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EDITORIAL

Crystal and Particle Engineering – An Indispensable Tool for Developing and Manufacturing Quality Pharmaceutical Products

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Design and manufacture of high-quality pharmaceutical products remains challenging due to the inherent complexities arising, in part, from multitudes of components in particulate forms, each having different functionality and potential for unwanted interactions during processing, storage, handling, or administration. Hence, it follows that particles and crystals play an essential role in pharmaceutical manufacturing. Successful manufacturing and quality of finished pharmaceutical products, even if the final dosage form may not be a solid, critically depend on powder properties, such as flowability, tabletability, wettability, and solubility. These powder properties, in turn, are controlled by the properties of constituting particles or crystals of active pharmaceutical ingredients (API) and excipients, such as size, size distribution, shape, porosity, mechanical properties, surface energy, and surface roughness [1, 2]. Hence, appropriate engineering of crystals or particles through various processes, such as crystallization, granulation (dry, wet, fluid bed), hot-melt extrusion, spray-drying, and dry coating, is necessary for the purpose of overcoming problems in pharmaceutical manufacturing. Thus, engineering pharmaceutical materials at particle level is an important step in solving many problems in pharmaceutical manufacturing. In summary, the interrelationships among structure, property, performance, and processing, succinctly captured through materials science tetrahedron (MST) [1], could guide research in understanding the performance of materials, molecular origin of certain properties, and engineering solutions to manufacturing problems.

The importance of seamlessly integrating materials sciences and engineering to overcome pharmaceutical manufacturing problems and to enhance the quality of pharmaceutical products has been recognized and adopted by the scientific community. Further progress in this direction requires focused, cross-disciplinary efforts towards developing predictive and materials-sparing techniques and tools to aid scientific product design and manufacturing decision, while leveraging data-driven empirical approaches. Towards that objective, the authors have recently established NSF Center for Integrated Materials Science and Engineering of Pharmaceutical Products (CIMSEPP). The CIMSEPP mission concerns [1] advancing predictive property enhancements in powders, blends and their compressed tablets through particle and crystal engineering, [2] enabling digital product design and manufacturing of high-quality, low-cost, and smaller tablet products, and [3] developing process understanding that facilitates successful scale up.

This special issue on Pharmaceutical Particle and Crystal Engineering is intended to reach prominent researchers engaged in synergistic activities, including the application of MST in pharmaceutical sciences, with an emphasis on particle and crystal engineering. This collection of papers are contributed by recognized experts from industry and academia, representing 5 countries. They cover both fundamental materials science and engineering topics, in three key categories; (1) crystal and particle engineering, (2) structure-property-performance understanding and enhancement of mechanical and physicochemical properties of crystals, and (3) processing and understanding of various industry relevant processes to attain improved manufacturability and performance of API, their blends, and dosage forms, at very low or high drug loadings. These contributions, often covering more than one of these three areas, are briefly summarized below.

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Crystal and Particle Engineering

Chang and Chan reviewed recent advancements in inhalation delivery of small molecules and biotherapeutics using particle engineering [3]. They detailed how physical and particulate properties, such as particle size, morphology and density, as well as chemical properties, can significantly impact aerosol performance of the powder. They further discussed critical particle attributes that can be engineered to enhance the dispersibility of inhalation powder formulations. Challenges in particle engineering for biotherapeutics formulation strategies for overcoming the hurdles were summarized. This contribution provides useful guidance to researchers that are tasked to develop a robust inhalation formulation and manufacturing process.

Ibrahim *et al*. described a workflow that can be used to predict the mechanical deformation properties of organic crystals from their crystal structures [4]. In their approach, type of intermolecular interactions, crystal morphology, and surface chemistry are modelled using force fields, which is combined with the analysis of lattice deformation using a statistical approach. The most likely slip planes are identified by considering the interaction strength and plane surface rugosity and surface energy. Then, the likely slip direction of slip planes is identified based on unit cell geometry. Finally, potential cleavage planes are identified from assessing intermolecular bonding anisotropy. The distinct deformation behaviors of pentaerythritol and its tetranitrate salt were successfully predicted using their approach. By introducing a systematic work flow, this work is an important step forward in the quest for reliable computational predictions of mechanical properties of pharmaceutical crystals.

Kim *et al*. considered several fine cohesive powders of poorly water-soluble API and examined interrelationships between dissolution and their particulate properties, such as cohesion, flowability, packing, and agglomeration [5]. They captured various particle-scale properties via dimensionless granular Bond number (Bo_g), defined as the ratio of cohesive forces to gravitational force. Their experimental approach, coupled with the available particle contact models, demonstrated that dry coating with either hydrophobic or hydrophilic nano-silica could lead to enhanced API processability. Specifically, flowability was improved by up to four flow regimes, bulk density was increased by up to 100%, cohesion and agglomeration were reduced by 1–2 orders of magnitude, and the area under the curve (AUC) of dissolution profile was enhanced by up to 60% even with hydrophobic silica coating. They demonstrated that the reduction in powder agglomeration ratio (AR), defined as the ratio of dry powder agglomerate size over primary particle size, due to dry coating with hydrophobic silica leads to enhanced dissolution rates despite the potentially higher surface hydrophobicity. The most important contribution of the paper is identifying the AR as a material sparing, early screening indicator of all key processability attributes, such as flow function coefficient (FFC), bulk density (BD), cohesion, and dissolution. They showed that both FFC and BD are correlated with Bo_g and AR is a power-law function of Bo_g. Hence, AR could be an easy empirical indicator of FFC, BD, and dissolution. In addition, they pointed out that the determination of the API surface roughness is critical since it has a significant impact on all key properties, and one cannot make the traditional assumption regarding the natural asperity size. Their findings simplifies the task for industry practioners, who could predict comparative performance of various batches of API powders by simply measuring their AR.

Wang and Sun explored the structural origins of the observation that a hydrate is usually more plastic than its anhydrous counterpart [6]. They showed that, in the five anhydrate/hydrate pairs examined, plasticization by crystal hydration is always accompanied by the introduction of facile slip planes, lower density, and lower molecule packing efficiency. They further showed that three different mechanisms are responsible for the generation of facile slip planes in different hydrates. Such structural understanding lays a foundation for effectively modify mechanical properties of APIs through crystal engineering. This is important particularly for APIs that need to be micronized or tableted as mechanical properties play a major role in both processes.

Structure–Property-Performance Understanding and Enhancement

Hansen and Kleinebuddde explored the role of polymeric stabilizer in a spherical crystallization process, i.e., quasi emulsion solvent diffusion (QESD) crystallizations [7]. Given the importance of solution viscosity on emulsion drop size, they showed that screening different polymers at a similar dynamic viscosity of polymer solution instead of the same polymer concentration is a more effective approach. The important role of solution viscosity on controlling quasi emulsion drop size and, therefore, size of spherical agglomerates, was further supported by the observation that similar agglomerate size could be obtained by keeping solution viscosity constant when HPMC of different molecular weights were used. Moreover, they showed that whether the polymers is present in the solvent or antisolvent phase affects the outcome of spherical crystallization. Their work shows the possibility and importance of modifying microstructures of particles through controlling process parameters during QESD.

Jia *et al*. investigated the interrelationships among microstructure, properties, and drug dissolution performance of amorphous solid dispersions (ASD) prepared by two distinct

processes, i.e., coprecipitation and spray-drying [8]. In addition to conventional techniques, they utilized X-ray microscopy (XRM) to characterize different ASD batches, which revealed a strong relationship between the total solid external surface area normalized by total solid volume and micro dissolution rate. The analysis of XRM data was facilitated by using an AI model trained to recognize the unique textural patterns using a set of results by a skilled analyst. This work highlights the effectiveness of investigating important pharmaceutical performance problems using the MST approach, which is facilitated by the use of powerful analytical tools for quantitatively describe material structure.

Kim *et al*. leveraged the advantages of reduced powder cohesion and agglomeration due to dry coating for the purpose of augmenting the design space for direct compression (DC) tableting at very low drug loading of cohesive fine APIs [9]. Their work elucidated the synergistic structural changes in the blend properties, arising from the silica transfer induced by mixing dynamics, and their impact on the performance of the tablets. It was demonstrated that even at a very low API loading, amounting to an extremely low silica fraction in the blend, dry coating of the API greatly influenced the flowability of multi-component blends having all fine sized excipients. It is important to note that without dry coating, the blend flowability was poor [9]. The analysis of surface hydrophobicity and agglomerate reduction for various coating formulations that included hydrophobic or hydrophobic silica, confirmed the significant role that API agglomeration (or lack of it) could play on tablet dissolution, negating even the adverse impact of increased drug hydrophobicity with R972P coating. This work furthers the potentially new paradigm focusing on the agglomeration as a key attribute dictating the properties of fine powders and their blends, where the reduced agglomeration by dry coating could have positive and synergistic impact on drug product performance, including the blend uniformity, dissolution, and overall processability through just a minute (e.g., 0.01 wt % of the blend) amount of silica.

Processing and Process Understanding

Capece and Larson paper is an example of employing process understanding to not only enhance the process effectiveness but also facilitate the translation from lab-scale to larger scale of a continuous and property enhancing dry powder coating process [10]. The paper considered examination of mean residence time (MRT) of the powder as an important factor, which is well-known in chemical and process engineering. MRT was previously shown as the main performance parameter that allowed selecting the optimal processing conditions, including the screen opening via screen blocking, screen hole size, the impeller speed, and powder feed rate [11]. Longer MRTs were attained either via pre-blending of the host powder with nano-silica [12] or by running multiple comilling passes [13, 14]. Capece and Larson paper demonstrated that for pre-blended host and silica powders, in comparison to the screens provided by the comill manufacturer, the partial blocking of screen holes increased mean residence time of the process and enhanced the flowability and bulk density of Avicel PH105, a cohesive fine grade of microcrystalline cellulose. Overall, this important work paves the way to broader use of dry coating in industrial setting. More research is necessary to examine if this approach is viable for fine APIs, which are more friable than Avicel PH105, and if a prolonged MRT via screen blocking could lead to excessive heat generation.

Chen *et al*. compared two different approaches to API milling and reinforced the importance of particle-scale properties, such as the particle size, particle size distribution (PSD), and particle morphology [15]. They considered an important topic of improving the manufacturability of cohesive and poorly compactable API for direct compression of mini-tablets at high drug loading. As is typical with dry API milling methods, hammer milled API powders were shown to have wider PSD and presence of many fines, including those attached to the larger particle surfaces, resulting in very rough surfaces. In contrast, the wet milling coupled with a thermocycling process, with a goal of API surface engineering, led to smoother API surface and narrower PSD without the presence of fines, resulting in better flow properties. Consequently, the mini-tablets produced with the wet milled APIs exhibited better weight uniformity, robust tablet mechanical strength, and ultimately better friability. Overall, their work indicates that if well-designed, wet-milling could be a good option to address the poor flow and processability of dry milled API, which usually has wider PSDs and the presence of fines and higher surface roughness.

Frank *et al*. considered enhancing downstream processability via co-precipitation for the formulation of compounds with poor solubility and demonstrated that high-shear conditions during co-precipitation produced a dispersion with increased bulk density without increased risk of crystallinity [16]. They also employed an antisolvent wash to produce amorphous dispersions amenable to delivery in suspension formulations as well as with improved mechanical properties and flowability to enable direct compression. The enhanced bulk density of co-precipitated material, as compared with the spray-dried counterparts, was likely due to the larger size of the powder product, which adversely impacted dissolution, as expected.

Goh *et al*. developed a new laboratory scale test rig to simulate agitated filter bed drying (AFBD) that could be used in a FT4 powder rheometer [17]. The intent was to capture the essential features of an industrial-scale agitated filter bed dryer, capable of filtration, programmable

axial and radial mixing, temperature and humidity control, vacuum and nitrogen purge, impeller blade customization, and process monitoring via built-in sensors for torque, temperature, pressure, and humidity. They examined the breakage patterns of carbamazepine dihydrate crystals having elongated platy morphology via optical image processing and analysis. They showed that the shift in particle size and shape follows typical self-similarity patterns as a function of the impeller-base clearance, and not necessarily the impeller tip for a given number of impeller rotations/revolutions. In addition, the mechanical energy expended by the impeller correlated well with the extent of particle breakage. Their work potentially offers a laboratory-scale instrument as a tool for comparative assessment of the propensity of particle attrition under agitated filter bed drying conditions.

Nakapraves et al. reported the development and application of machine-learning (ML) models to crystal engineering with an objective of predicting the crystal shape of mefenamic acid (MFA) recrystallized from organic solvents [18]. They considered several Molecular Operating Environment (MOE) descriptors, for example, atomic polarizabilities of all bonded atoms, log of the aqueous solubility, area of van der Waals surface, as main features for their ML algorithm. Several hundred experimental observations of MFA crystal shape in 30 different organic solvents at the range of supersaturation levels between S = 1.0 – 3.0 were then used as training data to reduce the feature set through random forest classification models. They showed that the ML approach allowed for selecting the best features and, as an example, reducing the feature set to only solvent physical property descriptors and supersaturations resulted in higher overall prediction accuracies than the models using atom count, bond count, and pharmacophore descriptors and the models using all solvent molecular descriptors. This paper offers an interesting approach to developing ML-based data-driven models when development of first-principle based models is not possible or too complex. Although the paper only considered one API, the ML approach could be broadened to cover a wider range of API molecular and crystal attributes, which are often collected during physical form selection, solubility assessment, and early development studies. Schmidt *et al*. employed an advanced regression model, based on an ensemble machine learning (ML) model, to predict median spray-dried particle size from formulation and process parameters [19]. Such a model is likely applicable across a diverse range of APIs, formulations, scales, and process conditions. The constructed model is expected to enable better understanding of how variations in the process parameters for a given API and formulation will affect the dried particle size. The developed optimization strategy could also allow for incorporating subject matter expertise to reduce the amount of experimental effort. It is expected that such models along with incorporation of available mechanistic understanding of the spray drying process, could help further reduce the amount of experimentation required.

Thakore *et al*. used twin-screw melt granulation as a continuous process to enable the development of a high dose tablet by overcoming the problem of poor tabletability [20]. Using acetaminophen and polyvinylpyrrolidone vinyl acetate (PVPVA) as a model system, they showed that high polymer concentration, lower feed rate, lower extruder screw speed, and higher processing temperatures favor granules with better flowability and tabletability. This is another example that shows the intricacy between process parameters and properties of the resulting pharmaceutical granules.

Outlook

Papers in this collection are just a snapshot of a fast developing research area with enormous value to the global healthcare. They showcase important advances, while pointing out the need for further work. In the area of developing better predictive understanding of crystal and particle properties, much work remains to be done. For crystal engineering, notwithstanding the challenges posed by the complex nature of molecular conformations, there is a need to go beyond calculation of attachment energy or visualizations. Despite recent developments, computational models that can accurately calculate intermolecular interaction strength and energy quickly remains a critical challenge to propel the research on the relationship between crystal structures and various pharmaceutical properties. In the area of particle engineering, better mechanistic understanding of the relative contributions of key particle properties, such as the particle size, shape, surface roughness, surface energy, on powder behavior are required. While there is good understanding of the role of the particle size, surface roughness and surface energy [2, 21, 22], understanding the impact of shape of the particle on powder behavior remains poor. Preliminary work indicates that for finer elongated powders having aspect ratios (length over diameter) of about 5 or less, the impact is equivalent to increased surface energy, hence the contact models developed for spherical particles could suffice [23]. However, extensive work may be required to develop better understanding for particles that are needle-shaped or having higher aspect ratios and/or multiple concavities/convexities in their morphology, such as microcrystalline cellulose. Most importantly, since the real powders have wide particle size distributions (PSDs) and cannot be represented by a single size, better models to include the ensemble averaging of the PSD impact on the powder properties, including tabletability, is required. Likewise, for all such problems, mechanistic models and related computational and measurement techniques are

required. For example, numerical and physical estimation of the bonding force between two particles at different normal compressions and the constraints imposed by their neighbors remains a formidable challenge, not to mention accounting for the plastic deformation, friability, etc. In the other two major areas of structure–property-performance and process understanding, there is much to be accomplished considering the complexity brought in by multitude of components and their cross-functionalities and influences. However, it is gratifying to note that various international groups are certainly recognizing the importance of making advances in those areas and have already made promising start, including potential mixing-induced synergistic impacts and identification of cohesive powder agglomeration as a parameter that could influence the final structure and performance. Lastly, most researchers have also recognized the need for refining the data-driven modeling by incorporating various types of ML algorithms, including potential application of multiple approaches to derive more useful algorithms. It is hoped that more researchers will use hybrid approaches that combine mechanistic models along with the ML techniques to significantly reduce the need for excessive experimentation currently needed, which often must be repeated for every new API molecule or even changes to the processing conditions for the same molecule.

We hope this collection will inspire scientists and engineers to carry out and publish many more exciting research. Joint research efforts through research centers that are well-aligned with the needs of the industry sponsors and patient needs, such as CIMSEPP, make us optimistic about seeing transformative research being published in the next 10 years.

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