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Perspective

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Molecules, Materials, Medicines (M3): Linking Molecules to Medicines through Pharmaceutical Material Science

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The first decade and a half of the 21st century has seen an awakening in the pharmaceutical community for increased and focused application of materials science and engineering principles for optimal pharmaceutical performance. The phrase "Molecules, Materials, Medicines (M3)" encapsulates the idea that drugs are a convergence of these three "M-words". Indeed, the authors have been involved in organizing M3 since its inception in 2007.[1] M3 is a conference series designed by influential scientific leaders in pharmaceutical and biotechnological areas, from academia and industry. In this perspective article, we reflect on the genesis of the M3 conference concept and give a brief synopsis of two particular material applications which have been key topics: stable amorphous dispersions and pharmaceutical cocrystals.

The genesis of the M3 conference was the recognition that the above materials science aspects needed a forum. At the national meeting of the Canadian Society for Pharmaceutical Sciences (CSPS) in June 2005, the authors of this article conceived of the M3 conference, which was first held in Reykjavík, Iceland, in May 2007. Subsequent meetings have been organized in Santa Barbara, California (2009) and Banff, Alberta, Canada (2012). The previous meetings of this forum brought together pharmaceutical scientists, chemists, and chemical engineers as well as others interested in the field, who brought fundamentals of materials science, engineering, and modeling/computation into the mix. The forum has fostered discussion of best practices and from it has evolved a community for ongoing dialogue on topics that enhance pharmaceutical material options. The next meeting will be held in Solomon Island, Maryland, in May 2016 as an American Chemical Society (ACS) Perspectives event.

A few different motivations exist for applying materials science-based innovations for pharmaceuticals, and the most common one has been the need for improvement in bioavailability for poorly soluble drug candidates having inadequate dissolution properties in physiologically relevant fluids. For example, oral bioavailability in clinical and (more frequently) preclinical species can be low and variable without an effort in material design to improve exposures. This continues to be a theme that is challenged each year with new candidate molecules. Two key topics that address the above motivation and which have been central in the early M3 meetings are the design of stable amorphous dispersions and crystal form modification, in particular, the development of pharmaceutical cocrystals.[2] Most recently, the M3 forum has considered evolving concepts in the field such as ionic liquids.[3]

Amorphous dispersion is the phase type produced when a crystalline drug, usually having poor aqueous solubility in that state, can be rendered amorphous. The amorphous state lacks long-range order, which is characteristic of crystals, and often has apparent solubility characteristics that are superior to the crystalline state. Critically, the materials science understanding that enables the pharmaceutical scientists to employ the amorphous phase successfully has developed substantially in the past two decades. That a poorly soluble drug in an amorphous dispersion can be maintained in this state in a stable fashion is in significant part due to the scientific dialogue in the M3 meetings.[4] The area of cyclodextrin-based formulations has also been considered within M3.[5] Alternatively, pharmaceutical cocrystals have emerged as a crystalline counterpart to solutions and amorphous dispersions. In this scenario, a poorly soluble compound that lacks attributes to form an ionized form (salt formation) can be rendered in a cocrystal with a pharmaceutically acceptable excipient with improved biopharmaceutical properties over the original crystalline form. The IUcr definition of a cocrystals is a solid consisting of a crystalline single phase material composed of two or more different molecular and/or ionic compounds generally in a stoichiometric ratio which are neither solvates nor simple salts. The cocrystal approach has been considered in pharmaceutics as a general answer to the so-called potency-insolubility conundrum'.[6] It is important to note that both material science approaches (as well as others not mentioned here) are needed as part of the arsenal of pharmaceutical formulation practice. Robust processes are also required to ensure that the selected form and formulation(s) can be made reliably and reproducibly to satisfy regulatory, commercial as well as patient needs.

An early example of how understanding material properties can advance development of a molecule was the absorption deficit faced by Merck with one of its leukotriene biosynthesis inhibitors, MK591.[7] The molecule formed crystalline material with a high melting point and very poor solubility in aqueous media, ~4 μg/mL at room temperature. The crystalline compound exhibited high solubility in PEG 400 (polyethylene glycol), and with the projected relatively low human doses the clinical formulation could be envisaged and prepared as a soft gel capsule formulation containing the drug as a PEG solution. The problem faced by the development group was how to support both the required preclinical evaluation of toxicology for an Investigational New Drug application (so-called IND-enabling tox studies) and ultimately long-term toxicology, including carcinogenicity, since PEG was considered an unsuitable toxicology vehicle in this case.

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Table 1. Materials Design in Translation from Molecule (Chemical Entity; CE) to Medicine

	Low hurdle for attaining performance	**High hurdle** for attaining performance
New CE	DEFENSIVE Innovator discovery of alternative material design options prior to patent expiry of CE	ENABLING Innovator requires significant material design investment prior to registration of CE as a drug
Old CE	PATENT PLAY Similar performance with a new material may create a competitive advantage beyond a generic product	NON-APPROVED CE, RE-INVESTIGATED (?) Good drug candidate may have been abandoned due to (perceived) lack of material options for required performance

The solution to the problem was provided by materials science. The compound could be rendered amorphous and was found to have low molecular mobility reflected in its high glass transition temperature, T_g, ≈ 125 °C. The amorphous material showed high solubility in aqueous media, affording supersaturated solutions in excess of 100 mg/mL, which represents a remarkable increase in solubility that opened up the way to long-term toxicology studies. The following questions had to be answered via techniques of materials science:

1. How stable was the molecule in the amorphous state and under what conditions?
2. What conditions might trigger crystallization?
3. How could the crystalline content in the amorphous substance be measured?
4. How long could we maintain the molecule in solution at the appropriate level of supersaturation?

While these questions may seem routine and trivial to pharmaceutical scientists today, these were not routine problems in the 1980s and early 1990s. Contrary to today's practices, the pharmaceutical industry did not purposefully take amorphous substances into development in that era. The Janssen/J&J group may have been the main exception to this rule with their work on itraconazole amorphous dispersion formulations.[8]

MK591 could be maintained in the amorphous state if protected from heat and moisture. This critical knowledge was gained using X-ray powder diffraction (XRPD), thermal analytical methods, solubility measurements, and well-defined stress conditions of heat and humidity. Room temperature storage and <30% RH were adequate storage conditions to promote long-term physical stability. Water plasticized the molecules and reduced T_g but only well above 50% RH, while temperatures normally encountered in a pharmaceutical laboratory had little or no effect. Using XRPD and doping the amorphous substance with crystalline MK591, a standard curve was created to measure crystalline content in the amorphous material. In this way, a control strategy (e.g., analytical methods, specifications, and other criteria) was enabled, and the amorphous form of MK591 could be employed for preclinical evaluation.[7]

Pharmaceutical cocrystals were proposed in the early 2000s as a way to enable new material options in pharmaceutical practice. The decade and a half in the 21st century has seen multiple examples of utility for this approach. Cocrystals represent drug candidate molecules in crystalline form where the crystal lattice also contains an excipient in well-defined stoichiometry. Cocrystallization is a path to new properties that are distinct from the pure drug. The cocrystal approach is complementary to amorphous dispersions when it comes to improving exposure, as has been exemplified by Vertex Pharmaceuticals in the case of hepatitis C protease inhibitor VX950 (telaprevir).[9] While the amorphous dispersion was chosen for the marketed product, the cocrystal diversity of the drug was explored and published. There is no doubt that this drug would not have been enabled to influence hepatitis C treatment without the efforts in materials science that were expended by the Vertex team.[10]

Another example of a development compound where a cocrystal had a remarkable impact was the AMG-517 cocrystal with sorbic acid.[11] AMG-517 was in development as a pain drug, and the Amgen team identified inadequate solubility and dissolution of the compound, which like telaprevir and MK591 does not have ionizable groups for salt formation. The sorbic acid cocrystal showed dramatic improvements in exposure that enabled the kinds of preclinical exposures to qualify the compound for development. While AMG517 did not advance to Phase 3 trials, it represents a good example of the potential of cocrystal formation for improvement in properties for development candidates. Recently, two late-stage cocrystals have emerged in the public domain. The first is ertugliflozin pyroglutamic acid, which is a 1:1 cocrystal that emerged after crystallization of the pure drug had posed challenges for the development team at Pfizer.[12] Scale-up of the process including cocrystallization was demonstrated.[13] The second compound is an ionic cocrystal of sacubitril (an NCE that inhibits neprilysin) and the well-known angiotensin antagonist valsartan. This unique combination was approved in July 2015 for heart failure, and it includes a single cocrystal of the two actives.[14]

In addition to these and other examples in the public domain, the authors are aware of additional examples waiting to be disclosed. The impact of discovery of useful pharmaceutical materials is felt in development, in terms of

I. enabling certain drug candidates to progress, when in the past they may have stalled,

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II. revealing early enhancements of performance, for a better first-time product,
III. catalyzing speed in development, reducing iterations and reformulation,
IV. contributing to improved process/product understanding, manufacturing improvements,
V. extending life cycle management in the case of new proprietary products.

The innovator industry and generic pharmaceutical companies have both had activities repurposing known drugs at or approaching the point of generic entry following expiry of compound base patents. The approaches used in these cases are both in the areas of crystal form selection and formulation design.

Table 1 represents one view of the intersection between novelty (New Chemical Entity vs Old drug) and the hurdles to attaining improved performance (e.g., improving bioavailability through materials design). This attempt to categorize scenarios applies to innovator and generic interests alike in pharmaceutical materials design, as evidenced by publications and patent applications in the last two decades.

Our view of the future is that pharmaceutical sciences will be applying sound principles of form and formulation discovery in the spirit of M3 as the field evolves in this century. The authors are looking ahead to further developments in the science and application of the dispersion and cocrystal technologies to small and medium (sometimes exceeding 1000 Da molecular weight) drug compounds. In addition, macromolecular impact in the design and characterization of significantly larger and more complex assemblies than small-molecule crystals and amorphous dispersions of water-insoluble drugs with polymers can be envisioned as modeling and characterization capabilities continue to improve. At the present time we conclude that much has been gained in the area of small molecule material design to advance the cause of M3 as a mindset and community. We invite the chemical, crystallography, drug delivery, and materials science community to join the discourse in the spirit of serving the ever-evolving needs of patients for better therapies based on our scientific and engineering capabilities.

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Notes

The authors declare no competing financial interest.

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