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Editorial

Materials Engineering of Solid-State Dosage Forms

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Organic crystalline materials play a central role in the pharmaceutical industry as well as in fine chemicals. Physicochemical properties not only affect formulation and production, but also the performance and stability of products. Because the majority of pharmaceutical materials are solid and most of the solid are crystalline, controlling crystal growth and consequent materials properties of drug substances and excipients has become one of essential tasks in the industry, demanding a considerable amount of investment and posing significant challenges for scientists. Crystal size and shape are known to have a great influence on formulation and unit operations including flow, blending, granulation and compaction. Uncontrolled and unpredictable properties may lead to product failure such as content inconsistency (e.g., sub- and super-potency) of solid dosage forms, cited as one of the main reasons for product recall by the FDA, which are often caused by segregation and poor flowability. Furthermore, being unable to identify or select a suitable polymorphic form of a drug makes its products susceptible to phase transformation, and consequently difficult to meet dissolution and bioavailability requirements, likely putting patients' life in jeopardy and throwing a company into a market crisis.

Understanding of crystal growth is critically needed in order to control particulate properties. In spite of vigorous research, our knowledge of nucleation and crystallization is far from being complete; our abilities to predict and control crystal morphology and polymorphism are disappointingly limited. It is widely recognized that solvents or additives can significant affect crystal growth including growth morphology (habit) and polymorphism of organic crystals. For instance, co-solvents have been utilized to control crystal morphology (1). Uncovering the mechanistic role played by solvent in enhancing or inhibiting crystal growth has been evolved in two general thoughts. In one theory, it is suggested that solvent–surface interactions result in the change of interfacial tension, causing so-called surface roughening and variations in growth rate of crystal faces (2). Alternatively, it is proposed that solvent molecules act in a similar way to additives, preferentially adsorbed on specific faces, posing an additional energy barrier for solute molecules to attach to solid surfaces (3). The effect of additives on growth morphology has been extensively examined by Lahav, Leiserowitz and co-workers (4). They demonstrated using "tailor-made" or structurally similar additives to alter crystal morphology. It is postulated that additive molecules adsorb and replace host molecules on crystal surfaces due to similar molecular geometries. Depending on the structural difference between the host and additive molecules, attachment of solute molecules to specific faces may be hindered, leading to a different morphology. Interestingly, one of our earlier studies showed the appearance of a new face of acetaminophen single crystals by using a tailor-made additive, which may not be solely due to the geometry hindrance (5). Nonetheless, the theoretical models that are available for crystal growth morphology prediction are incapable of modeling the solvent or additive effect; a systematic approach considering different growth environments remains being discovered.

Because of the significance of polymorphism in the drug development, a huge amount of experimental observations have been made, stimulating vast interests and discussions about properties, analysis, preparation and manufacture of polymorphic systems of drug crystals. Polymorph screening of a new drug becomes routine, not only because of the requirement by the FDA, but also due to the fact that a different polymorph may give a company an extra edge to extend the patent life and protect the market of a high-profit drug. It is not surprising to see high-throughput crystallization (HTC) developed in the last few years. In fact, a new form of acetaminophen was reported by one HTC company (6). It appears supportive to the often-quoted McCrone's argument that the number of forms discovered is up to the time and resources spent on them (7). Growing different polymorphs of organic crystals in solvents has been widely reported. Few attempts, however, can be found in the literature illustrating the use of additives in nucleation of different forms. Additives do show the potential to stabilize one form over others in a solvent (8). Collective effects by solvent and additive make it difficult to elucidate and design additives to control poly-

morphs. Fueled by recent interests in nanotechnology and supra-molecular chemistry, crystal engineering is attracting tremendous attentions from various fields. It is still embryonic, demanding much more fundamental studies. The current approach based on designing synthons for a specific architecture lies in molecular shape and stereochemistry. Co-crystallization of drug compounds has recently attracted lots of attention due to the potential for improving solubility as well as for extending intellectual properties of drug products (9). In addition, many novel approaches for controlling crystal forms have been reported, including epitaxy (10), self-assembled monolayer (SAM) (11), polymers (12), capillary (13) and even laser (14). A recent study of seeding one form by another is intriguing (15). The paper by Lee, Lee and Myerson in this theme section highlights their recent effort in using SAMs to produce polymorphs of two model drug compounds, mefenamic acid and sulfathiazole. By applying microfabrication techniques, they formed alternating micropatterns on glass substrate with two SAMs of different lyophilic properties on which uniform droplets of drug solutions were formed. Upon evaporation, crystalline particles were developed from the droplets; more interestingly, different polymorphs could appear on the same substrate concomitantly.

The mechanistic understanding of polymorphic formation of organic crystals, however, remains to be a great challenge. Polymorphs of an organic crystal have different energies and thermal stabilities. Theoretical studies have been focused on thermodynamics and kinetics of crystal growth regarding polymorph formation, resulting in development of several widely adopted phenomenological and thermodynamic rules (Ostwald rule, phase rule, density rule, etc.). The role of a solvent has been thought as a kinetic factor that may trap a metastable form of a crystal due to its higher solubility in the solvent. However, why a unique crystal structure is formed in a specific solvent remains unanswered. Furthermore, to predict polymorphic structures is even more challenging. Most of current approaches (16), which try to search the global energy space and identify low-energy crystal structures, face a monumental hurdle in tackling this problem, because the intermolecular interactions in organic crystals are weak and the energy difference between a stable form and a metastable form can be as small as a few kilojoules/mol, or even smaller, beyond the certainty of suitable energy calculation methods. Due to the limitation of energy models such as force field to calculate molecular interactions, limited success has been achieved. Using quantum mechanical methods is out of question at present because computation of the whole energy space is overwhelming. In lieu of searching endless combinations of molecules in the crystalline state, the electronic structure of crystal needs to be studied and the intrinsic electronic property of molecule may provide further insights on the intermolecular interactions and molecular packing in solid state, likely inspiring the development of new prediction methods. The paper by our group in this theme section discusses two polymorphs of indomethacin by electronic calculations and conformational analysis. The unique electronic structure of the molecule as unveiled by density functional theory concepts is likely to account for the conformational flexibility and subsequent polymorphic formation.

Despite crystalline materials being dominant in drug development and manufacturing, amorphous substances are also playing a key role for two reasons. First, the amorphous state may provide desirable properties such as higher dissolution rate than the crystalline counterpart particularly when handling poorly water soluble drugs (17). Compared with crystals, the amorphous state has higher internal energy and higher apparent solubility due to the lacking of the long-range order. Second, unintended amorphous particles may be produced during the manufacturing process, such as milling, resulting in the variation in the manufacturability and subsequent concerns of product quality. Because the amorphous state is thermodynamically unstable, it can transform into a more stable crystalline form. To prevent the phase transformation, amorphous drugs are typically dispersed into a polymer matrix forming a solid solution, called solid dispersion. Mobility of drug molecules is reduced by the interaction between drug molecules and polymers, minimizing the chance of recrystallization of amorphous drugs. Nonetheless, solid dispersion systems may still face stability challenges and, over time, drug molecules may aggregate and crystallize with or without help of temperature oscillation, moisture adsorption, or other conditions under which polymer chains fail to prevent the nucleation and crystal growth. To maintain the amorphous state in solid dispersions has been a huge task. Therefore, understanding the interaction between drug molecules and polymers in solid state requires considerable attentions and investigations. The paper by Konno and Taylor in this theme section offers a fresh glimpse on stabilizing solid dispersions of a drug compound, felodipine, stored at different relative humidities. By measuring the nucleation rate and collecting infrared spectra along with thermal and moisture sorption analyses, it was found that although polymers in the solid dispersions enhanced the water uptake, they were still capable of reducing the nucleation of the amorphous drug.

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TONGLEI LI, PH.D.

He joined the University of Kentucky as assistant professor in July 2002. He obtained his doctoral degree in pharmaceutical sciences in 1999 under Prof. Kinam Park at Purdue University, IN. He then became a visiting assistant professor at the Department of Industrial and Physical Pharmacy at Purdue University, working closely with Profs. Ken Morris and Steve Byrn before his current post. He has published more than 30 peer-reviewed papers and served on the editorial boards of *Pharmaceutical Research* and *Journal of Controlled Release*. He has received the AAPS New Investigator Award, the PhRMA Research Starter Award, the AACP New Investigator Award, and the NSF CAREER Award. His research group is working on the area of solid-state organic chemistry with focus on crystal growth, surface characterization, and electronic structure calculations.

Interview Questions for Dr. Tonglei Li

1. What do you think holds the key to your success as a pharmaceutical scientist?
   – Understanding of fundamental sciences as well as what the pharmaceutical industry needs.
2. What do you consider to be your key research accomplishments?
   – Exploring molecular packing and intermolecular interaction of organic crystals with computational tools and atomic force microscopy.
3. What was the turning point in your career?
   – Beginning as an independent researcher when trying to establish a niche of its own.
4. Who are the individuals who most influenced your research career?
   – Kinam Park, Ken Morris, Steve Byrn, and George Zografi.
5. Pharmaceutical scientists are faced with the dilemma of having to publish in biomedical or basic science journals. Does it mean cutting edge science will not likely be featured in the Pharmaceutical Research?
   – Pharmaceutical Research is still and will be the flagship journal in pharmaceutical sciences, so I believe it will and should disseminate any significant work that is interesting to the whole pharmaceutical field, be it biomedical or fundamental.
6. Where is the field of materials engineering of solid dosage forms going, and how do the articles in the theme section fill the gap?
   – The field is facing pressures from the industry, regulatory agencies and consumers for the drug products to be of high quality and accountability. It will become the reality that every manufacturing step needs to be thoroughly studied and understood. Therefore, particle engineering is playing a more and more important role in the materials engineering of solid dosage forms, requiring comprehensive understanding and control of particle properties. For this purpose, more and more microscopic and molecular techniques will be employed. The three articles in the theme section offer a glimpse of fundamental studies of pharmaceutical solid-state materials, including understanding and control of crystal structure and investigation of molecular interactions of the amorphous state.
7. What are the challenges for materials engineering of solid dosage forms and how can they be overcome?
   – A vast amount of literature exists focusing on the large-scale, phenomenological, and empirical aspects of that solid dosage form development. What is lacking and requires tremendous efforts is the fundamental understanding and control of particle properties. Such efforts can address not only the solubility, dissolution, and bioavailability issues, but the handling and processing difficulties during formulation and manufacturing of solid dosage forms as well.
8. What is the key to developing successful collaborative relationships?
   – Specialty and commitment. Not only is your contribution unique, but you also need to be willing to take a lead at the infant stage and sometimes to put in significant efforts on minor issues like scheduling a meeting and following up on a memo.
9. What is your philosophy of educating graduate students?
   – My advising philosophy is to give students the freedom to explore, allow them to make mistakes, and stimulate their research interests. I value their motivation, creativeness, attention to details and honesty to the greatest.
10. What are the challenges facing the pharmaceutical sciences?
    – Pharmaceutical sciences have always been at the merging point between materials engineering and biomedical research. The balance of the two facets is determined by the funding trend (or lack of funding); for the last decade, more focus has been shifted to biological and clinical studies,

while the pharmaceutical materials science and engineering remain significantly underfunded. As a result, there is an enlarging gap in the graduate education between what the industry needs and what the university can provide. How to fill the gap, I believe, is the biggest challenge facing the pharmaceutical sciences.

11. What is the place for collaboration with industry in academia?
– First of all, there should be more conversations between the industry and academia. Such efforts remain sporadic and unsystematic. Second, the graduate education needs a great participation by the industry. As fewer and fewer faculty members come from industry, many education programs become isolated from the real world. Third, there should be more funding support from the industry. A few consortia currently support some academic research, but the scale of support is limited and a general, systematic mechanism is needed. Finally, a closer working relationship would be greatly beneficial between the industrys inhouse scientists and academic researchers.

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