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 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., 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—Reincarnation or Reincarnation?” 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. Later, in the 1940s, semi-synthetic cellulose 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, and he went on to publish more than 300 articles that described a wide variety of work that might today be...
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 physical behavior and arrangement of the various material components) is common 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.

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.

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 bio compatible 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.

References

James Elliott, Guest Editor for this issue of *MRS Bulletin*, has been a university lecturer in materials modeling in the Department of Materials Science and Metallurgy at the University of Cambridge since 2001. Elliott earned his master’s degree in physics and theoretical physics from Cambridge. During his PhD degree studies in polymer physics at the University of Bristol, Elliott investigated particle movement and ion transport mechanisms of polymer electrolyte membranes for fuel cells. He continues to be active in this area.

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.

Elliott can be reached at the University of Cambridge, Department of Materials Science and Metallurgy, Pembroke Street, Cambridge, CB2 3QZ, UK; tel. 44-1223-335-987, fax 44-1223-334-567, and e-mail jaell010@cam.ac.uk.

Bruno Hancock, Guest Editor for this issue of *MRS Bulletin*, is a research fellow at Pfizer Inc. in Groton, Connecticut. Hancock holds a bachelor’s degree in pharmacy from the University of Bath and a PhD degree in pharmaceutical technology from the University of Bradford. Hancock leads a group in Pfizer global research and development responsible for developing techniques to characterize the physical and mechanical properties of powdered and compacted pharmaceutical materials. Also, he is an adjunct professor at Purdue University and has served as an advisor to the US Pharmacopoeia on the use and testing of pharmaceutical materials since 1995.

Hancock has published more than 45 research papers and holds several patents. He received the Royal Pharmaceutical Society of Great Britain Science Medal in 2000 and is a fellow of the American Association of Pharmaceutical Scientists.

Hancock can be reached at Pfizer Inc., MS 8156-006, Eastern Point Road, Groton, CT 06340 USA; tel. 860-715-2484, fax 860-715-7972, and e-mail brunoc.c.hancock@pfizer.com.

Jennifer Sinclair Curtis is a professor and chair of the Chemical Engineering Department at the University of Florida. She received a BS degree in chemical engineering from Purdue University and a PhD degree in chemical engineering from Princeton University. Curtis has an internationally recognized research program in the development and validation of numerical models for the prediction of particle flow phenomena. She serves on the editorial advisory boards of the *American Institute of Chemical Engineers Journal*, *Powder Technology*, and *Journal of Pharmaceutical Development and Technology*. Curtis has received the NSF Presidential Young Investigator Award, the Eminent Overseas Lectureship Award by the Institution of Engineers in Australia, and ASEE’s Sharon Keillor Award for Women in Engineering.

Curtis can be reached at the University of Florida, Department of Chemical Engineering, 229 Chemical Engineering Bldg., PO Box 116055, Gainesville, FL 32611-6055 USA; tel. 352-392-0882, fax 352-392-9513, and e-mail jcurtis@che.ufl.edu.

William Jones is Reader in Materials Chemistry and co-director of the Pfizer Institute for Pharmaceutical Materials Science.
Science in the Chemistry Department at the University of Cambridge. He also is a fellow of Sidney Sussex College. Jones earned his PhD degree in transmission electron microscopic studies of organic molecular crystals from the University of Wales in 1974. He has worked on the subject of organic molecular solids since his graduate studies, which explored the role of defects in controlling reactivity in organic crystals. After a post-doctoral period at the Weizmann Institute, Jones became interested in the area of crystal engineering. Recently, his group has focused on cocystal formation for controlling the solid-state properties of pharmaceutical systems. In addition to his interest in organic solids, Jones has published extensively on layered inorganic solids.

Jones can be reached at the University of Cambridge, Department of Chemistry, Lensfield Road, Cambridge, CB2 1JP, UK; tel. 44-1223-336-6570, and e-mail alfred.y.lee@gsk.com.

Alfred Y. Lee recently joined GlaxoSmithKline Inc. as a principal scientist in the Particle Sciences group. Previously, he had been a post-doctoral researcher at the Illinois Institute of Technology (IIT). In 2005, he completed his PhD degree in chemical engineering at IIT under the supervision of Allan S. Myerson. His scientific interests include solution crystallization, nucleation and growth of molecular crystals, and polymorphism. He is the recipient of the 2003 AIChE Separations Division Graduate Student Research Award in Crystalization and Evaporation.

Lee can be reached at GlaxoSmithKline Inc., 709 Svedeland Road, UW2830, PO Box 1539, King of Prussia, PA 19406 USA; tel 610-270-5947, fax 610-270-6570, and e-mail alfred.y.lee@gsk.com.

W.D. Samuel Motherwell is a research manager at the Cambridge Crystallographic Data Centre (CCDC). He has held the position since 1992. Motherwell graduated from St. Andrews University with a BSc degree in chemistry and a PhD degree in x-ray crystallography. After receiving his degrees, Motherwell joined the CCDC in 1968. His research group carries out CSD-based research both internally and in collaboration with external groups. His particular interest is to promote the use of the Cambridge Structural Database in crystal structure prediction and crystal engineering. Also, Motherwell represents the CCDC on the board of the Pfizer Institute for Pharmaceutical Materials Science.

Motherwell can be reached at the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK; tel. 44-1223-336-408, fax 44-1223-336-033, and e-mail motherwell@ccdc.cam.ac.uk.

Allan S. Myerson is the Phillip Danforth Armour Professor of Engineering, provost, and senior vice president at the Illinois Institute of Technology in Chicago. Myerson earned his BS degree at Columbia University and his MS and PhD degrees at the University of Virginia in chemical engineering. Prior to his position at IIT, Myerson served on the faculties of Polytechnic University in New York, the Georgia Institute of Technology, and the University of Dayton. His research focuses on crystallization from solution with an emphasis on nucleation, polymorphism, and industrial applications of crystallization.

Myerson has published five books, including the Handbook of Industrial Crystallization; 140 papers; and 20 patents on crystallization and related areas. He also serves as associate editor of Crystal Growth and Design, a journal published by the American Chemical Society.

Myerson can be reached at the Illinois Institute of Technology, Office of the Provost, 10 W. 33rd Street, Suite 223, Perlestein Hall, Chicago, IL 60616-3793 USA; tel. 312-567-3163, fax 312-567-7018, and e-mail myerson@iit.edu.

Nicholas A. Peppas is the Fletcher S. Pratt Chair in Chemical Engineering, Biomedical Engineering, and Pharmaceutics at the University of Texas at Austin. Peppas earned his Dipl. Eng. degree in chemical engineering from NTU Athens in 1971, and his ScD degree in chemical engineering from MIT in 1973. He is a recognized leader in the fields of controlled drug delivery, biomaterials, bionanotechnology, and biological recognition processes.

Peppas has been a visiting professor at multiple universities throughout Europe, Asia, and the United States. He is the chair-elect of the AIMBE College of Fellows; a past president of the Society for Biomaterials and the Controlled Release Society; a past director of AIChE; and a fellow of APS, AIMBE, AMED, SFB, AAPS, and AAAS. Peppas is a member of the National Academy of Engineering and the French Academy of Pharmacy. His work has been published in more than 950 publications, and he is the co-author or co-editor of 31 books, including Hydrogels in Medicine and Pharmacy (CRC Press, 1987). He holds 30 U.S. and international patents and has been recognized by more than 100 international research awards, including the 2006 William H. Walker Award for Excellence in Contributions to Chemical Engineering Literature and the 2006 James E. Bailey Award, both from AIChE.

Peppas can be reached at the University of Texas at Austin, Departments of Chemical and Biomedical Engineering, 1 University Station C0400, Austin, TX 78712-0231 USA; tel. 512-471-6644, fax 512-471-8227, and e-mail peppas@che.utexas.edu.

Parag Shah is a senior scientist in the Parenteral Center of Emphasis at Pfizer Inc. He holds an MS degree and a PhD degree in chemical engineering from the University of Texas at Austin and served as a visiting professor at multiple universities throughout Europe, Asia, and the United States. He is the chair-elect of the AIMBE College of Fellows; a past president of the Society for Biomaterials and the
Austin. Shah joined Pfizer two years ago after completing his PhD degree in the area of nanocrystal synthesis and stabilization in supercritical fluids. His current research interests include understanding the synthetic and colloidal aspects of pharmaceutical nanoparticles. In addition, he is working on understanding the impact of nanoparticles on the pharmacokinetics of the drug.

Shah can be reached at Pfizer Inc., MS 8156-051, Eastern Point Road, Groton, CT 06340 USA; tel. 860-686-2485, fax 860-441-0467, and e-mail parag.shah@pfizer.com.

Andrew V. Trask is pursuing legal studies at Fordham Law School in New York City while serving as an intellectual property legal intern at the international law firm Jones Day. He earned his PhD degree in 2005 in the Chemistry Department at the University of Cambridge. His research project in the field of solid-state materials chemistry was supervised by William Jones and W.D. Samuel Motherwell within the Pfizer Institute for Pharmaceutical Materials Science. His interests lie at the intersection of science, law, and healthcare policy. Trask can be reached at Jones Day, 222 East 41st Street, New York, NY 10017 USA; tel. 212-326-3939, fax 212-755-7306, and e-mail avtrask@jonesday.com.

Carl Wassgren is an associate professor of mechanical engineering and industrial and physical pharmacy (by courtesy) at Purdue University. He received a BS degree in aeronautical and astronautical engineering from the University of Illinois at Urbana-Champaign in 1990. Wassgren joined Hughes Space and Communications in 1991 as a systems engineer before returning to graduate school to receive MS and PhD degrees in mechanical engineering from the California Institute of Technology in 1992 and 1997, respectively. Wassgren was an assistant professor at Clemson University, starting in 1996, and joined Purdue University in 1998. His research interests include modeling pharmaceutical-related processes, such as tablet coating, high-shear wet granulation, hopper flow, and particle attrition.

Wassgren can be reached at Purdue University, School of Mechanical Engineering, 1288 Mechanical Engineering Bldg., 585 Purdue Mall, West Lafayette, IN 47907-2088 USA; tel. 765-494-5656, fax 765-494-0539, and e-mail wassgren@purdue.edu.