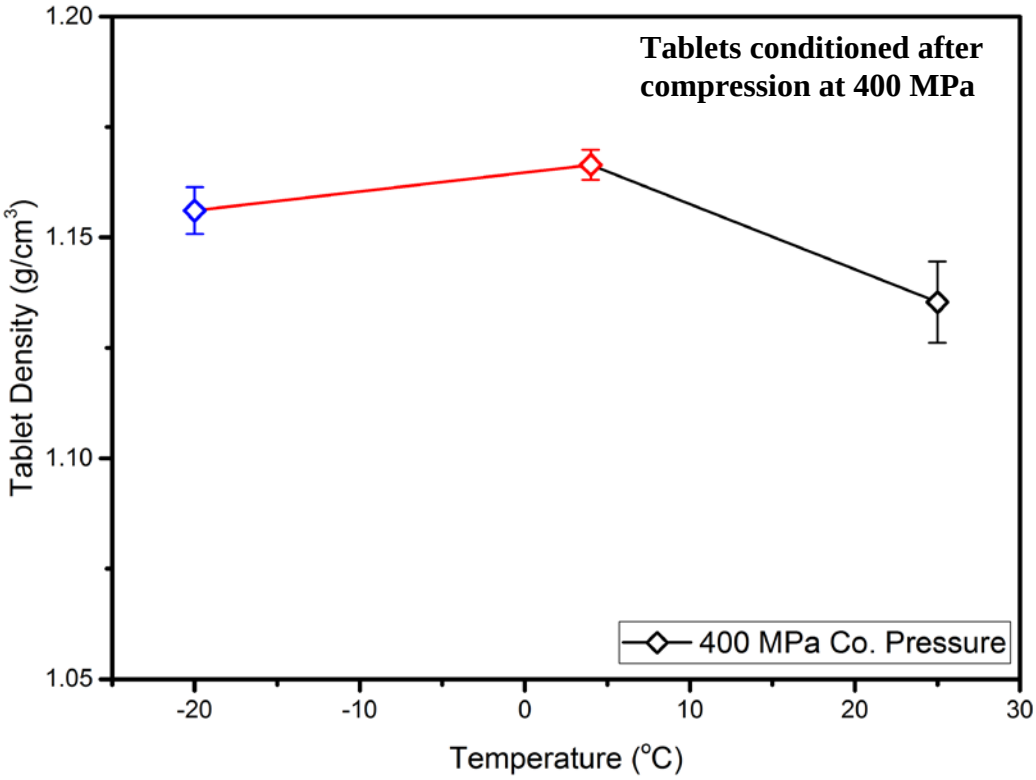

0.05
0.00
-0.05
-0.10
-0.15
-0.20
Heat Flow (W/g)
32.39°C
36.70°C(I)
38.55°C
-60
-40
-20
0
20
40
60
80
100
Exo Up
Temperature (°C)
Universal V4.2E TA Instruments

Figure 7.2 Tableting data (n = 5): (A) powder equilibrated at different temperatures; (B) tablets (compressed at 25 ^{o}C and 400 MPa) equilibrated at different temperatures; (C) powder and tablets equilibrated at respective temperatures.



(B)


Tablets conditioned after compression at 400 MPa
Tablet Density (g/cm3)
1.20
1.15
1.10
1.05
-20
-10
0
10
20
30
Temperature (°C)
400 MPa Co. Pressure

(C)

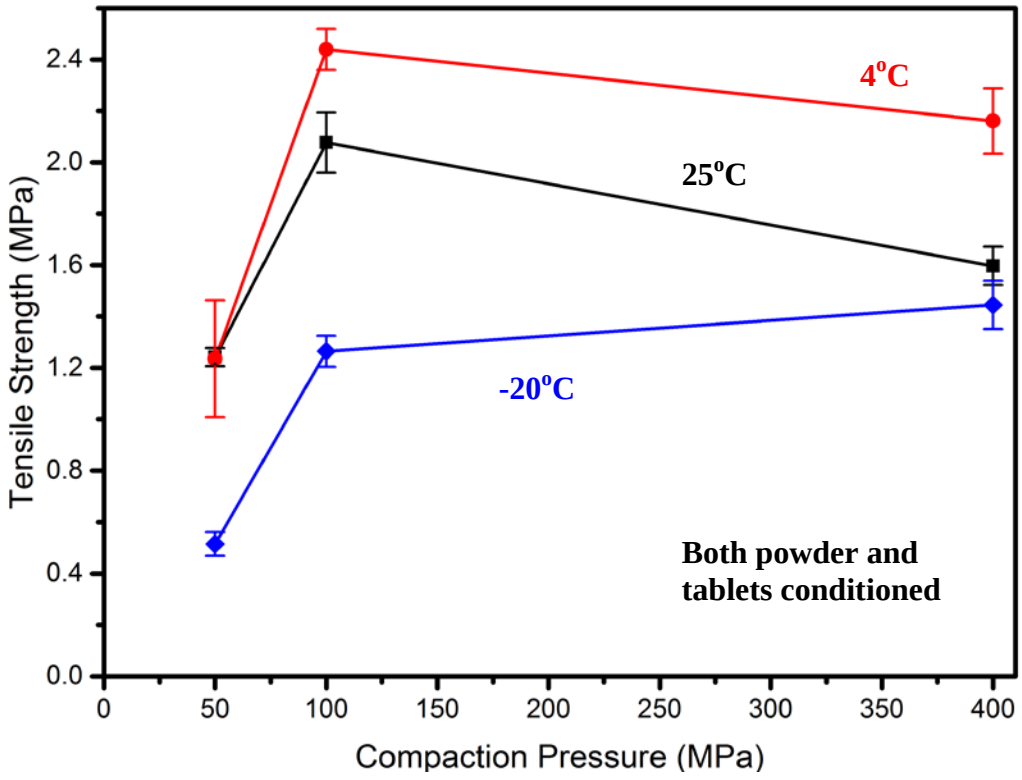
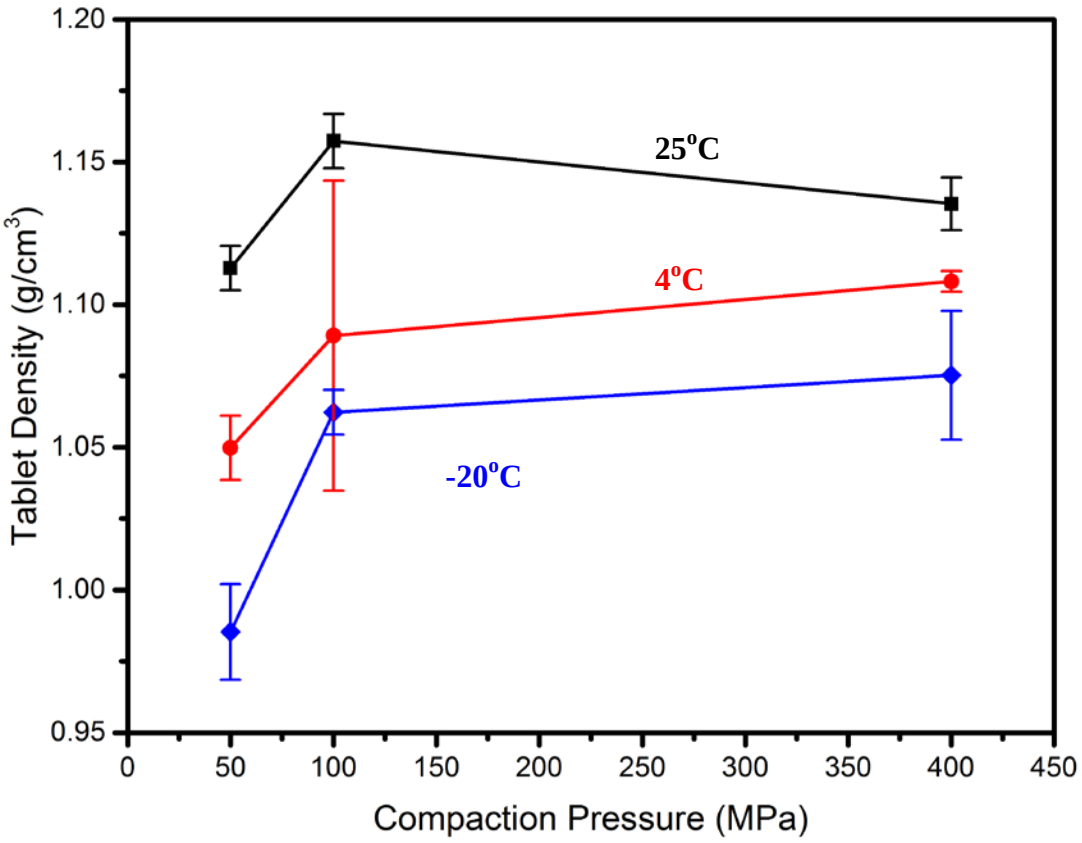
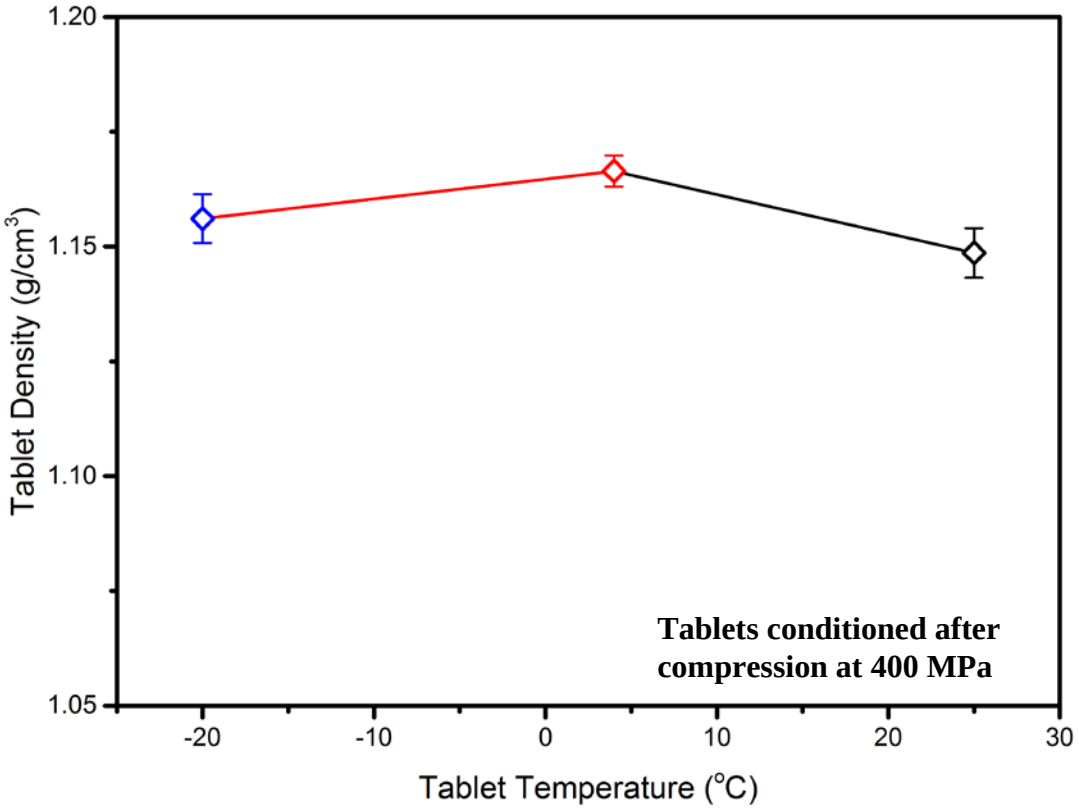

Tensile Strength (MPa)
Compaction Pressure (MPa)
0.0
0.4
0.8
1.2
1.6
2.0
2.4
0
50
100
150
200
250
300
350
400
4°C
25°C
-20°C
Both powder and
tablets conditioned

Figure 7.3 Dependence of tablet density on pressure and equilibration temperature: (A) tablets compressed at different temperatures and stored at 25 ^{o}C; (B) tablets (compressed at 25 ^{o}C and 400 MPa) and equilibrated at different temperatures; (C) powder equilibrate, compression, and tablets equilibration carried out at constant temperatures; (D) powder equilibrated at -20 ^{o}C, tablets stored at 25 ^{o}C and -20 ^{o}C.

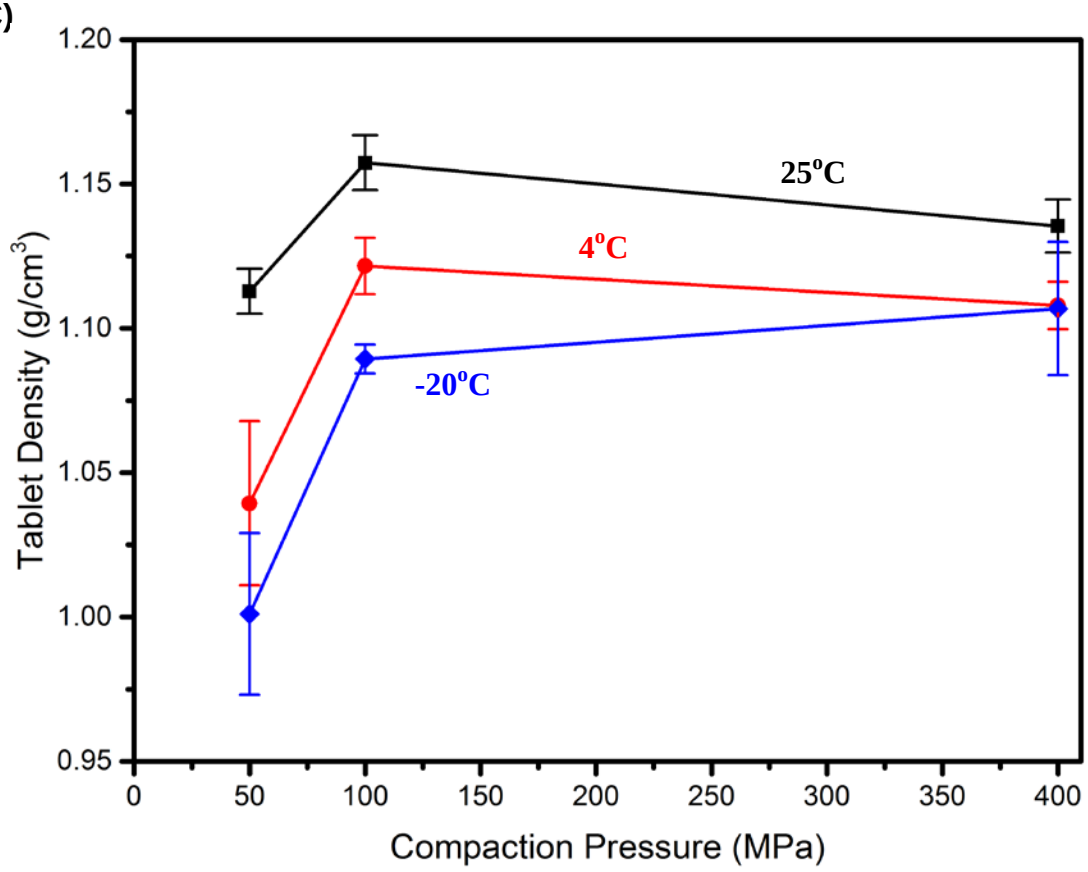
(A)



(B)


1.20
1.15
1.10
1.05
Tablet Density (g/cm3)
-20
-10
0
10
20
30
Tablet Temperature (°C)
Tablets conditioned after
compression at 400 MPa

(C)


1.20
1.15
1.10
1.05
1.00
0.95
Tablet Density (g/cm3)
0
50
100
150
200
250
300
350
400
Compaction Pressure (MPa)
25°C
4°C
-20°C

(D)

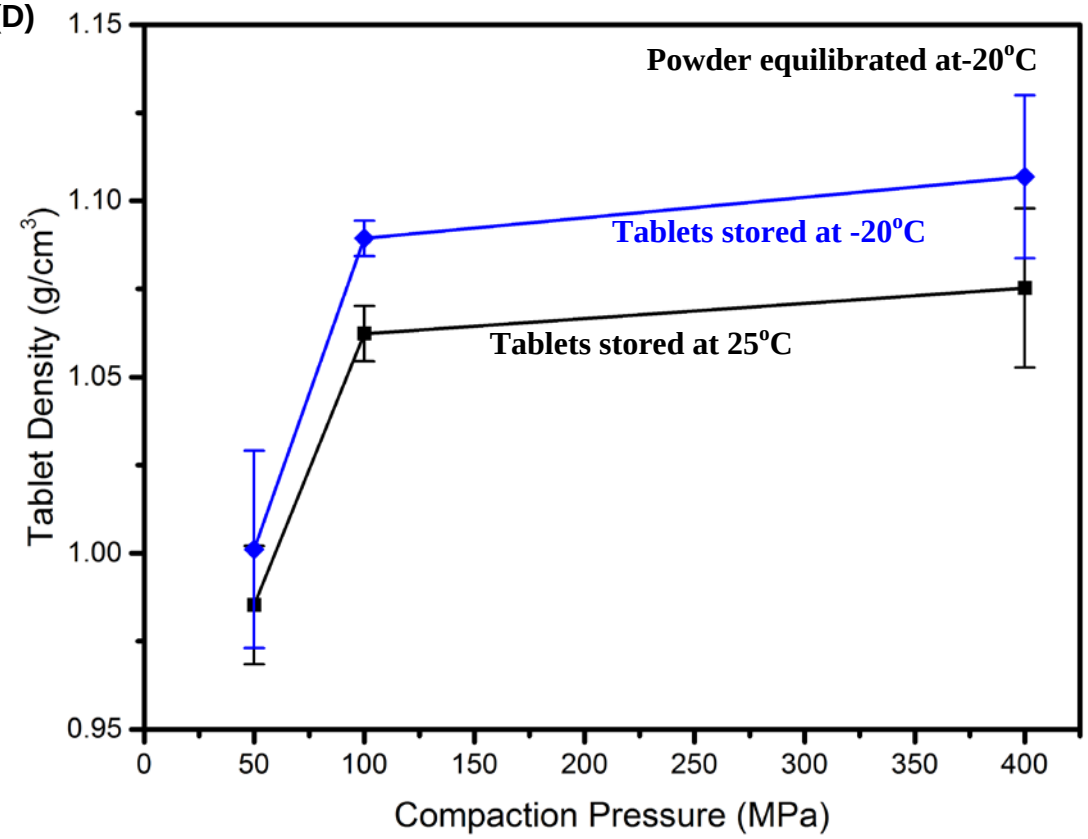
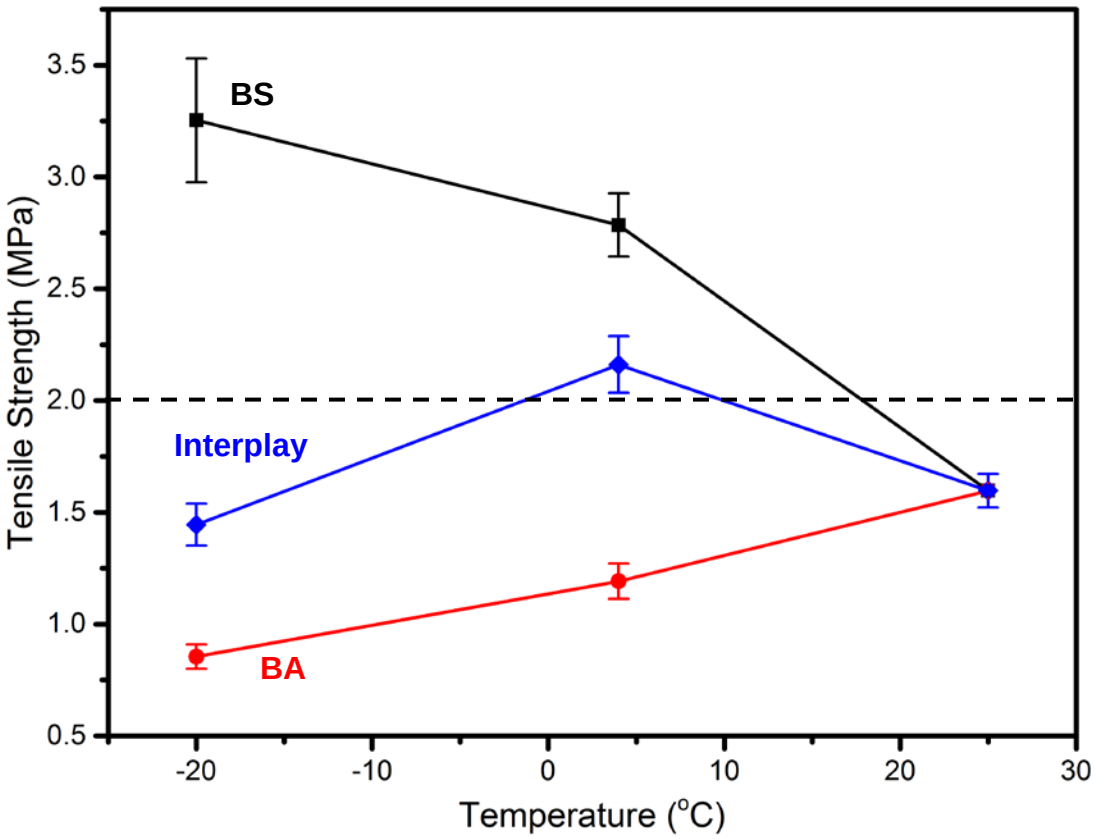

Powder equilibrated at-20°C
Tablets stored at -20°C
Tablets stored at 25°C
Tablet Density (g/cm3)
Compaction Pressure (MPa)
1.15
1.10
1.05
1.00
0.95
0
50
100
150
200
250
300
350
400

Figure 7.4 Tensile strength of tablets compressed at 400 MPa and under different combinations of compression temperature and tablet equilibration temperature showing impact of Bonding Strength (BS), Bonding Area (BA) and the Interplay between BA and BS (Interplay).



CHAPTER 8. RESEARCH SUMMARY AND FUTURE WORK

Research Summary

Through materials engineering, the composition and structure of particles were changed to modulate the mechanical properties of pharmaceutical powders, and the effects of the key properties of the powders on tableting performance were studied.

High Shear Wet Granulation (HSWG) granules have been observed to undergo substantial loss of the ability to be compressed into tablets of sufficient strength, a phenomenon called “over-granulation”. We have investigated this over-granulation phenomenon using microcrystalline cellulose (MCC)-polyvinylpyrrolidone (PVP) system lubricated with magnesium stearate (Chapter 2). The results show that tabletability of MCC granules deteriorated rapidly with increasing granulating water. Granule size enlargement, surface rounding, decreased granule porosity and densification have been shown to all contribute to reduction in tabletability by reducing granule deformability and intergranular bonding area. These mechanisms are similar to those of previous findings using MCC-water system; however, the transition to over-granulation is much quicker (at lower granulating water level) when PVP is used as a binder.

One effective approach to address the over-granulation problem is granule size reduction. Since granule size reduction can effectively improve powder tabletability through creation of larger surface areas available for bonding in a tablet, brittle excipients

(lactose monohydrate and dibasic phosphate calcium) were incorporated in the otherwise plastic powder (MCC matrix) to enhance brittleness of HSWG granules (Chapter 3). Brittle granules predominantly fracture when deformed during ordinary powder compaction process which minimizes initial particle size difference of the granules during compaction. The incorporation of brittle excipients induced more extensive granule fragmentation, hence overcoming the over-granulation problem.

Formulation of drug-loaded/layered beads into oral controlled release tablets, i.e., multiple-unit pellets systems (MUPS) suffers from the severity of damage to the functional coating layer and poor tablet mechanical strength which is strongly associated with the mechanical properties of the coating layer. Experiments using pyridoxine HCl and caffeine-layered, enteric coated microcrystalline cellulose (MCC) beads, top-coated with polyvinyl pyrrolidone, PVP K30 and polyvinyl pyrrolidone vinyl acetate,(PVP/VA 64) have been carried out to show that top-coating highly bonding polymer coupled with moisture activation is an effective strategy for improving tabletability of MUPS (Chapter 4 & 5). Moisture effectively plasticizes the top-coating polymer. Due to the minimal stress required to form adequately strong tablets by this approach, the integrity of the functional coating layer is mostly preserved. Results from a study of drug release revealed minimal damage to functional coating layer.

Using Celecoxib-PVP/VA64 as a model Amorphous Solid Disperion system, the impact of drug loading and environment relative humidity (moisture), over a wide range, on

mechanical properties of ASDs and their tableting performance has been investigated (Chapter 6). Nanoindentation, a depth-sensing technique has been used to evaluate the material mechanical properties; Hardness, *H*, and elastic modulus, *E*. *H* and *E* are obtained under well-controlled protocol of force and displacement. Through this study, it has been shown that higher RH corresponds to lower *H* & *E* for PVP/VA64, and the celecoxib ASDs due to the well-known plasticization effect of water. At low pressures (50 MPa), higher RH leads to higher tablet tensile strength because of the larger bonding area formed between more plasticized particles. At higher pressure (300 MPa), tensile strength is high and meets the 2 MPa criterion for adequate tablet mechanical strength because all particles sufficiently deform regardless of their plasticity. Overall, particle composition including moisture significantly influences the mechanical properties and tableting performance of polymer-based drug delivery systems. The complex behaviors could be well explained by the effect of moisture and composition on mechanical properties as well as the interplay between bonding area and bonding strength in tablet. These effects when studied thoroughly can guide the design of any new ASD based tablet formulation in order to ensure robust manufacturability.

The interplay between bonding area (BA) and bonding strength (BS) was demonstrated by varying them independently and also simultaneously (Chapter 7). This was achieved by varying compaction pressure and temperature of an amorphous polymer, or during tablet breaking. A higher temperature corresponds to a higher particle plasticity

(therefore larger BA during compression) and a lower BS during tablet breaking (due to higher molecular thermal energy that reduces interparticulate forces of attraction). The powder exhibits lower tabletability when equilibrated and compressed at a lower temperature which is consistent with the expectation that particles become harder as temperature is farther below the polymer's T_g. Therefore, BA within the tablets decreases with lower powder storage and compression temperature. When identical tablets compressed at high pressure were stored and broken at different temperatures, the tablet tensile strength increases with decreasing storage temperature which is proves that BS is higher at lower temperature. When both the powder compression and tablet breaking are carried out at the same temperature, the interplay between the two factors ensues. The opposite effects by BA and BS lead to similar tensile strength at -20 ^{o}C and 25 ^{o}C. At 4 ^{o}C, tablet tensile strength is the highest because the positive effect of higher BS overpowers the negative effect of smaller BA. Based on this knowledge, the temperature effect on tableting behaviors of Soluplus can be clearly explained by considering the interplay between BA and BS.

Future Work

In the field of pharmaceutical tablet manufacturing, effective particle engineering based on a clear understanding of the effects of processing on particle structure and properties is critical to successful product development.[1] Engineering particle composition, at molecular level (e.g., PVP VA64-celecoxib ASD) & particle level (e.g., HSWG), and structure (bead coating) to overcome powder compaction problems is common in modern pharmaceutical tablet product development. Understanding the compaction behavior of drugs and excipients based on the qualitative "interparticulate bonding area – bonding strength" model has been shown to be adequate to enable the development of strategies to overcome poor powder tabletability.[2-5]

High shear wet granulation (HSWG) is a powder engineering technique used frequently in pharmaceutical manufacturing to improve flow and compressibility of powders, increase bulk density, enhance content uniformity, and prevent segregation. It has demonstrated that transition of plastic Microcrystalline Cellulose (MCC) to MCC–Lactose/Dicalcium Phosphate (Dical) granules by increasing lactose/Dical concentration, minimizes loss of tablet strength to over-granulation (Chapter 2, 3). Although the system studied was more complex in terms of composition than a simple MCC-water system[6], the impact of incorporating active pharmaceutical ingredients (APIs) was not explictly demonstrated. The use of model drugs with different mechanical properties and at different dug loadings will bring the formulation close to reality in tablet development.

This project can potentially show the influence API mechanical properties have on the mechanics of tablet formulations with respect to the over-granulation phenomenon. Secondly recommendations can be made to formulators on formulation strategies based on the consideration of mechanical properties of drug, the drug loading etc. This will highlight the importance of characterizing API mechanical properties before drug development.

Tableting of MUPS into adequately strong tablets is challenging (Chapters 4, 5).[7] However this polymer-coating approach for improving tablet strength will eliminate the need of incorporating a large amount of excipients in a tablet. Consequently, the reduced tablet size, especially for high dose drugs, will improve patient compliance, and significantly reduce the total cost of production (considering the possible reduction in the number and quantity of excipients and packaging material). Mastering of the polymer coating strategy so that the technique becomes adequately mature and robust for adoption in commercial tablet manufacturing, is required. Thus, there is the need for further studies on other top-coating polymers.

Incorporating caffeine enhances the moisture-activated tabletability improvement. There is the need to identify other small molecule drugs as model compounds to further investigate this phenomenon. This can have potential application for developing fixed-dose combination drug products (the immediate release layer is also the “glue” layer for forming intact tablets). Silica coating can make disintegration easy. Upon release of this

drug layer in stomach, enterically coated drug layer will release in intestine. Currently, such controlled release is achieved by mixing beads prepared differently (immediate release or modified release). This work will allow the delivery of such effects using one type of beads. Therefore, there is no risk of segregation.

To make an impact on product development, plasticizers must be incorporated into the coating layer (PVP, PVP VA/64) to reduce the amount of moisture (or critical RH) required for activating powder tabletability. This requires a systematic study. A benefit of this strategy is the significantly lower tablet weight by not coating with a complex bonding layer as done in the past (onion ring structure)[8].

By systematically developing a relationship between particle mechanical properties and powder tabletability, strategies can be developed to effectively solve powder compaction problems. However, strong tablets can be formed when the polymer is plasticized because the increased plasticity leads to more extensive plastic deformation and, thereby, larger bonding area. This knowledge is important for selecting formulation parameters appropriate for quality tablet products.

Polymers are the most common non-active ingredients, i.e. excipients, found in the amorphous solid dispersion (ASD) tablet drug products. The composition and structure of such composites influence the mechanical properties and tableting performance.[9,10] The impact of drug loading and environment relative humidity on mechanical properties

of ASD and its tabletability is systematically shown (Chapter 6). Harder composites (low RH and high drug loading) may not always form sufficiently strong tablets under typical compaction pressures due to their low plasticity, especially when particle size increases. There is the need to study the impact of other polymers, for example of higher Tg and different chemical nature on ASD mechanical properties and tableting. Perhaps a systematic study of particle size effect can also be incorporated once the effects can be effectively decoupled by methods such as principal component analysis. There are several mechanisms by which amorphous drugs are stabilized by polymer in an ASD, e.g., by hydrogen bonding.[11] It is yet to be known whether the propensity to form hydrogen bonding with drug will have an impact on the mechanical properties and tableting performance when drug loading and RH are changed. A systematic study to establish a relationship can inform the choice of other excipients to formulate an ASD. The degree of hydrophilicity of polymers used in ASDs varies. Environment RH affects the tableting performance. Understanding the influence of the degree of affinity for moisture on the mechanical properties and tableting performance will be useful to design of ASD formulations.

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APPENDICES

APPENDIX I. VALIDATION AND APPLICATIONS OF AN EXPEDITED FRIABILITY METHOD

Appendix I has been published as a research article in the International Journal of Pharmaceutics, 2015, 484: 146 – 155

Summary

The harmonized monograph on tablet friability test in United States Pharmacopeia (USP), European Pharmacopeia (Pharm. Eur.), and Japanese Pharmacopeia (JP) is designed to assess adequacy of mechanical strength of a batch of tablets. Currently, its potential applications in formulation development have been limited due to the batch requirement that is both labor and material intensive. To this end, we have developed an expedited tablet friability test method, using the existing USP test apparatus. The validity of the expedited friability method is established by showing that the friability data from the expedited method is not statistically different from those from the standard pharmacopeia method using materials of very different mechanical properties, i.e., microcrystalline cellulose and dibasic calcium phosphate dihydrate. Using the expedited friability method, we have shown that the relationship between tablet friability and tablet mechanical strength follows a power law expression. Furthermore, potential applications of this expedited friability test in facilitating systematic and efficient tablet formulation and tooling design are demonstrated with examples.

Introduction

Tablet friability is the tendency of a tablet to lose component particles due to abrasion, friction, or mechanical shock.[1,2] High friability leads to unacceptable loss of drug content during downstream processing (e.g., film coating), storage, and handling.[3] Besides the potential loss in therapeutic effects due to sub-potency, damaged tablet appearance also creates doubts by patients on tablet quality. Although empirical in its origin,[1,4] tablet friability has become an important tablet performance and quality attribute to assess during tablet product development.[5,6] To put things in perspective, friability test may be compared to dissolution test as a tool for assessing critical performance of any tablet product.

The standard pharmacopeial method for measuring tablet friability requires a set of "identical" tablets from the same batch. A total of at least 6.5 g of tablets is required for a single test. Tablets are dropped 100 times from a fixed height, as the friabilator rotates. Tablets are then recovered, dedusted, and weighed to calculate weight loss of the set of tablets. Generally, ≤1% weight loss is acceptable for an existing compressed and uncoated tablet product. However, a more conservative weight loss of ≤0.8% is recommended for new formulations not yet having sufficient packaging data.[7-9] Lower limits may be set for specific products or for certain unit operations.[3,10,11]

Ideally, friability test could have been used extensively to facilitate tablet product development. In reality, however, the standard friability test is routinely carried out "to

supplement other physical strength measurements, such as crushing strength"[7], tablet tensile strength[12], and indentation hardness[13], to ascertain whether a batch of tablets will pass or fail the acceptance criterion. Failed friability test result triggers a change in formulation or compaction parameters, e.g., compaction pressure, speed, or tooling design. A new batch of tablets is then made and tested for friability. This process is repeated until a batch of tablet passes the acceptance criterion. Because the required test iterations demand the manufacture of batches of tablets, a significant amount of active pharmaceutical ingredient(s) and efforts are required in this kind of formulation development process. Friability test is most useful in guiding formulation development when it has been determined as a function of compaction force/pressure, from which the minimum compaction force/pressure required to make sufficiently strong tablets can be identified. This is much more effective than the trial and error approach described earlier. With such information, it is easy to determine the tablet mechanical strength that is necessary for adequate handling and shipping.[14] The traditional friability approach, however, does not provide the kind of quantitative information useful to guide formulation development unless multiple batches of tablets are prepared under different compaction conditions and tested. This is labor and material intensive, hence, unfit for adoption in early formulation development. Essentially, friability test has been mostly used as a tool for quality control.[15,16] The use of friability testing as a formulation characterization tool or early formulation screening tool is rare, if any.

Tabletability (tablet tensile strength as a function of compaction pressure) of a formulation can be assessed using a relatively small amount of material (a few grams or less) for acceptability by applying an empirical acceptance criterion, e.g., >2 MPa tensile strength.[17] Since the tensile strength of non-cylindrical tablet is more difficult to obtain[2], a target tablet breaking force (frequently termed "tablet hardness" in the pharmaceutical industry) may be set for making a batch of tablets. However, even tablets meeting these criteria may still exhibit overly high friability because higher tablet breaking strength does not always lead to lower friability[18,19] and density variation within a tablet can affect friability.[2] In addition, tablet tensile strength or breaking force is only one of the many factors that affect tablet friability, such as tablet size, tablet shape, or even tablet surface roughness.[18-20] Furthermore, in the development of certain products, such as orally disintegrating tablets, tablet tensile strength cannot be very high because of the requirement of a short disintegration time.[21] Consequently, acceptance criteria based on mechanical strength will not be suitable. Alternatively, tablet friability profile (friability as a function of compaction force/pressure) can be used to more reliably assess the manufacturability of a formulation than tabletability profile because friability is a direct test of tablet performance. The kind of stresses endured by tablets during friability test is relevant to those experienced during storage and handling.[1]

To successfully integrate friability measurement into tablet development for fully realizing its potential benefits, the availability of a material-sparing and expedited

friability method is critical. Therefore, the goals of this research are twofold: (1) to develop and validate a time and material sparing friability test method, and (2) to demonstrate some of the potential applications of this method in product development, especially in the areas of tooling design and formulation optimization. We hypothesize that the replacement of the batch of "identical" tablets in the USP friability test by tablets varying in mechanical strength does not significantly alter the stress state experienced by individual tablets and friability of individual tablets is an acceptable approximation of corresponding batch friability determined using the standard pharmacopoeial method. The availability of such an "expedited method" makes it possible to readily determine tablet friability as a function of compression conditions in a material- and time-sparing manner.

Materials and Methods

Materials

Materials used in this study were: microcrystalline cellulose (MCC, Avicel PH102, Lot. P208819889, FMC Biopolymer, Philadelphia, PA), croscarmellose sodium (Ac-Di-Sol- Lot. TN08819630, FMC Biopolymer, Philadelphia, PA), dibasic calcium phosphate dihydrate (DCPD, Emcompress, Lot. 7100X, JRS Pharma, Chicago Heights, IL), acetaminophen (APAP, Lot. 124K0165, Johnson & Johnson Company, New Brunswick,

NJ), celecoxib (Lot. CBX/1010121, Aarti Drugs Ltd., Maharashtra, India), and magnesium stearate (Lot. J03970, Mallinckrodt, St. Louis, MO). All materials were used as received.

Methods

Blending and Compaction

Powder mixtures of MCC and DCPD were prepared at various ratios (20–80% w/w, 100 g batch size) by hand-mixing in a pan, followed by blending for 10 min in a 2 quart (1.89 L) twin shell blender (Patterson-Kelley, East Stroudsburg, PA) operated at 25 rpm. Two formulations containing 40% of APAP or celecoxib in an excipient matrix consisting of MCC (34.5% w/w), DCPD (20% w/w), Ac-Di-Sol (5% w/w), and magnesium stearate (0.5% w/w) were prepared using the same blending procedure. Tablets were compressed using a variety of toolings on a universal material testing machine (model 1485, Zwick, Germany) at ambient laboratory conditions (37 ± 9% RH and 24 ± 1 °C, Table AI.S1). The tableting speed used in this study was 100 mm/min unless indicated otherwise. Except for the two formulations that contain 0.5% magnesium stearate, compaction of other powders was carried out using tablet toolings coated with 5% (w/v) suspension of magnesium stearate in ethanol and air dried. Mean compaction pressure was calculated from the force and cross-sectional area of the punch tip.

Tensile Strength and Porosity Determination

To obtain tablet tensile strength – porosity relationship, cylindrical tablets (10 mm diameter) were made under different pressures. Tablet dimensions were measured using a digital caliper immediately after ejection and tablet density was calculated from tablet weight and volume. Tablet diametrical breaking force was determined using a texture analyzer (Texture Technologies Corp., Scarsdale, NY/Stable Micro Systems, Godalming, Surrey, UK), at a speed of 0.01 mm/s with a 5 g trigger force. True density of each mixture powder was calculated from the true densities of pure powders (ρ_{true}), which were obtained by fitting their tablet density (ρ_{tablet}) – compaction pressure (P) data using *Equation AI.1*. [22,23]

$$P = \frac{1}{C}\left[(1-\varepsilon_c) - \frac{\rho_{tablet}}{\rho_{true}} - \varepsilon_c \ln\left(\frac{1-\frac{\rho_{tablet}}{\rho_{true}}}{\varepsilon_c}\right)\right] \qquad AI.1$$

where C (M Pa^{-1}) and ε_c are constants related to powder consolidation properties under pressure. Helium pycnometry is unable to yield accurate true density values for water-containing powders, such as MCC.[24]

Tablet porosity was calculated from tablet density and true density. The function that describes the relationship between tablet tensile strength (σ) – porosity (ε) for each powder was obtained by fitting data to *Equation AI.2*[25] which was then used to calculate tensile strengths of tablets used in friability test from their porosity (Figure AI.S1).

$$\sigma = \sigma_o e^{-b\varepsilon} \qquad AI.2$$

where b and σ_o are empirical constants.

Conventional USP Friability Test

USP friability tests were conducted using batches of compressed tablets that were coded and weighed individually (Mettler Toledo, AG245, Columbus, OH). The number of tablets used in a batch was chosen to afford a total weight of at least 6.5 g. The friability test was conducted using a dual drum, automatic tablet friabilator (Pharma Alliance

Group Inc., Model F2, Santa Clarita, CA) at 25 rpm for 4 min. After the friability test and dedusting as per the USP procedure, weight loss of both each tablet and the batch was determined. The friability, expressed as a percentage of the initial weight, of individual tablets and the whole batch was calculated. Determination of individual tablets weight loss enabled calculation of the standard deviation for the percentage friability of the batch.

Expedited Friability Test

For each powder, a set of 20 tablets prepared under different compression forces were loaded into the friabilator. Twenty tablets usually yield a reasonable friability plot. However, more or less tablets can be used if desired. The tablets were individually coded and weighed before loading into the friabilator. The percentage weight loss was calculated for individual tablets (% friability) and was plotted against compaction pressure/force, tablet porosity, or tensile strength. The threshold tensile strength, porosity, or compaction pressure/force corresponding to 0.8% friability was determined from respective friability plots.

Data Fitting and Statistical Analyses

Data fitting and statistical analyses were carried out using Origin® (v.9.1, OriginLab Corp., Northampton, MA) and Minitab® (v.17, Minitab Inc., State College, PA).

Results

Validation of the expedited friability method

The tensile strengths and breaking force of tablets increased with increasing compaction pressure for all the materials tested, confirming compaction pressure is a dominant process parameter for attaining tablet mechanical strength.[26]

The friability plots of MCC and DCPD tablets using both the expedited method and the conventional USP method are shown in Figure AI.1. The results from both methods are similar within the accuracy of the experiments. Generally, tablet friability (tablet performance) decreases with increasing compaction pressure (a process parameter) as expected.[11,27] This relationship is shown to follow a power law (log–log linear) relationship. (*Equation AI.3*)

$$y = ax^b \qquad AI.3$$

where a is a constant and b is the allometric scaling exponent.

Results of the statistical analyses suggest a strong correlation between tablet compaction pressure and tablet friability for both MCC and DCPD using either friability methods with $R^2 \geq 0.98$ (Table AI.1). The beneficial effect of compaction pressure in reducing friability is closely related to its effect on tablet mechanical strength. As routinely observed, friability is lower when a tablet is stronger[21] because it is more difficult to remove individual particles from the stronger tablet by mechanical impact during the friability tests. However, if the compaction pressure is so high that the over-compression mechanism is activated, tablet friability may be higher at higher pressures or even exhibit capping tendencies.[18] The trends in our data suggest that over-compression mechanism is not present under the compaction conditions employed in this study.

Results from non-linear regression of the two types of friability data were analyzed for statistically significant difference using both 2-sample *t*-test and paired *t*-test. The 2-sample *t*-test was conducted using the data summary mode in Minitab® because it permits the use of the mean values of a and b, their standard deviations, and the sample size to obtain the significance level (p values). Two sample *t*-test results show that the two friability methods yield functions that are not statistically different ($p$values ≥ 0.06). Additionally, paired *t*-test carried out on friability data at the same compaction pressures from the two methods ($n \geq 7$) show no statistical difference (p values ≥ 0.13). To satisfy the requirement of normality of data distribution, paired *t*-test was carried out after

transforming data to logarithmic form before conducting the test.[28] The slopes, i.e., parameter *b*, of the lines are not significantly different for both MCC (*p* value = 0.15) and DCPD (*p* values = 0.06). Although the friability data obtained using the conventional USP method visually fall slightly to the right side of the expedited method, the paired *t*-test shows such visual shift is not statistically significant (*p* values $\geq$ 0.13). Overall, the statistical analyses results confirm that the expedited method is valid, i.e., it yields the same friability information as the standard USP friability method. The main difference between the two methods is that the expedited method calculates friability based on weight loss of individual tablets but the USP method uses the weight loss of the entire batch of tablets. The validity of the expedited method also suggests that tablets in the expedited method experience similar stress conditions as those in the standard USP test method. Individual tablets in the expedited method respond differently to the stress because of their different mechanical strengths, i.e., they lose varying amounts of materials depending on the individual tablet's strength.

A conceivable limitation of the expedited method is when accurate weight loss cannot be measured using a single tablet because of very low friability. If the friability test is conducted using tablets of 200 mg weight and a balance accurate to 0.1 mg, the smallest percent weight loss that can be accurately determined is 0.05%. Since this is much below the USP acceptance criterion of 0.8%, the expedited method can be applied without problem for determining whether or not a batch of tablets passes friablity criterion. The

expedited friability method can be adopted for characterizing API powders or screening early tablet formulations since it takes only 4–6 g of material to obtain a complete friability plot. This study can be carried out to assess any powder that can be compacted into intact tablets as long as compaction force can be controlled.

Applications of the expedited friability method

Having validated the expedited friability method, we now explore some possible applications of this method in characterizing compaction properties of a powder and guiding formulation development. To facilitate the ensuing discussion, we classify three types of friability plots: Type I shows the relationship between friability and compaction force or pressure; Type II shows the relationship between friability and tablet porosity; Type III shows the relationship between friability and tablet tensile strength.

Tablet friability is a critical performance test for assessing tablet quality[6] as it has been widely recognized that, sufficiently low friability is a key acceptance criterion for tablets. Conventional USP friability test yields results that can be used for assuring adequate tablet mechanical properties.[15] However, it is unable to provide a clear explanation as to why a batch of tablet has high friability or how to reduce it. As per the Materials Science Tetrahedron principle, mechanistic insights to a performance problem come from an understanding of the structure–property relationship in connection with the performance

in question.[29] Such understanding is critical for effective engineering of formulation or compaction process to improve tablet friability as shown by modeling.[2] By using the expedited friability method, the relationship between friability and tablet tensile strength (tablet mechanical property) or porosity (a measure of tablet structure) can be readily obtained.

Guiding effective troubleshooting of high friability problem

The friability of cylindrical MCC tablets (400 mg, 10 mm diameter) is 2.79% and 0.26% when prepared at 10 MPa and 25 MPa, respectively. The one order of magnitude of reduction in friability with an increase of 15 MPa suggests its extreme sensitivity to compaction conditions. In fact, when pressure is 100 MPa, friability of MCC tablet was too low to be accurately measured. With this data, it immediately becomes clear that controlling compaction process is effective for addressing friability problem, if encountered, for this powder. On the contrary, the friability of DCPD tablets (650 mg, 10 mm diameter) was 7.1% and 1% at 50 MPa and 250 MPa, respectively. Even at a relatively high pressure of 250 MPa, tablet friability is still higher than 0.8%. This suggests controlling compaction alone is not very effective for this powder. Instead, reformulation or change of tooling should be sought to address the high friability problem.

Understanding the relationship between tablet structure and friability

Although it is clear from Figure AI.1 that MCC is much less friable than DCPD, the exact reason for the superior performance of MCC is not revealed by the Type I friability plot. Friability is affected by tablet mechanical strength, which determines how easily particles can be dislocated from their original places in the tablet when subjected to an external shear or impact stress.[2] Friability is also affected by the mechanical property of the material).[27] More brittle materials are less able to reduce the effect of local stresses at contact points through plastic deformation. In addition, they are more to fracture (crack propagation) and separation of contact during deformation.[30] All these factors lead to higher friability for more brittle materials. Tablet size and shape are also known to affect friability because of their impact on the intensity of stress at the points of contact during friability test.[18] Either one or a combination of these three factors can be responsible for problematically high friability of a batch of tablets. Effective solutions to this problem come from a clear understanding of its underlying cause(s). In the following part of the discussion, we only concern ourselves with cylindrical (10 mm flat faced) tablets, which significantly simplifies the effort to obtain tablet porosity and tensile strength information required for constructing Type II and III friability plots. Effect of tablet size and shape will be separately discussed later in this report.

Since tablet tensile strength test is destructive, tensile strength of tablets used for friability tests was calculated from porosity using a separately determined relationship between tablet porosity and tensile strength by fitting data to *Equation AI.2*. The friability – tablet porosity relationship is log-linear (exponential decay), while both friability - tensile strength and friability – compaction pressure relationships are log–log linear, i.e., they follow a power law relationship (Figure AI.2). Although the empirical power law relationship holds for all materials tested in this study, it is possible that other mathematical equations may also adequately describe these data. In addition, these relationships may not hold for the entire range of porosity, tensile strength, or compaction pressure. Extrapolation to outside of the range covered by the data should be carried out with caution.

When compared at the same porosity, DCPD has two orders of magnitude higher friability than MCC. When compared at the same tensile strength, the relative difference is less but DCPD tablet is still significantly higher than MCC tablet. This suggests DCPD is inherently more prone to high friability even when tablet structure and property are considered. The higher brittleness of DCPD is a likely reason for the higher friability because individual particles do not readily undergo plastic deformation to dissipate stresses during friability test, which also causes easier crack propagation to eventually separate particles from the tablet. Based on the three types of friability plots shown in Figure AI.2, we can also identify the values of tablet descriptors that correspond to the

0.8% friability, which can be used as threshold values for adequate performance. For example, the minimum tensile strength values of cylindrical flat face tablets of MCC and DCPD are 1.03 MPa and 4.03 MPa, respectively (Figure AI.2). Although we chose the more conservative 0.8% weight loss as the threshold value, limits corresponding to other friability values can be set as needed for a specific investigation. In addition, the same exercise can be carried out to determine critical values of other properties of interest, e.g., breaking force, hardness, elastic modulus, and brittleness, for any given tablet size and shape.

Effect of tablet shape and size on friability

It has long been known that tablet shape and size affect friability.[18] Here, we quantitatively compared friability of oval convex, bevel edged, cylindrical, and rectangular flat face tablets. As observed for cylindrical tablets, ductile MCC always exhibits significantly lower friability than brittle DCPD for all tablet shapes. For these tablets with different shapes, the average compaction pressures required to obtain 0.8% friability is in the order of oval convex < bevel edged < cylindrical < rectangular for both MCC and DCPD (Figure AI.3A). Here, we use compaction pressure instead of compression force because mechanical strength of a tablet is determined by pressure. For achieving the same pressure, higher compaction force is required to make larger tablets.

For both MCC and DCPD, the pressure required to meet the 0.8% friability ranges from 2.8 MPa for oval convex MCC tablets to 319.1 MPa for rectangular DCPD tablets. These strikingly different behaviors are easily revealed using the expedited friability method but would have been extremely tedious to obtain using the conventional friability test.

To study the effect of tablet size on tablet performance, 8 mm and 10 mm cylindrical tablets of MCC (200 mg and 400 mg) and DCPD (400 mg and 650 mg) were used (Figure AI.3B). Target tablet weights were based on die fill capacity and our intention to keep the density and porosity of differently sized tablets approximately the same for a given material. While the minimum compaction pressure for 8 mm and 10 mm MCC tablets remain similar, ~62 MPa higher pressure is required for 10 mm DCPD tablets than the 8 mm tablets to meet the 0.8% friability requirement. The difference in sensitivity to tablet size (weight) change between MCC and DCPD is attributed to their different mechanical properties. The more brittle DCPD tablet is more sensitive to the increase in impact stress intensity by the higher tablet weight than MCC tablet. Again, this result is qualitatively expected based on experience. However, quantitative understanding like this would have been extremely tedious to obtain without using the expedited friability method.

Effect of material properties on friability

The different friability between MCC and DCPD tablets suggests the impact of material mechanical properties on friability performance. We now systematically show such an impact using the binary mixtures of MCC and DCPD (Figure AI.4). Compaction properties of powders containing these two excipients have been well studied before.[31,32] For both cylindrical and bevel edged tablets, the compaction pressure corresponding to 0.8% friability increases with DCPD content. This is consistent with results from an earlier study: (1) at the same compaction pressure, tablets containing more DCPD exhibited higher friability; and (2) friability decreases with higher compaction pressure for a given material.[32] The critical compaction pressure increases slowly up to 60% DCPD for cylindrical and 80% DCPD for bevel edged tablets. With further increase in DCPD percentage, the critical compaction pressure increases sharply (Figure AI.4A). The average difference in switching from cylindrical to bevel edged tablets is 9.3 ± 2.7 MPa in the 0–60% DCPD range. However, for the powder containing 80% and 100% DCPD, the difference in compaction pressure is 52.8 MPa and 154.9 MPa, respectively. Consistent with the observation made earlier in this study, bevel edged tablets generally perform better than cylindrical tablets. It is interesting to note that the relationship between tablet tensile strength that satisfies the friability criterion and the concentration of DCPD exhibits a minimum at 40% DCPD for the cylindrical tablets (Figure AI.4B). This suggests that tablet mechanical strength alone is not always a

reliable parameter for predicting tablet friability among different materials or formulations. The minimum tensile strength, consistent with the required minimum compaction pressure, increases sharply in the 80–100% DCPD range. The previously suggested value of 2 MPa as a critical tensile strength threshold for adequate tablet mechanical strength[17] seems a reasonable criterion for this series of mixtures containing up to 80% DCPD.

Comparing formulations

To demonstrate the application of this expedited method to formulation development and scale up, we prepared APAP and celecoxib formulations (40% drug in a common excipient blend) and determined their three types of friability plots using cylindrical tablets (10 mm diameter) (Figure AI.5). Compaction pressure may also be used for flat face toolings. However, the use of compaction force is applicable to any tooling. From Figure AI.5A, we determine that minimum compression forces corresponding to 0.8% friability are 17.24 ± 0.03 kN and 17.84 ± 0.03 kN for APAP and celecoxib formulations, respectively. Even though the critical compression forces are similar, the tablet structure and properties of the two formulations are very different. The corresponding tablet porosity/tensile strengths are 8.34%/1.7 MPa for APAP and 1.75%/4.2 MPa for celecoxib (Figure AI.5A and C). The knowledge of critical tablet porosity indicates that increasing

pressure is more effective to further reduce friability for the APAP formulation than for the celecoxib formulation, which has been nearly fully consolidated at ~18 kN.

Guiding scale up of tablet formulations

Finally, the expedited method can be used to guide scale up by assessing impact of process parameters, such as tableting speed, on tablet manufacturing. In this example, we use bevel edged tooling to prepare 500 mg tablet. We first obtain the friability plot of the celecoxib formulation at a slow speed (1 mm/min). From the friability plot, we determine the 95% confidence interval (CI) of the compression force corresponding to 0.8% friability is 7.1–8.4 kN (with a mean of 7.74 kN) (Figure AI.6A). The breaking force of three tablets produced at the upper confidence limit of 8.4 kN lies in the narrow range 124.1–126.6 N. Similar to a state function, breaking force (a tablet property) directly correlates to friability (a tablet performance) irrespective of the tableting speed (or the path through which the tablet property is obtained). To achieve the same tablet mechanical strength under a higher tableting speed (100 mm/min), compaction force is expected to change. The upper 95% confidence limit of compaction force required to prepare tablets of 126.6 N breaking strength at 100 mm/min is 7.5 kN from the corresponding breaking force – compaction force curve (Figure AI.6B). This is to say, a compression force of 7.5 kN at 100 mm/min is predicted to be sufficient for making

tablets that meet the 0.8% friability requirement. To verify this prediction, two batches of tablets produced at 7.5 kN and 100 mm/min were tested by the USP friability method, which resulted in the friability values of 0.52 ± 0.09% and 0.58 ± 0.13%. These friability values are below 0.8% friability because of the conservative use of upper confidence interval limit to allow a safety cushion for the predicted manufacturing conditions. In fact, the predicted friability at 8.4 kN and 1 mm/min, with the 95% CI of 0.55–0.8%, is in agreement with the USP friability (Figure AI.6A). These results confirm the reliability of predicting suitable compaction force at a higher tableting speed based on the expedited friability test results obtained at a slower speed. Figure AI.7 summarizes the process that can be used to guide tableting process scale up.

Discussion

Friability is an important, but under-studied, tablet performance. The standard USP friability test method requires the use of a batch of tablets, but only yields a very limited amount of information. As such, it has been used mostly as a quality control tool instead of a formulation research tool. The expedited friability method is material sparing and allows the collection of a wealth of information at an early stage of product development. With this method, tablet friability can be routinely measured to guide formulation and process development and optimization. As a performance test, it is more reliable than other tests, including tablet tensile strength and hardness measurements, in guiding

formulation design and it provides information useful for understanding structure–property–performance relationship. Since the expedited test does not require a specially designed apparatus, it can be easily adopted by the industry.

The expedited friability method permits a readily quantitative assessment of the effect of material mechanical properties (ductile or brittle) on friability using a small amount of material. The USP friability test method is not suitable for this because making batches of tablets at different pressures is labor intensive and requires much material. As shown by some of the examples, possible applications of the expedited friability test are many. It will enable the early collection of friability data to guide the development of robust tablet formulation. Again, the roles of friability measurement may be compared to that of dissolution test in the sense that they both cover an important performance of tablet products. The difference is that the friability test is pertinent to the mechanical strength of tablet products while the dissolution test is to bioavailability.

Based on data obtained from the expedited method, the lower friability of MCC tablets than the DCPD tablets at comparable tensile strengths, regardless of tablet shape, is another manifestation that materials with different ductility will respond to external stresses differently.[13] The brittle DCPD tablets are likely to lose more material because of the easier crack propagation and chipping when subjected to a mechanical shock.[27] The clear demonstration of the effect of tablet shape and size on tablet friability confirms the empirical observation.[18,33] In this study, we had the opportunity to examine the

pattern of material loss from tablet, which provides more insights on the mechanism of high friability of different tablets. For all materials, friability strongly correlated with the appearance of sharp edges or corners. That is to say, particles that form the sharp edges or corners tend to be removed during the friability test. This is not surprising because, under similar impact intensity, sharp corner or edge will generate higher local stress during an impact than side or flat surfaces. Therefore, particles at these places tend to be dislocated more easily. This explains why higher compaction pressure is required to maintain the 0.8% friability for the rectangular flat face tablets, which have more sharp edges and corners, than other tablet shapes (Figure AI.3). It also emphasizes the already widely adopted view that, when sufficiently strong tablets cannot be made, sharp edges and corners should be avoided to minimize tablet friability. Because the density distribution in tablets of different shapes may be different, the variation in density distribution could also contribute to the effect of tooling/tablet shape on tablet friability.[18,26] However, such effect is likely significantly less than that by sharp edges and corners. Regardless the exact mechanism, the overall effect on friability can be easily quantified using the expedited friability method. This provides useful information to tooling selection for robust tablet performance when reformulation is not possible or if insufficient resource is allowed for reformulation. If tablet shape is not finalized at the time of a study, bevel edged tablets may be used for characterizing friability. This tablet shape likely resembles the final tablet shape more than cylindrical or rectangular tablets. Yet it corresponds to higher friability than oval shaped tablets. Therefore, friability

determined with bevel edged tablets is more conservative, which builds in a safety cushion in the estimate.

Since more brittle materials, e.g., DCPD, are more prone to wear and tear than plastic materials, e.g., MCC, the use of brittle excipient should not be at a very high fraction unless required to correct for formulation deficiencies. The significant deterioration of friability of bevel edged tablets is observed only when more than 80% DCPD is present in the binary mixtures with MCC. This suggests the plastic excipient(s) may play a dominant role in controlling tablet friability.[18] In any case, a balance between plasticity and brittleness of a formulation must be maintained.[34,35] Extremely plastic powders are susceptible to problems of over-granulation during high shear wet granulation[36] or loss of tabletability during dry granulation[37]. Extremely brittle powders tend to face the challenge of overly high friability, as shown in this work. Reaching such a balance requires access to information on relevant performance. This is one reason why the development of material-sparing expedited friability test is important to the successful and economic development of high quality tablet products.

Changes in formulation composition have been shown to affect tablet friability.[18,38] Using the expedited friability method, such effect can now be quantified early in development using a small amount of material. This information will effectively guide formulation optimization. Since this is a performance test, the impact of any formulation variable is directly assessed without the need of characterizing other tablet properties,

such as tensile strength and hardness, unless an understanding of the differences in performance is desired. In that case, the simultaneous access to all three types of friability profiles may be employed as demonstrated using the APAP and celecoxib formulations in Figure AI.5. From this, the tablet tensile strength, porosity, and compaction force required for meeting target performance of 0.8% friability can be determined. Although tablet tensile strength must be substantially higher for celecoxib formulation than APAP formulation (Figure AI.5C), it does not necessitate higher compression forces (Figure AI.5A) because it is more compressible than the APAP formulation (Figure AI.5B). In other words, celecoxib formulation can form a less porous tablet at the same compaction force than APAP formulation. This understanding of the unique relationship between structure, property, processing, and performance builds a solid foundation for developing high quality tablet products.[29] This, in combination with other tablet characterization techniques, such as X-ray computed tomography, can provide useful information for developing better understanding to the tablet structure and property relationship. Finally, the tensile strength of the celecoxib formulation corresponding to 0.8% friability is 4.2 MPa. This is an exception to the empirical rule of >2 MPa criterion as an acceptable tablet mechanical strength, i.e., tablets may still not meet friability performance criterion even when tensile strength is much higher than 2 MPa.

In tablet manufacturing, scale-up may require adjustment to some of the processing conditions, e.g., the press speed.[39] The integration of the expedited friability method into a scale-up plan, summarized in Figure AI.7, will help to eliminate scale up surprises. The objective is to determine the tableting condition, i.e., compression force, that will be amenable to a successful compression of tablets with ≤0.8% friability when the tableting speed has been changed. In the example of celecoxib formulation, the use of upper confidence intervals is intended to provide a margin of safety in the processing parameters that may be required in the large scale manufacturing (Figure AI.6). Once the tablet breaking force for achieving <0.8% friability is determined, the compaction force required for achieving this performance can be determined for any tableting speed, i.e., 8.4 kN at 1 mm/min and 7.5 kN at 100 mm/min. This makes possible data-driven scale up decision to replace empirical ones. For example, it is counterintuitive to use lower compaction force at higher tableting speed. Without this information, an overly high compaction force may have been used at higher speed, which can potentially lead to problems such as over-compaction of tablets[40], excessive wearing of tablet toolings[26], slow tablet disintegration[21], and delayed drug dissolution and absorption.[41] These are just a small sample of possible applications of this expediated friability method. Systematic future applications of this method will lead to answers to many more interesting questions surrounding tableting formulation development and tablet manufacture.

Conclusion

We have shown that an expedited and material-sparing friability method can be used to produce data equivalent to those from the conventional pharmacopoeial friability method. The expedited test can be easily adopted by the pharmaceutical industry since only the standard friability apparatus is used. We have also shown several examples of possible applications of this method to facilitate tablet formulation development, guide scale up of tablet manufacturing process, and gain mechanistic insights on tablet friability.

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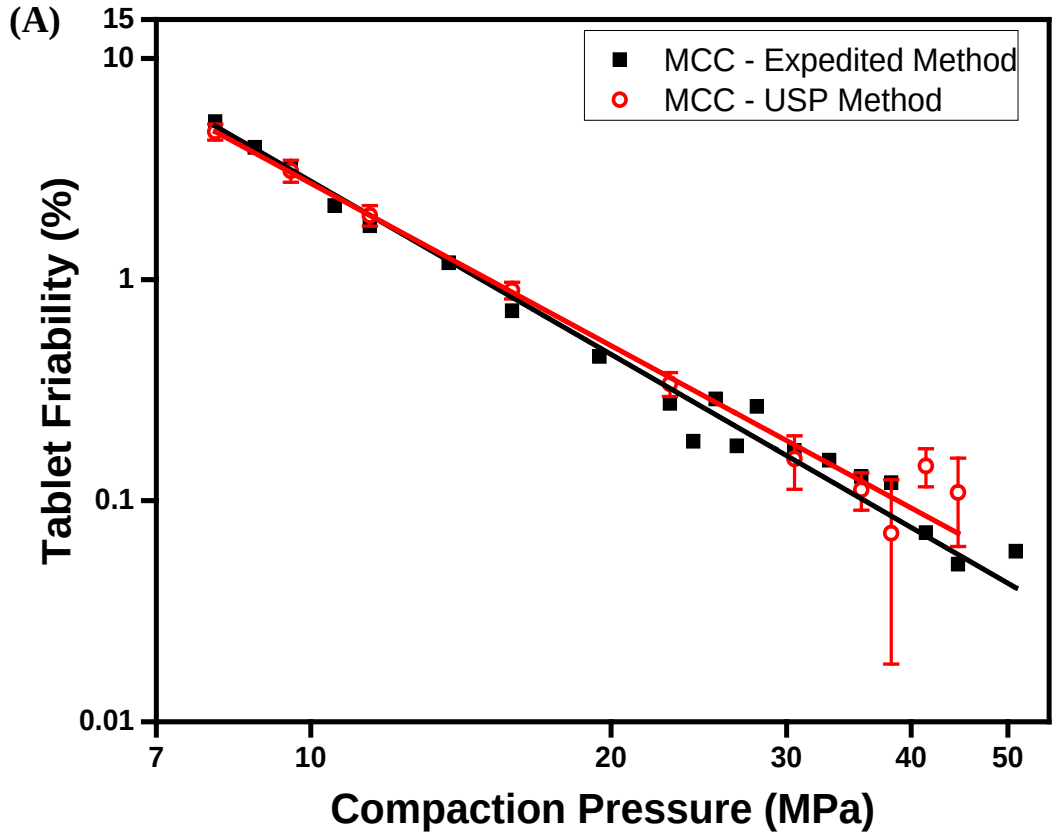
Table AI.1 **S**tatistical analyses of the data from the expedited method and the USP method using the power law relationship, $y = ax^b$

Material	**R^2**	***a*/10^3 (SE)** [a]	**2-Sample t-test *p* value**	***b* (SE)** [a]	**2-Sample t-test *p* value**	**Paired t-test *p* value**
$MCC_{Expedited}$	0.99	1.11 (0.19)	0.15	-2.60 (0.08)	0.15	0.4
MCC_{USP}	0.98	0.75 (0.15)		-2.44 (0.08)		
$DCPD_{Expedited}$	0.99	0.93 (0.13)	0.09	-1.24 (0.03)	0.06	0.13
$DCPD_{USP}$	0.98	0.63 (0.11)		-1.15 (0.04)		

[a] SE = Standard Error;

Figure AI. 1 Friability Plot (Type I) of (A) MCC and (B) DCPD used for validating the expedited friability test method by the conventional USP method



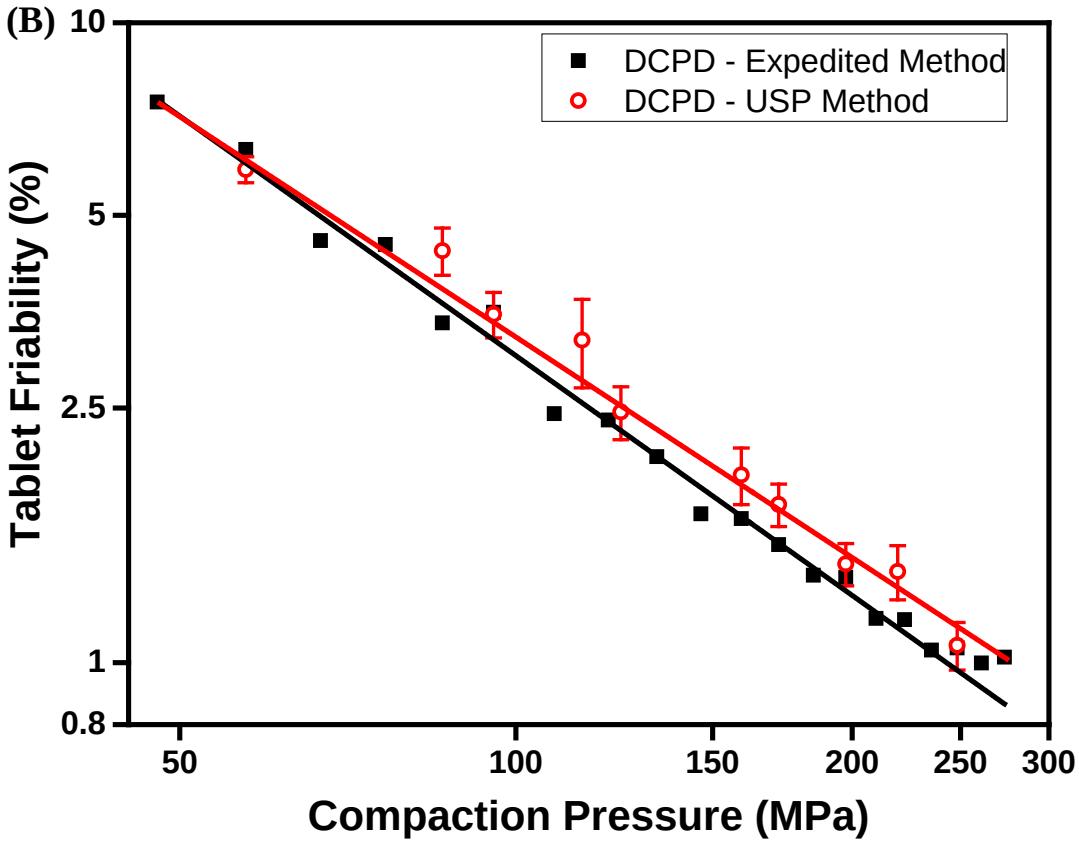
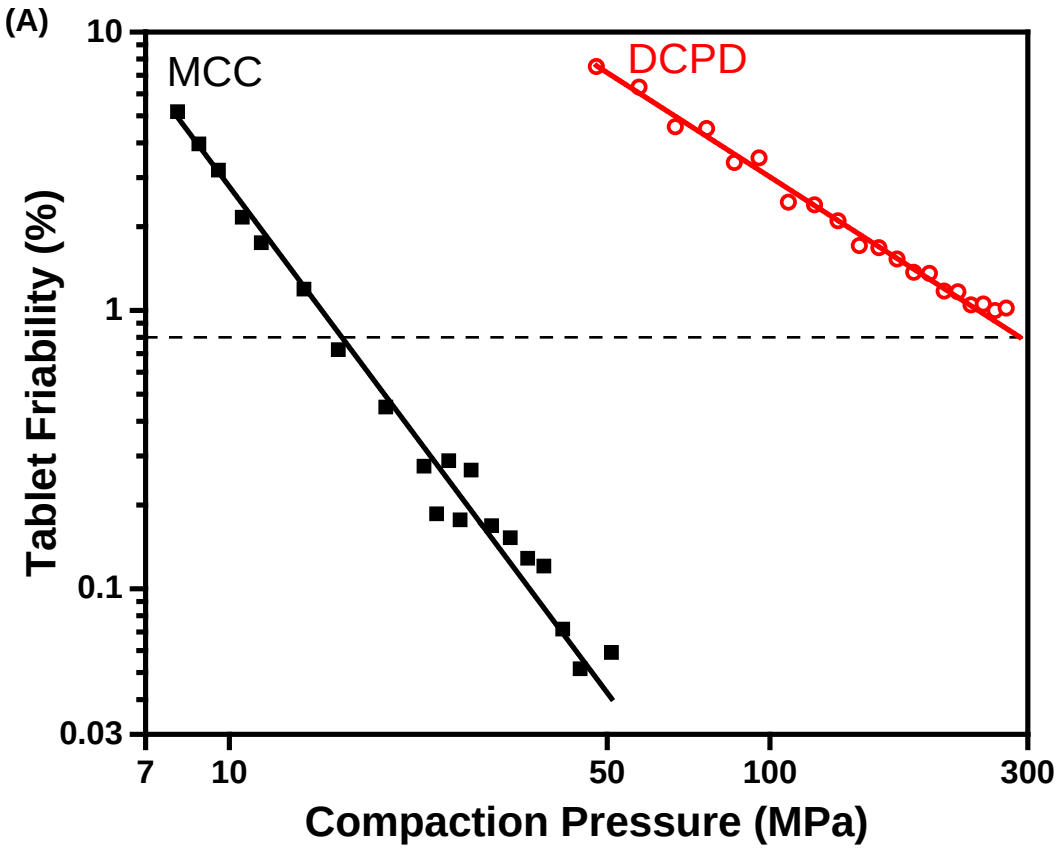
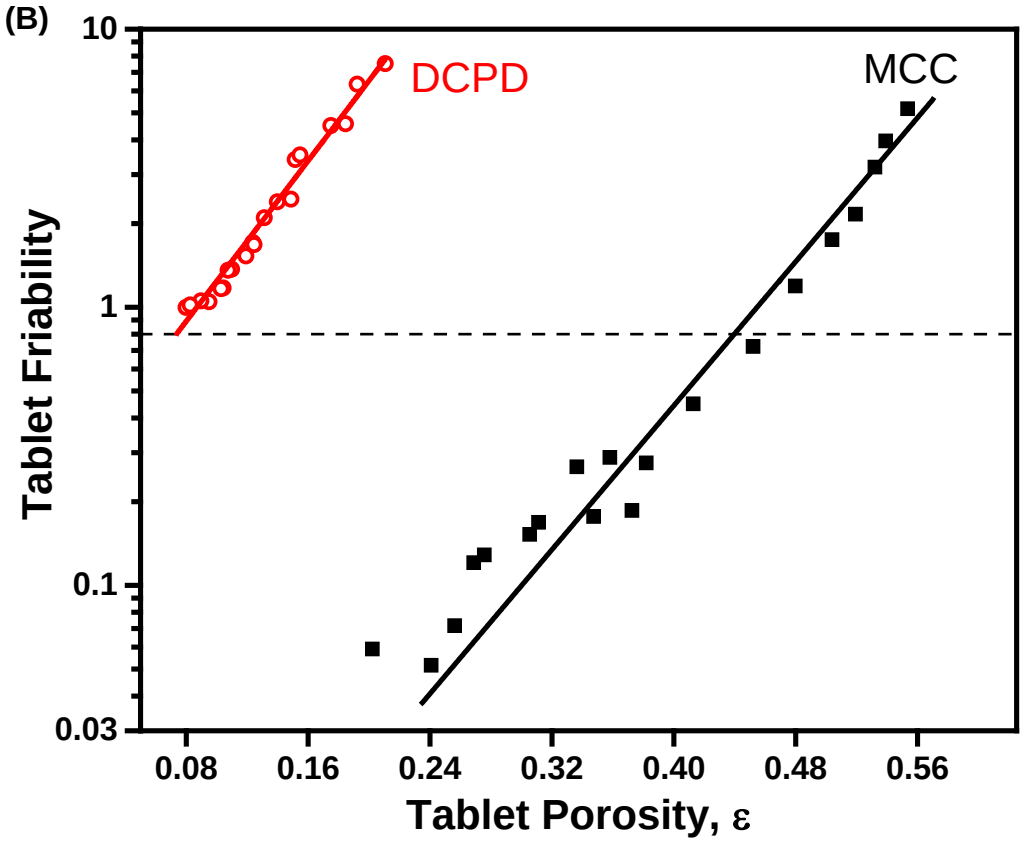

(B)
DCPD - Expedited Method
DCPD - USP Method
Tablet Friability (%)
10
5
2.5
1
0.8
50
100
150
200
250
300
Compaction Pressure (MPa)

Figure AI. 2 Friability plots of MCC and DCPD (A) Type I (B) Type II and (C) Type III. 10 mm cylindrical flat faced tablets were used




(B)
10
1
0.1
0.03
Tablet Friability
DCPD
MCC
0.08
0.16
0.24
0.32
0.40
0.48
0.56
Tablet Porosity, ε

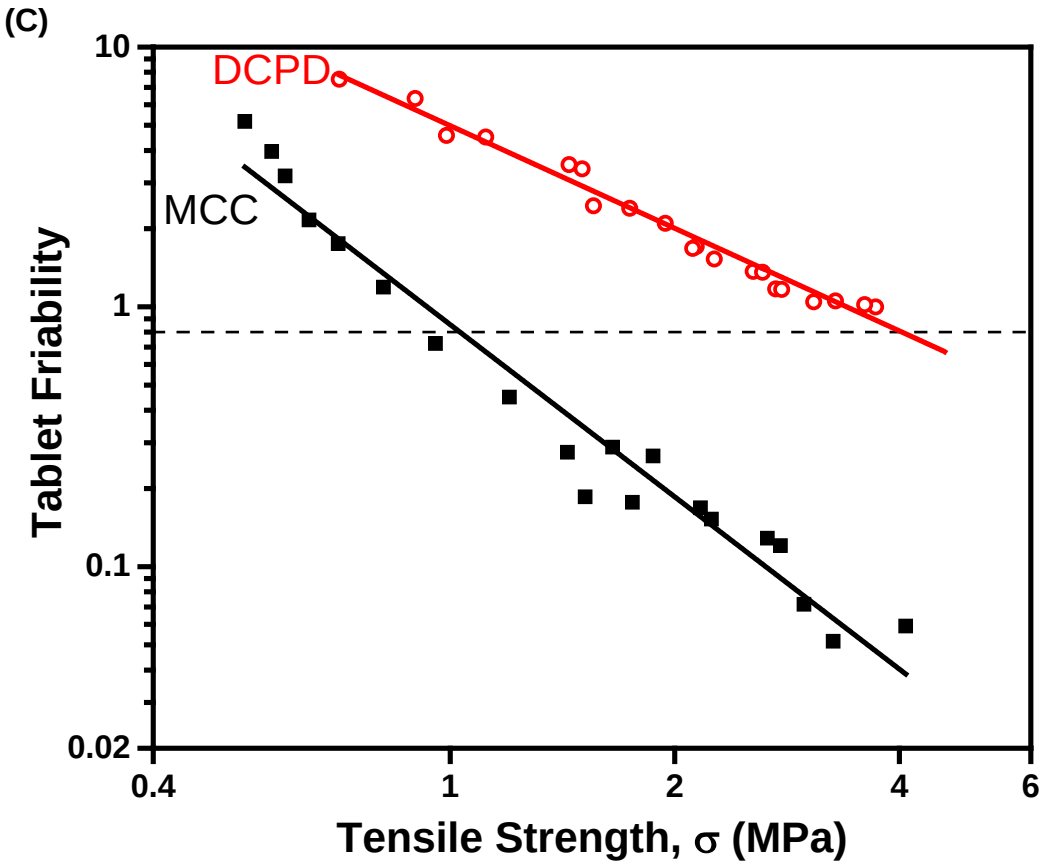
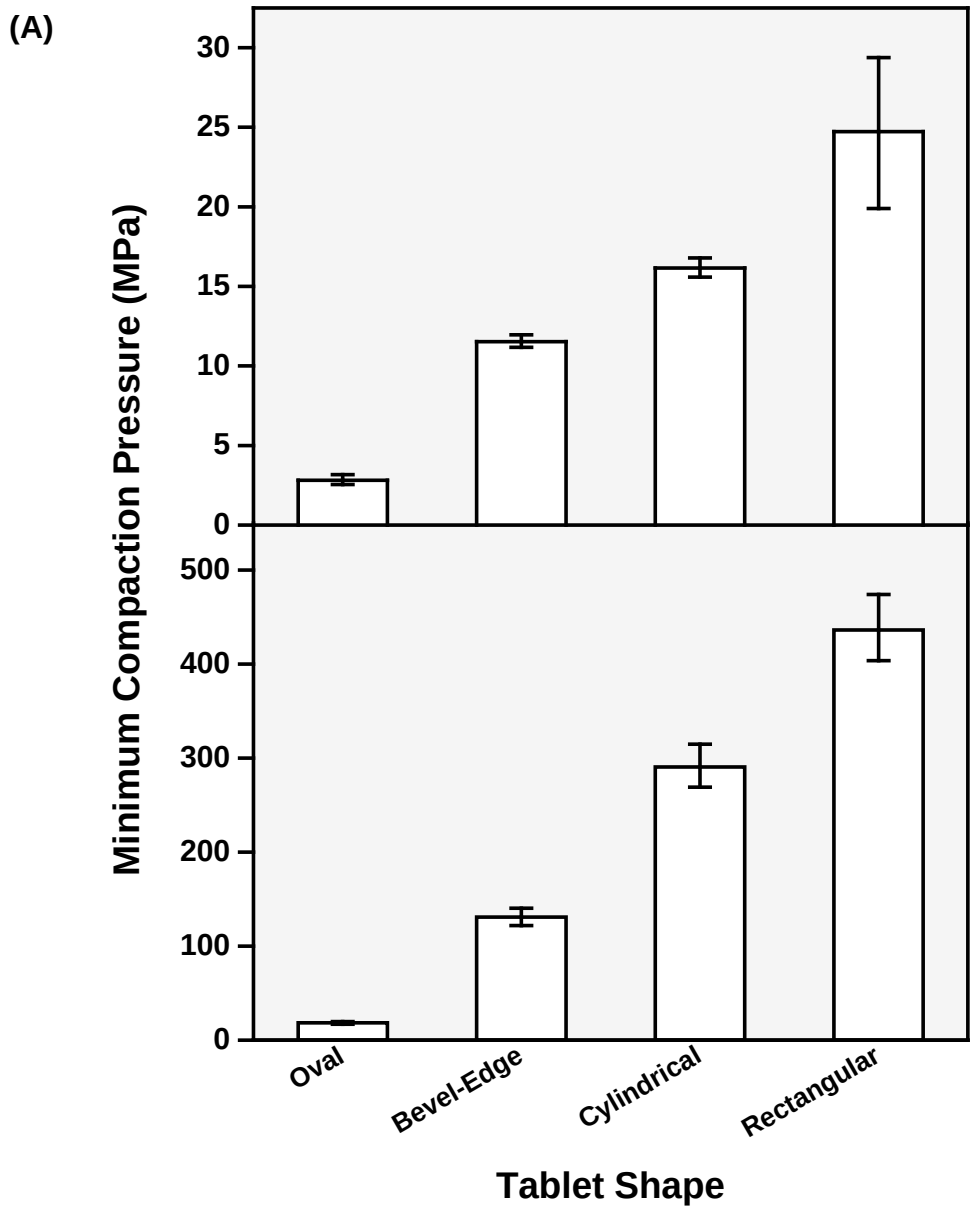

(C)
10
1
0.1
0.02
DCPD
MCC
Tablet Friability
0.4
1
2
4
6
Tensile Strength, σ (MPa)

Figure AI. 3 Effect of (A) tablet shape (tooling type) and (B) tablet size (8 mm and 10 mm cylindrical tablets) on the minimum compaction pressure required to achieve 0.8% tablet friability for MCC (0.92 g/mL tablet density) and DCPD (1.88 g/mL tablet density); error bars indicate 95% confidence intervals of predicted values.



(B)

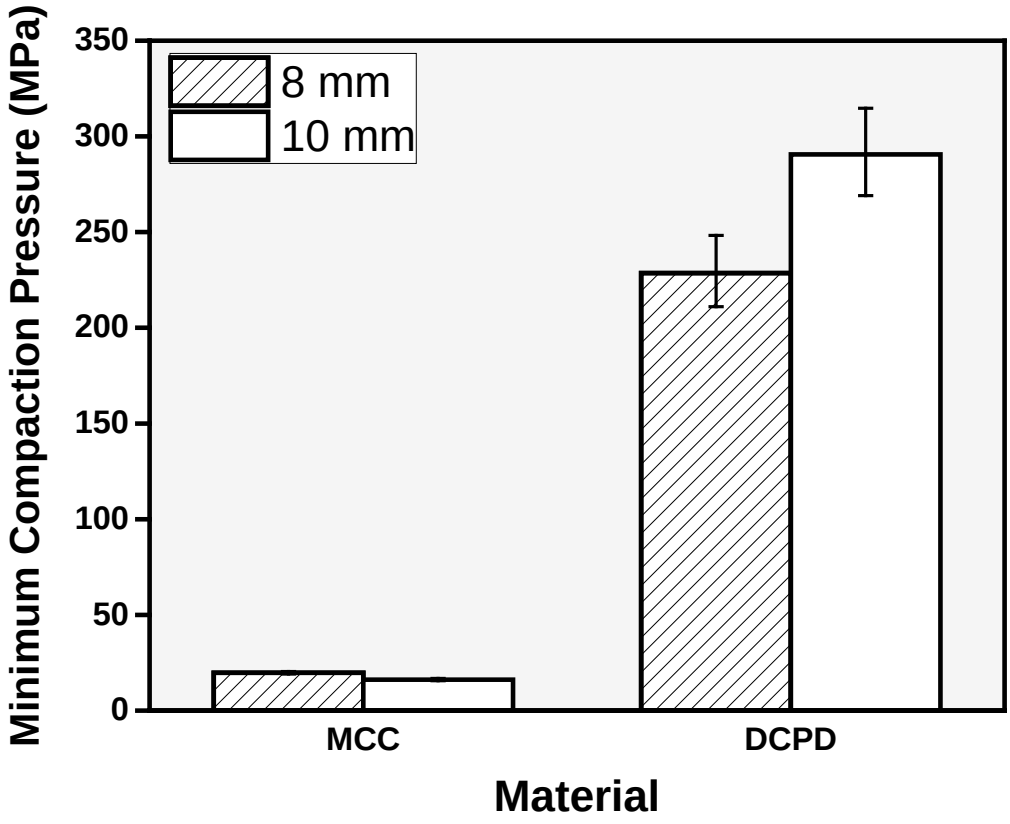
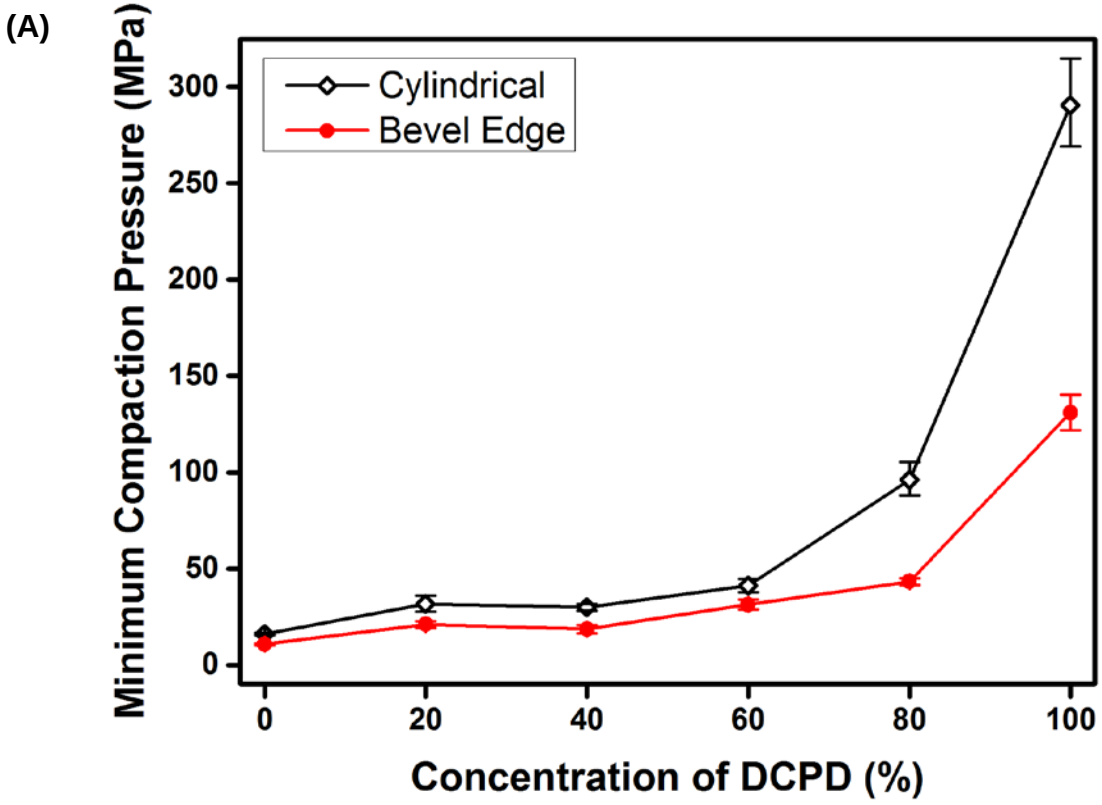

Minimum Compaction Pressure (MPa)
350
300
250
200
150
100
50
0
8 mm
10 mm
MCC
DCPD
Material

Figure AI. 4 Effect of powder composition in the MCC-DCPD binary mixtures on the (A) minimum compaction pressure using two types of tooling and (B) minimum tensile strength using cylindrical tablets (error bars indicate 95% confidence intervals of predicted values)



(B)

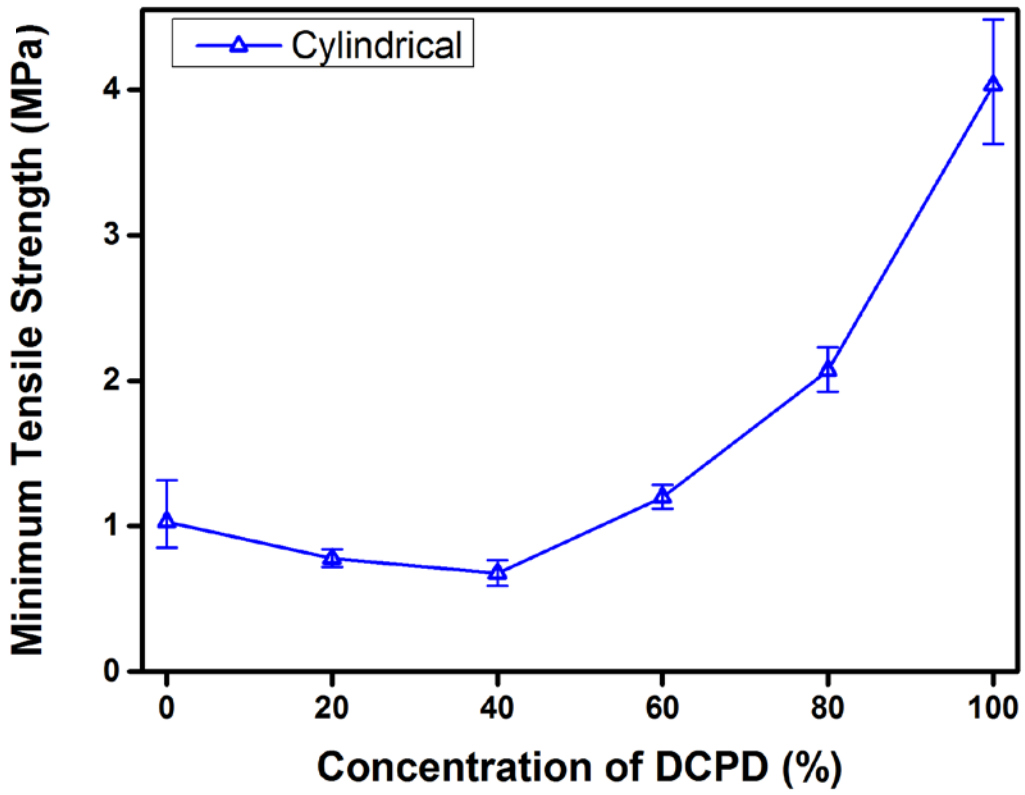

Cylindrical
Minimum Tensile Strength (MPa)
0
1
2
3
4
0
20
40
60
80
100
Concentration of DCPD (%)

Figure AI. 5 Friability Plots of Acetaminophen (APAP) and Celecoxib (CEL) formulations (10 mm cylindrical tablets), showing correlation between friability (a tablet performance) and (A) compaction pressure (a process parameter) (B) porosity (a tablet structure descriptor), and (C) tensile strength (a tablet property)

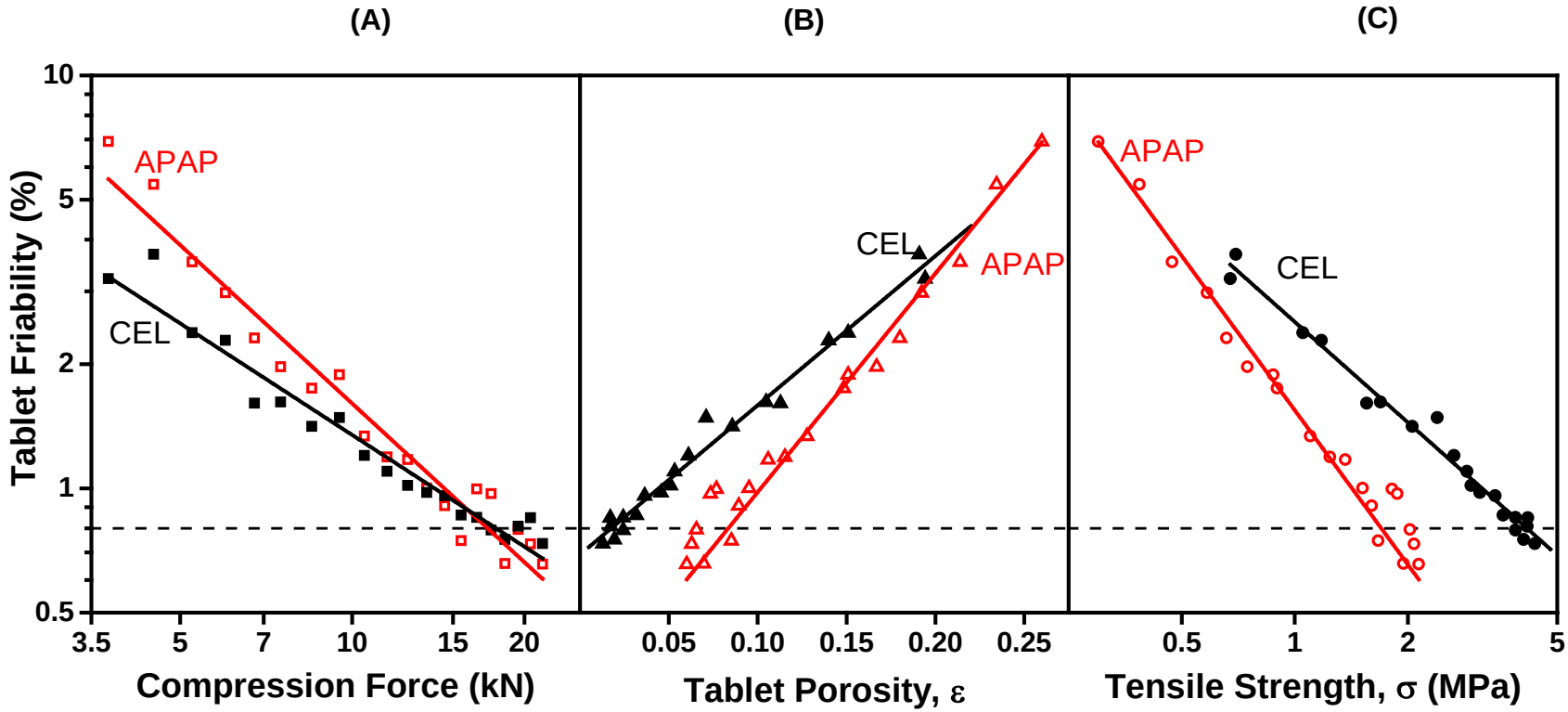


Figure AI. 6 Determination of compression force at a higher speed for producing tablets of Celecoxib formulation (500 mg round bevel edged) that meet the friability criterion of 0.8%. (A) friability plot at 1 mm/min compression speed, (B) manufacturability profile at 100 mm/min compression speed. 95% confidence interval of each fitted line is shaded (B.F. = breaking force).

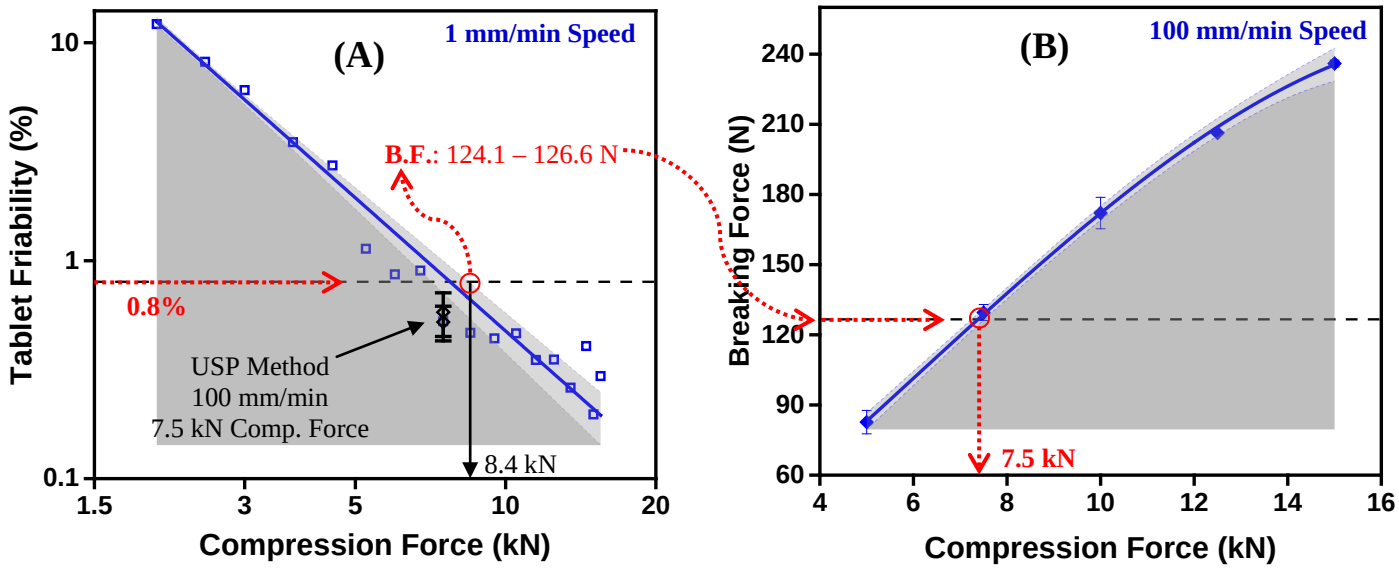


Figure AI. 7 Steps for scaling up tablet production based on friability as performance criterion. Use the upper confidence interval of the compression force as margin of safety if possible. Breaking force is specific to tooling and tablet weight

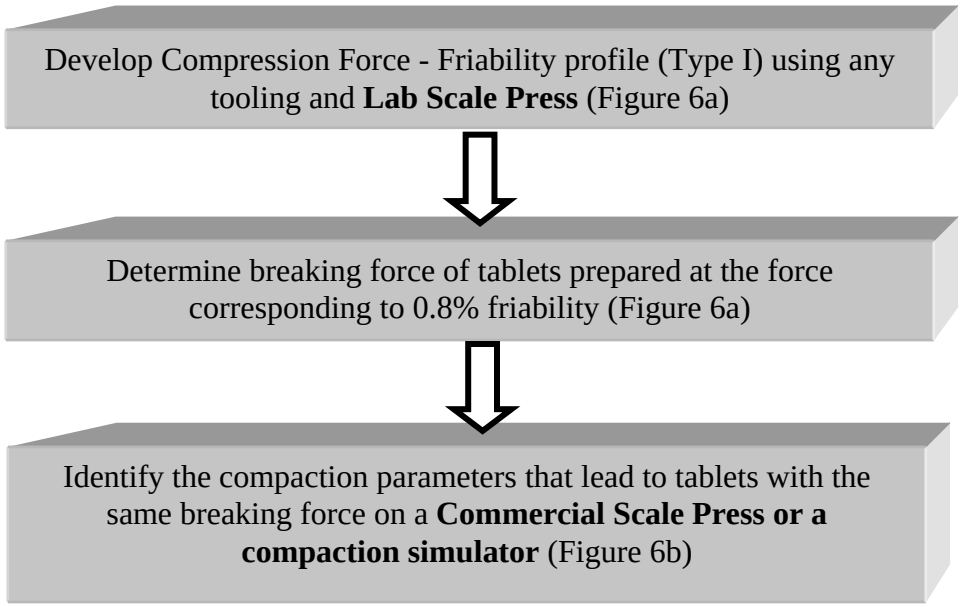


Figure AI.S 1 Prototype tensile strength – porosity (compactibility) profile for calculating tensile strength of tablets used for friability test

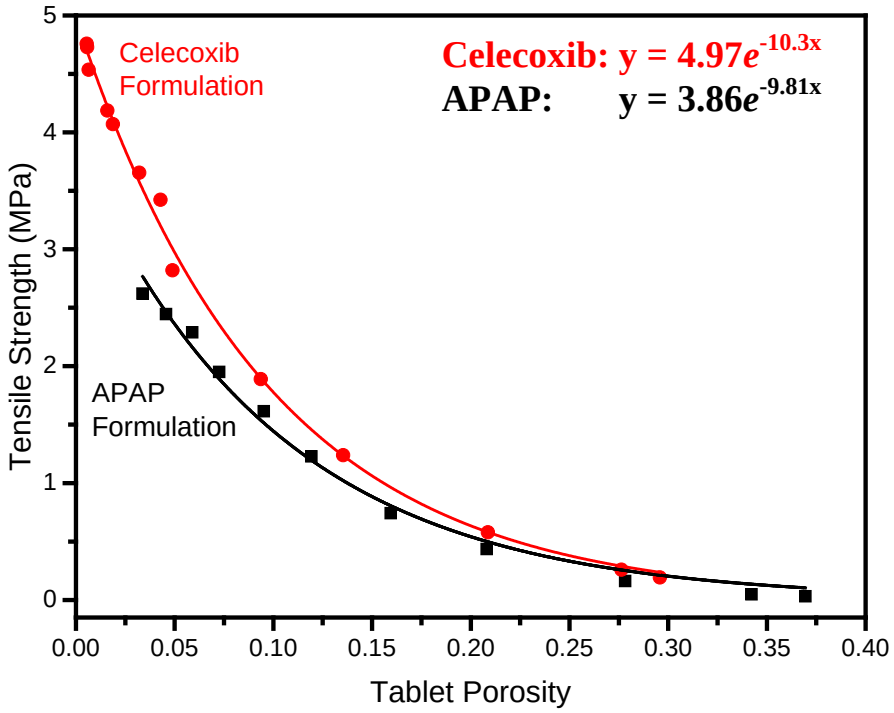


Table AI.S 1 Description of tablets and toolings

Test Method	Material	Tooling	Press Speed (mm/min)	Target Tablet Weight (mg)	Diameter or Dimension (mm)
USP	MCC	Cylindrical Flat Face	100	400	10
Expedited	MCC	Cylindrical Flat Face	100	400	10
Expedited	MCC	Cylindrical Flat Face	100	200	8
Expedited	MCC	Round Bevel Edged	100	400	10.32
Expedited	MCC	Oval Convex*	100	600	8.7 x 13.9
Expedited	MCC	Rectangular Flat Face	100	650	9.57 x 16.54
USP	DCPD	Cylindrical Flat Face	100	650	10
Expedited	DCPD	Cylindrical Flat Face	100	650	10
Expedited	DCPD	Cylindrical Flat Face	100	400	8
Expedited	DCPD	Round Bevel Edged	100	650	10.32
Expedited	DCPD	Oval Convex*	100	1000	8.7 x 13.9
Expedited	DCPD	Rectangular Flat Face	100	1000	9.57 x 16.54
Expedited	MCC 80% DCPD 20%	Cylindrical Flat Face	100	400	10
Expedited	MCC 60% DCPD 40%	Cylindrical Flat Face	100	440	10
Expedited	MCC 40% DCPD 60%	Cylindrical Flat Face	100	520	10
Expedited	MCC 20% DCPD 80%	Cylindrical Flat Face	100	560	10
Expedited	MCC 80% DCPD 20%	Round Bevel Edged	100	400	10.32

Test Method	Material	Tooling	Press Speed (mm/min)	Target Tablet Weight (mg)	Diameter or Dimension (mm)
Expedited	MCC 60% DCPD 40%	Round Bevel Edged	100	440	10.32
Expedited	MCC 20% DCPD 80%	Round Bevel Edged	100	560	10.32
Expedited	APAP Formulation	Cylindrical Flat Face	100	500	10
Expedited	Celecoxib Formulation	Cylindrical Flat Face	100	500	10
Expedited	Celecoxib Formulation	Round Bevel Edged	1	500	10.32
USP	Celecoxib Formulation	Round Bevel Edged	100	500	10.32

* 1.57 mm cup depth for oval convex

APPENDIX II. A PITFALL IN POWDER COMPACTIBILITY DATA FITTING USING NON-LINEAR REGRESSION

Appendix II has been published as a lesson learned in the Journal of Pharmaceutical Sciences, 2013, 102: 1135 – 1136

Tablet tensile strength has been observed to decay exponentially with porosity, a relationship that is described by the empirical Ryshkewitch-Duckworth equation (*Equation AII.1*).[1]

$$\sigma = \sigma_o e^{-b\varepsilon} \qquad \textit{AII.1}$$

where ε is the tablet porosity, σ is the tablet tensile strength, *b* and σ_o are constants. The constant σ_o is the maximum tensile strength a powder can attain, at zero porosity, and may be used to quantify the bonding propensity of a powder. *Equation AII.1* has been routinely used to describe the compactibility of a powder (dependence of tablet tensile strength on tablet porosity). Since powder compactibility is relatively independent of tableting speed,[2] it is useful in guiding the scale up of a tableting process where tableting speed usually increases significantly.

The constants *b* and σ_o are commonly obtained by fitting experimental tensile strength – porosity data to *Equation AII.1*. Subsequently, tablet tensile strength at a porosity that is experimentally inaccessible may be predicted based on the fitted function. For example, some powders are difficult to be compressed into low porosity tablet under common compaction pressures because of their high hardness or elasticity. Other powders do not form intact tablet at high pressures because of over-compaction.

For routine non-linear fitting of data using *Equation AII.1*, Microsoft Excel® is commonly used because of its wide availability and familiarity by researchers. However, we recently encountered a case of unusually poor fitting of compactibility data of microcrystalline cellulose (MCC, Avicel PH102, FMC Biopolymer, Philadelphia, PA) and some of its mixtures with dicalcium phosphate dihydrate (DCPD, JRS Pharma, Cedar Rapids, IA). A visual inspection of the fitting suggests that both σ_o and *b* were overestimated when MCC is the major component in a mixture (up to 60% MCC) (Figure AII.1). There are two possible reasons to this problem: 1) *Equation AII.1* is invalid for these powders, and 2) non-linear regression is not appropriately carried out. Since we are not aware of similar observation in the open literature, we examine the second possibility before questioning the validity of *Equation AII.1*.

During non-linear regression, the best fit function is obtained by systematically varying the values of σ_o and *b* until the residuals sum of squares (RSS) between the experimental data and predicted values reaches a global minimum, which yields the best fitting function. However, it sometimes happens that the iteration process falls into a local RSS minimum. In that case, the function does not correspond to the global best fit and poor fitting results.[3] A good way to address this issue is to re-start the iteration process with a different set of initial parameters to avoid the local minima so that the global minimum can be reached.[3] This is done in this work using a statistical software, Origin labs (Origin® 8.0, OriginLab Corp. Northampton, MA), which allows the user input of initial

parameters for non-linear fitting. By using user-defined initial values for fitting, we obtain satisfactory fitting using Eqn. 1 to all data using Origin (Figure AII.2). This result suggests that *Equation AII.1* remains valid for these powders. Besides the flexibility in initial values, the Origin software also yields estimated errors to each of the fitted parameters.

When the σ_o and b values yielded by Excel are used as the initial values in the Origin fitting, functions essentially the same as those by Excel are obtained. This confirms that the observed poor fitting with Excel is indeed a problem with data fitting not the equation itself. Since mechanical properties of this series of powders (MCC, DCPD, and their binary mixtures) span a wide range, *Equation AII.1* is likely broadly applicable to other pharmaceutical powders.

The lesson learned is that, when performing non-linear fitting, one should critically assess the goodness of fitting of the resultant function to data points, perhaps through both visual observation and a residuals plot. Learning how to use powerful statistics software is a worthy investment of time for a bench researcher. The Ryshkewitch-Duckworth equation satisfactorily describes compactibility of powders with very different mechanical properties.

References

1. Ryshkewitch E 1953. Compression strength of porous sintered alumina and zirconia. J Am Ceram Soc 36:65-68.

2. Tye CK, Sun CC, Amidon GE 2005. Evaluation of the effects of tableting speed on the relationships between compaction pressure, tablet tensile strength, and tablet solid fraction. J Pharm Sci 94:465-472.

3. Weisberg S. 2005. Applied linear regression. 3rd ed.: John Wiley & Sons.

Figure AII. 1 Non-linear regression of compactibility plot of microcrystalline cellulose to Eqn. 1 by Microsoft Excel®

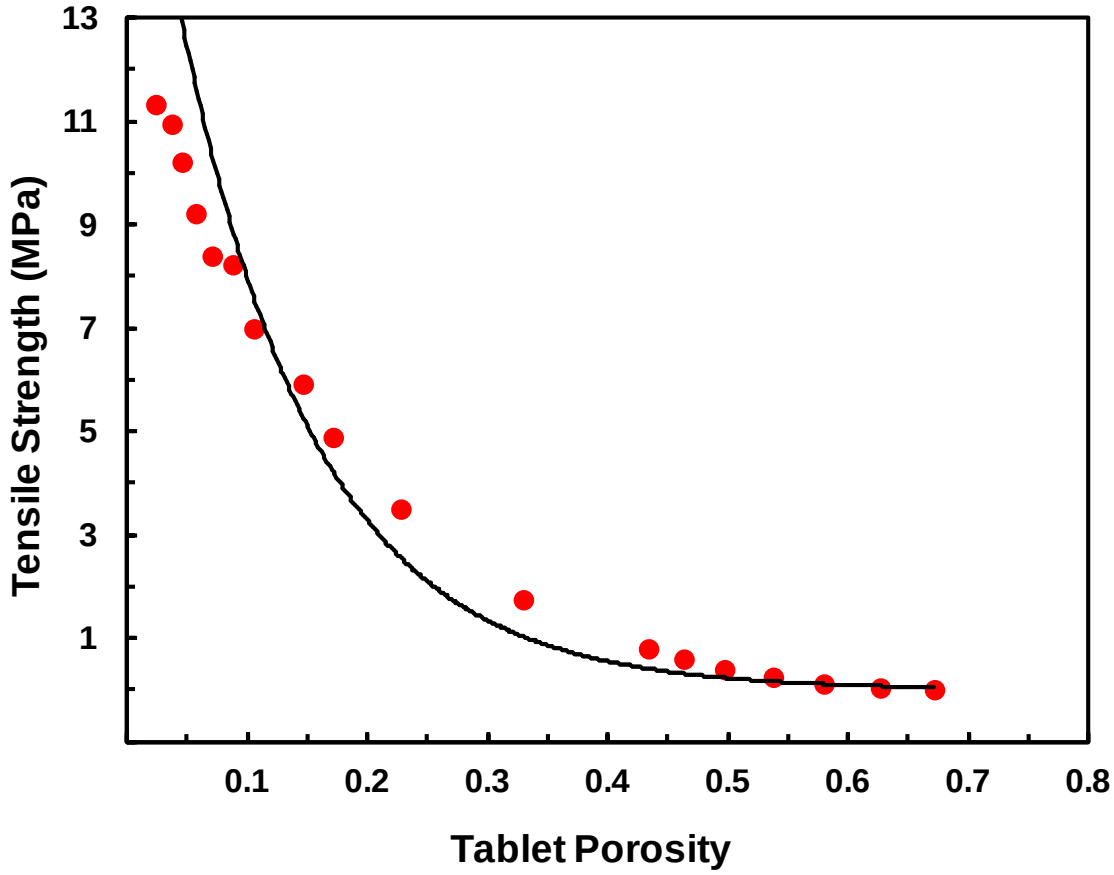


Figure AII. 2 Non-linear regression of compactibility plot of microcrystalline cellulose to Equation AII.1 by Origin Lab®