Pharmaceutical Materials Science: An Active New Frontier in Materials Research

James Elliott and Bruno Hancock,
Guest Editors

Abstract

The discipline of materials science has most commonly been associated with the study of structural or functional materials for engineering applications, such as metals, ceramics, and composites, but there are now, increasingly, great opportunities involving applications to soft matter, including polymers, powders, and biomaterials. The emerging discipline of pharmaceutical materials science attempts to apply physical principles common in materials science to challenges in such areas as drug delivery, control of drug form, manufacture and processing of nanoscopic and microscopic particle systems, and the structure and properties of bulk powders and their assemblies (e.g., tablets) for use in pharmaceutical applications. In this issue of *MRS Bulletin*, we have attempted to capture a snapshot of this rapidly developing new area of materials research, in order to bring it to the attention of the wider materials science community.

Keywords: *biomedical, crystallization, nanoscale, particle.*

Introduction

The essence of pharmaceutical materials science is the application of fundamental concepts in the physical sciences to the challenges of understanding the behavior of soft, mostly organic, crystalline, and amorphous materials of relevance to the pharmaceutical industry. Like its parent discipline, pharmaceutical materials science is concerned with connecting phenomena occurring on the molecular scale, such as crystallization and polymorphism, to metrics of macroscopic performance, such as hydration rate and mechanical strength, and their consequences for industrial processes such as powder flow or compaction. The relationships between some of the aspects highlighted in this issue are summarized diagrammatically in Figure 1, which shows the progression from crystal engineering of active pharmaceutical ingredients (APIs) through processing and manufacturing of particles and powders into dosage forms such as tablets, culminating with therapeutic action in the patient.

Some key concepts in materials science with direct pharmaceutical application include the design of custom materials with specific physical and chemical properties, the use of theoretical models to predict material performance in biological environments, and the development of novel characterization techniques for nanoscopic and micron-sized particles. For example, a biocompatible polymer may be required that can control the diffusion of a biologically active protein over a 24-hour treatment period. Likewise, it may be necessary to predict how inhaled submicron-sized drug particles are deposited in the airways of the lung without the use of costly and time-consuming *in vitro* and *in vivo* experimental studies.

Background

Although research in pharmaceutical materials science historically has been concentrated in pharmacy departments, the rapid pace of development and highly interdisciplinary nature of the work has meant that it is increasingly becoming delineated as a subject area in its own right, with materials scientists playing a key role in this process. The first documented use of the term "pharmaceutical materials science" that we have been able to locate in the open literature was in a 1991 article by Franks et al.,[1] describing the application of materials science concepts to the production of freeze-dried biological molecules for therapeutic uses. Just five years later, Craig was already contemplating the future of the discipline in a paper entitled "Pharmaceutical Material—Resuscitation or Reincarnation?"[2] so it is clear that this terminology must have been in popular use well before the 1990s.

In fact, scientific articles describing the study of pharmaceutical materials and their unique range of applications and properties have appeared in the chemistry, physics, and pharmaceutical literature for well over a century. One of the first patents on a method for forming tablets by uniaxial die compaction, a process still widely used in the pharmaceutical industry today, was granted in the United Kingdom to William Brockendon in 1843. Smith and co-workers at the Monsanto Chemical Company described an apparatus for testing the hardness and mechanical modulus of pharmaceutical tablets in 1936.[3] Later, in the 1940s, semi-synthetic cellulosic polymers were introduced specifically for use in the manufacture of pharmaceutical dosage forms. However, it was not until the early 1950s that the pharmaceutical industry began to apply principles from metallurgical powder compaction and to analyze powder behavior using concepts such as plastic flow and brittle fracture. At about this time, the discipline of pharmaceutics—in other words, the science of drug delivery—was also making significant strides, driven in large part by the work of Takeru Higuchi and his contemporaries. In 1953, Higuchi reported studies on the influence of electrolytes, pH, and alcohol concentration on the solubilities of acidic drugs,[4] and he went on to publish more than 300 articles that described a wide variety of work that might today be

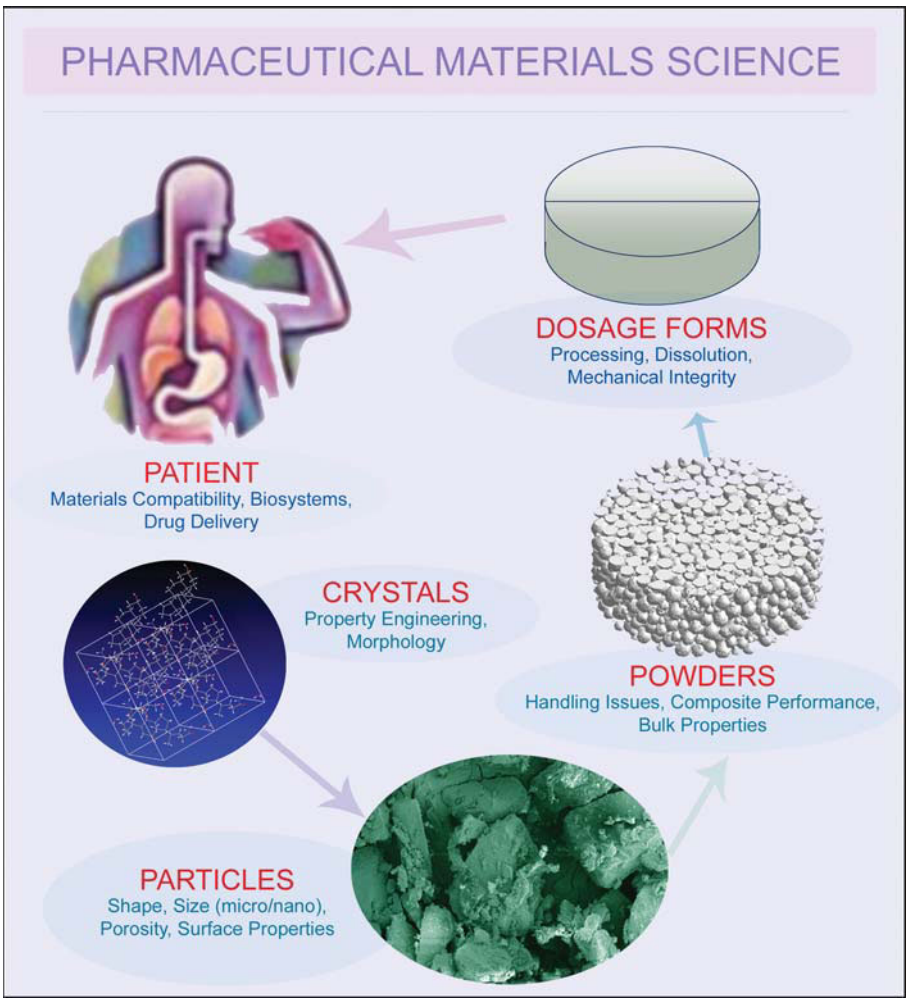

Figure 1. Diagram showing the progression from crystal engineering of active pharmaceutical ingredients through processing and manufacturing of particles and powders into dosage forms such as tablets, culminating with therapeutic action in the patient.

described as the genesis of pharmaceutical materials science. The field steadily grew during the 1960s and 1970s, and the concept of using custom materials for drug delivery applications was popularized by several research groups, notably those of Robert Langer at the Massachusetts Institute of Technology and Nicholas Peppas at Purdue University.

During the past half-century, pharmaceutical materials science has matured considerably, and it is now commonplace for pharmaceutical materials to be studied using state-of-the-art analytical tools that originated in mainstream physical sciences. The structure of APIs and excipients (additives used to enhance the solubility and stability of dosage forms, e.g., tablets, capsules, etc.) is commonly probed at the molecular level using vibrational spectroscopy, thermal analytical methods, and particle scattering techniques to gain insights into their chemical structure, such as crystalline form, and their molecular interactions with coprocessed additives. At a larger scale, the use of fracture mechanics, rheological tools, tomographic imaging, and continuum and discrete element modeling approaches give complementary information on the physical behavior and arrangement of the various material components. The understanding of how these materials perform during manufacturing and in normal use has also advanced considerably, and common engineering and biochemical approaches have achieved widespread acceptance for studying pharmaceutical materials. Despite these advances, there are still many additional exciting opportunities for workers in this field, some of which are highlighted by our contributing authors in this issue of *MRS Bulletin*.

A Growing Field

Whatever the terminology used to describe the study of pharmaceutical materials, it is clear that this field is growing at a faster pace than ever before. It is also clear that there is great potential for further growth with the advent of new approaches for designing and fabricating biocompatible materials and the significant advances that have been made in experimental and computational chemistry, physics, and biology in the past few years. These advances have enabled the previously unrelated fields of computational chemistry, physics, and biology to be combined to create many new opportunities for focusing on materials relevant to pharmaceutical industries at the molecular and supramolecular levels. This situation provides many new avenues for the traditional materials scientist to explore. Novel pharmaceutical applications are being found every day for existing materials and characterization techniques, while whole classes of new therapeutic materials with unique properties are being created each year.

Excellence in pharmaceutical materials science clearly has both a high human value and a high economic value, and it has become a significant driving force in the global economy of the 21st century. Several national centers have been established in the Americas, Europe, and Asia to focus solely on this area of research: for example, the Pfizer Institute for Pharmaceutical Materials Science in Cambridge (U.K.), the Center for Pharmaceutical Processing Research (Indiana, U.S.), and the Institute for Pharmaceutical Innovation in Bradford (U.K.). Numerous specialized research groups have also developed, such as those at MIT, Rutgers University, and the University of Texas, to name but a few. For the researcher in this field, this means that there are ample opportunities for collaborations between private industry, government, and academia.

In This Issue

The aim of this issue of *MRS Bulletin* is to introduce this novel and exciting area of research to the wider materials science community. We aim to do this by focusing on some selected hot topics of current interest to researchers in academia and industry. These topics include the design of custom drug forms using supramolecular chemistry and computational approaches, the use of crystal engineering for enhancing the bulk physical properties of active pharmaceutical materials, the custom synthesis of biocompatible polymers for controlled drug delivery applications, pharmaceutical applications of nanomaterials, and

theoretical modeling of solids performance during common pharmaceutical manufacturing operations.

In the first article, Jones and co-workers describe the emerging field of cocrystal design (i.e., using lattices incorporating two or more molecular species) and its potential for revolutionizing the development of active pharmaceutical ingredients (APIs). They explain the advantageous molecular properties of pharmaceutical cocrystals and contrast these properties with those of the traditional acid, base, and salt forms of APIs.

In the second article, Lee and Myerson review the latest approaches for forming and recovering pharmaceutical particles and bulk powders. They highlight opportunities for the control of particle properties, such as morphology, size, and polymorphic form, through the careful and systematic manipulation of crystal nucleation and growth processes.

The compatibility of materials with biological systems and the ability to control their performance and properties in a biological environment are key themes in the article by Peppas. This internationally recognized expert in the field of controlled drug delivery provides a unique perspective on the future uses of custom polymeric materials in pharmaceutical dosage forms.

Nanoparticle applications and manufacturing techniques for pharmaceutical use are the focus of the fourth article, by Shah. He describes how such systems are experiencing a renaissance in the pharmaceutical industry, as new developments in nanoparticle formation and characterization have the potential to enable the viable commercial use of nanoparticles in a range of drug delivery systems.

In the final article, Wassgren and Curtis consider the development and application of computational approaches, such as computational fluid dynamics and discrete element methods, to pharmaceutical materials science. They provide examples of how continuum and discrete modeling approaches are used to obtain enhanced understanding of biological systems and manufacturing processes, and they review the considerable opportunities for future developments in this area.

We sincerely hope that you will enjoy this issue of *MRS Bulletin* devoted to the topic of pharmaceutical materials science. In our view, the pharmaceutical arena provides some very exciting opportunities for materials scientists from all branches of the discipline. The articles contained herein are intended to provide a brief sampling of these opportunities and to illustrate the broad range of topics that can be considered a part of this sophisticated and highly innovative field of research.

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At Cambridge, Elliott has built up a research group with expertise in molecular and mesoscale computational modeling of synthetic and biological polymers, carbon nanotubes, and their electrically active composites. He also supervises several industrially funded projects within the Pfizer Institute for Pharmaceutical Materials Science at Cambridge that examine compaction behavior of soft granular materials using granular dynamics and finite element techniques.

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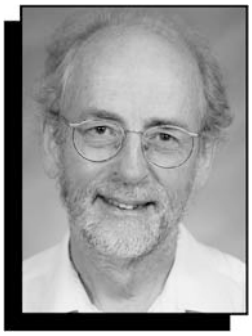

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