A Comprehensive Approach to Pharmaceutical Engineering Training

Benjamin J. Glasser,* Jack Cole, and Fernando J. Muzzio

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New discoveries in drugs and medicinal products are happening rapidly. One of the greatest challenges to the pharmaceutical industry is to design and optimize manufacturing processes for the efficient and safe production of future pharmaceutical products. To achieve this, the authors maintain that a new type of professional must be trained to be fluent in the language of basic chemical process engineering and knowledgeable in the engineering science and unit operations of pharamaceutical manufacturing.

Benjamin J. Glasser, PhD, is a faculty member and associate director; Jack Cole is industrial liaison; and Fernando J. Muzzio, PhD, is a faculty member and director of the Pharmaceutical Engineering Training Program (PETP) in the Department of Chemical and Biochemical Engineering at Rutgers University, 98 Brett Rd., Piscataway, NJ 08854, tel. 732.445.6278, fax 732.445.6758, bglasser@sol.rutgers.edu.

*To whom all correspondence should be addressed.

Most people know that developing new drugs requires an enormous amount of time and money. On average, introducing a new drug product to market takes approximately 15 years and $650 million. A drug product consists of therapeutics and excipients combined in a delivery system. A drug product's success lies in its ability to deliver the drug at a certain rate in a certain environment in the body. This is a function not only of the drug's chemical and physical attributes but also the patient's metabolism. Thus, one of the main challenges to pharmaceutical scientists and engineers is the interplay of drug discovery, effective drug delivery, and efficient production of drug products.

Drug manufacturing relies on chemistry, pharmaceutics, and engineering. In contrast, research and education activities in these areas often are constructed around individual disciplines. Engineering students largely are lacking in knowledge of pharmaceutical issues; pharmaceutics students often know little about manufacturing; and biology and chemistry students usually know very little about either. As a result, the industry generally lacks a source of trained professionals, and its incorporation of material science and modern manufacturing technology is suboptimal.

A comprehensive multidisciplinary program in pharmaceutical engineering should combine graduate research, course work, and extensive exposure to industrial applications to develop high-impact research programs and to generate a reliable stream of highly trained professionals for both industry and academia. It must intimately combine engineering, pharmaceutics, and biomedical science to develop an innovative research program in drug manufacturing. Furthermore, it must develop an effective educational program that will train a new type of professional equipped to develop and implement emerging technologies for pharmaceutical product production.

At Rutgers, the State University of New Jersey, the Pharmaceutical Engineering Training Program (PETP) was initiated in 1995 and was the first in the nation to formally combine the disciplines of engineering and pharmaceutics to provide comprehensive training in drug manufacturing. The program's location (Piscataway, NJ) is not surprising, perhaps, considering that New Jersey is the national epicenter of pharmaceutical research and development. The program's strengths are in pharmacy, biotechnology, medicine, biomaterials, membrane technologies, and powder technology, and it is one of a select group

of training programs throughout the country funded by the National Science Foundation. PETP is a joint venture of the Department of Chemical and Biochemical Engineering and the College of Pharmacy at Rutgers and is located on the Busch Campus, where it has an integral role in the activities of the College of Pharmacy and the departments of chemical and biochemical engineering, ceramics, industrial engineering, and mechanical engineering.

New discoveries in drugs and medicinal products are happening rapidly. One of the greatest challenges to the pharmaceutical industry is to design and optimize manufacturing processes for the efficient and safe production of pharmaceutical products. To achieve this, a new type of professional must be trained to be fluent in the language of basic chemical process engineering principles and knowledgeable in the engineering science and unit operations of pharmaceutical manufacturing such as blending, crystallization, compaction, sampling, and granulation.

The program's purpose is to provide predoctoral students with integrated, interdisciplinary didactic and research training in pharmaceutical engineering. Students are trained to become professionals who are well educated within a single discipline and who also have the crossdisciplinary skills required to support the needs of the industrial and academic pharmaceutical sectors.

Clearly, developing a drug that cannot be delivered is useless, and designing a drug product that cannot be efficiently manufactured is pointless. Hence, the long-term interest of both the public and the industry is to develop new and more effective methods for drug discovery, delivery, and — the current program's focus — manufacturing. Even after discovery and development of delivery methods become available, difficulties in the development of appropriate manufacturing methods capable of ensuring the quality and uniformity of millions of units per batch often contribute significantly to the 15 years required, on average, to bring a drug product to market. Because the typical annual sales of a drug product are approximately $200 million, the economic costs of delays are on the order of many millions of dollars per month for each product. Typically, only one in several thousand candidate molecules survives the development process, using an immense amount of effort wastefully assigned to drug substances that are doomed from the start. The public pays for this waste both in higher drug costs and in delayed access to treatment. Thus, the program addresses the overall need of establishing cohesive and self-sustaining research and training with the long-term goal of teaching how to systematically manufacture drugs easily and reliably.

Product manufacturing (process development research)

Once a delivery system is properly developed, one must focus attention on the development of a process capable of manufacturing millions of product units with tightly uniform properties. As raw materials enter the process, they are modified through a chemical or biological reaction to turn them into desired molecules, which subsequently undergo an initial separation step. For solid dosage forms this usually is followed by crystallization (or precipitation). The newly formed particles are separated from the crystallization liquor through filtration. Solvents are recovered through drying, and the dry powder undergoes further processing such as milling or granulation (if particle size requires modification), coating, blending, tableting or encapsulation, and finished-product coating. Although drug products with precisely controlled delivery properties require highly precise manufacturing processes, at present our understanding of such operations is crude at best. Consider just a few, very typical, examples.

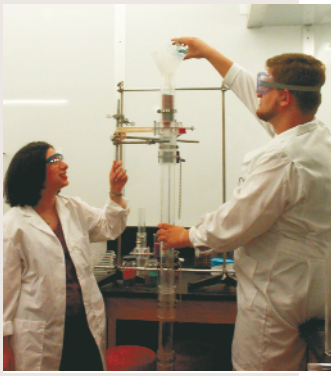
- Reactors are designed by trial-and-error methods; effective computational models of reactive processes currently are unavailable.
- The technology for sampling batch powder processes is so inadequate that sampling errors sometimes outweigh actual inhomogeneity of active ingredients.
- Poor flow properties of dry powders often cause flow stoppage and overall system shutdown.
- Granular materials with variations in particle size, density, and shape often display strong segregation phenomena, resulting in high product composition variability.

Research performed within the program is directed toward developing new technologies to overcome these problems. Relevant research areas include

- organic and biological synthesis
- crystallization
- drying
- flow, mixing, and segregation of powders
- compaction
- coating

Student profile — Elizabeth Liss

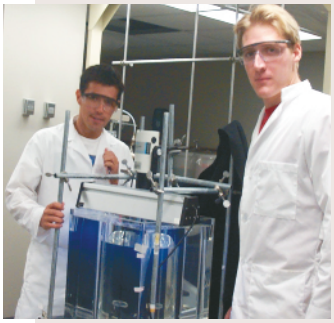
Graduate student **Elizabeth Liss** conducts an experiment with undergraduate assistant James Lowden to examine the segregation of granular materials during vertical drops. Elizabeth joined PETP after receiving a BS and MS in chemical engineering from Columbia University. Together with Professor Benjamin Glasser, she has been studying the fundamental flow behavior of granular materials using a combination of particle dynamic simulations and experimental techniques. Although powders are common in many industrial processes, a limited understanding of the causes of segregation still exists. In the preparation of solid dosage forms, an exact mixture of active ingredients and excipients is needed. Even though much time and energy is expended to ensure that a product is well mixed, the products must be moved during the final phases of processing, and segregation often occurs during transport (e.g., to the feed frame of a tablet press).



In the experimental setup above, Elizabeth investigates the segregation of different-sized glass beads and pharmaceutical excipients during vertical drops. This simple process has been shown to cause significant segregation because of the drag force of air on the particles.

Student profile — Paulo Arratia

Although non-Newtonian fluids are easily found in nature and widely used in a variety of pharmaceutical processes, much remains to be learned about the fundamental phenomena that control the flow and mixing of such fluids. In fact, the basic flow phenomena are partially understood at best. As a result, designing and scaling up mixing and reaction operations is largely an "art." Graduate student **Paulo Arratia** (far left) performs a liquid-mixing experiment using a UV-fluorescence dye advection technique with undergraduate assistant Michael Birnkrant. In the experiment, Paulo is investigating the flow patterns produced by a viscous, highly shear-thinning, and moderately viscoelastic fluid in a batch-stirred tank reactor under laminar conditions.



Paulo joined PETP after receiving a BS in chemical engineering from Hampton University. Under the direction of Professor Fernando Muzzio, he has been studying how rheologically complex fluids (non-Newtonian) affect the mixing process in stirred tank reactors using experimental techniques such as particle image velocimetry and planar laser induced fluorescence, among others. Of particular interest is the role of elastic polymers on the flow behavior, which because of flexible chains, produce a variety of flow instabilities. In addition, viscosity and stress constitutive models currently are being implemented into a computational fluid dynamics code for flow simulations.

- process design, synthesis, and optimization
- reaction engineering
- mixing in reactive and multiphase flows.

The program provides an integrated approach to research and education. In particular, research experiences in the laboratory form an important part of the students' training (see "Student profile" sidebars).

Education and training

PETP trains both graduate and undergraduate students in areas that focus on pharmaceutical manufacturing. In developing the program, our intent was to capitalize on two main strengths: relevance and uniqueness. To date, the pharmaceutical industry is perhaps the largest segment of the chemical industry whose products, processes, and operations typically are "designed" and "controlled" by nonengineers. The enormously wasteful manner in which the industry currently operates is a direct consequence of the fact that drugs are discovered and processes are developed largely by trial and error. The program's goal is to generate a new breed of professionals with the knowledge and skills to implement major changes in the current situation. Although we cannot hope to train sufficient numbers entirely by ourselves, we intend to create a new standard of training for engineers in the pharmaceutical industry that will be adopted by other institutions to properly educate large numbers of professionals at all levels. Since the inception of PETP at Rutgers, we have received numerous inquiries both in and outside the United States asking for our support in developing related curricula, and several other institutions have launched programs organized along the same lines as PETP.

The curriculum is broadly aimed at processing in a regulatory environment and focuses on the following domains of the pharmaceutical and other related industries: chemical processing of drugs and fine chemicals; pharmaceutical processing of dosage forms and devices; and bioprocessing for biologicals. Course work at Rutgers focuses on

- advanced transport phenomena
- industrial organic chemistry
- kinetics, catalysis, and reactor design
- advanced engineering mathematics
- powder technology
- advanced engineering thermodynamics
- bioseparations
- mixing, theory and applications
- colloids and surface science
- biochemical engineering
- pharmaceutics
- pharmacokinetics
- biochemical plant design.

The program also includes courses in engineering, pharmacy, and sciences that cover many other relevant topics such as advanced medicinal chemistry; drugs, structure and function; controlled drug delivery technology; dermaceutics; biotechnology processing; and biomaterials characterization. The variety of topics allows students to tailor their course work to their individual backgrounds, interests, and needs.

An important aspect of the program is close collaborative partnerships with major companies in the industry. These corporate sponsors participate in the program's advisory board, which provides direction on the priorities for sponsored research and reviews academic aspects and makes appropriate recommendations. The sponsors also have the opportunity to meet with faculty, staff, and students and report their findings to the appropriate university officials. Their ongoing support is recognized as being key to the continued success of the program.

The ultimate goal of the program is to train professionals to design and implement successful approaches for understanding and optimizing methods for drug discovery, delivery, and manufacturing. With this level of integrated and comprehensive training in the pharmaceutical sciences, innovation in the complete process of drug product development should redound to the overall healthcare effort by providing process economies to the manufacturer, a faster track to approval, greater opportunities to industry professionals, and obvious advantages to the consumer. **PT**