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Integrating Continuous Pharmaceutical Manufacturing into the Chemical Engineering Curriculum

Prof. Alexander Vincent Struck Jannini, Rowan University

Alexander Struck Jannini is an adjunct professor at Rowan University. His previous work has been focused on incorporating aspects of pharmaceutical engineering into the undergraduate curriculum. Alex plans on continuing his education and receiving a Ph.D. in chemical engineering. His areas of interest are drug delivery and drug loading characteristics of dissolvable thin films.

Dr. C. Stewart Slater, Rowan University

C. Stewart Slater is a professor of chemical engineering and founding chair of the Chemical Engineering Department at Rowan University. He has an extensive research and teaching background in separation process technology with a particular focus on membrane separation process research, development and design for green engineering, and pharmaceutical and consumer products. He received his Ph.D., M.S., and B.S.in chemical and biochemical engineering from Rutgers University. Prior to joining Rowan University he was a professor at Manhattan College.

Integrating Continuous Pharmaceutical Manufacturing into the Chemical Engineering Curriculum

Abstract

Over the past several years we have explored ways to incorporate concepts of pharmaceutical engineering within the chemical engineering curriculum. Our initial efforts in this area have been directed towards the integration of these concepts in freshman and sophomore level courses. This provides an experience that reinforces core educational objectives and increases student interest in the pharmaceutical field. This paper is a continuation of our educational methods development, and will describe several pharmaceutical and consumer product educational modules. These modules include both laboratory and course-related activities for both lower and upper-level chemical engineering courses. These are based on API manufacturing and finished drug production processes. We are exposing students to the important area of continuous manufacturing of pharmaceutical products. This is a growing area of interest for the drug industry. This work is part of the educational outreach efforts of the NSF ERC for Structured Organic Particulate Systems (NSF grant # ECC0540855).

Introduction

The pharmaceutical sector is one of the most prominent sectors of the worldwide economy. In 2014, the industry was expected to generate 1 trillion USD in revenue [1]. American companies make up a majority of this profit, with five of the top ten pharmaceutical companies being headquartered in the United States [2]. These economic factors and the shifting paradigms of the industry to changing existing processes have led to an increased demand for chemical engineers with pharmaceutical training [3]. Indeed, there has been an increase in the employment of chemical engineers by pharmaceutical companies. From 2012 to 2022, the amount of chemical engineers that will be employed by pharmaceutical engineers will increase by 4.1 percent, while traditional chemical manufacturing positions will fall by 9.8 percent [4].

Due to this demand increase from the pharmaceutical industry, universities have developed methods for including pharmaceutical engineering education into their existing programs. Pharmaceutical engineering can be defined as the design of manufacturing processes for pharmaceutical and diagnostic products [5]. Institutions such as Rutgers University, University of Michigan, New Jersey Institute of Technology, and Stevens Institute of Technology all offer graduate degrees in pharmaceutical engineering, or offer it as a specialization for degrees in traditional engineering sections. There has also been diffusion of pharmaceutical engineering principles into the undergraduate level. The University of Basel in Switzerland is one of the few universities that offer an undergraduate degree in pharmaceutical engineering [6]. Most other universities with pharmaceutical engineering programs offer this education as a specialization for

undergraduates, such as Stevens Institute of Technology and University of Iowa [7, 8]. This increased interest in pharmaceutical manufacturing in academia led to the funding of an engineering virtual organization, known as PharmaHUB.org; where professors and instructors share simulations, presentations, and other academic tools to increase the amount of resources available to those wishing to teach pharmaceutical engineering topics [9].

With the inclusion of specializations, a majority of the educational differences appear in the upper-level undergraduate courses with the inclusion of a special topics course. For example, the New Jersey Institute of Technology and Georgia Institute of Technology both offer engineering electives that focus on aspects of pharmaceutical engineering [10, 11]. This method is the most popular method for incorporating pharmaceutical engineering education because of its simplicity. By comparison, developing pharmaceutical engineering educational material for lower-level undergraduates can be more challenging. Issues such as determining appropriate content for students who are just beginning their engineering education, making the content applicable for different engineering majors, and the addition of new courses into saturated curriculums have to be addressed appropriately in developing this material for lower-level undergraduates. An approach that has been used in the past is to modify pre-existing courses so that they focus on pharmaceutical engineering while also meeting the original learning outcomes. Rowan University has made problem sets and laboratory experiments for use in lower-level engineering courses that focus on aspects of pharmaceutical engineering. The problem sets contain mainly material and energy balance problems, which would make them useful in introductory chemical engineering courses [12, 13]. The laboratory experiment focuses on controlled release principles of drug delivery methods through the dissolution of a lozenge [14]. Recently, several experiments were developed for use in lower level undergraduate courses that focus on pharmaceutical engineering [15].

In terms of pharmaceutical manufacturing, current research is finding ways to incorporate more continuous manufacturing methods in process development. The pharmaceutical industry has historically relied on batch, semi-batch, or semi-continuous processes. This is especially evident in tablet manufacturing processes [16]. The Food and Drug Administration (FDA) have recognized that continuous processing has the potential to improve product quality, and have begun to encourage industry to investigate areas where this technology can be used [17]. Researchers are now investigating ways to incorporate continuous manufacturing into pharmaceutical processes.

Experiments were developed to introduce lower-level undergraduates to aspects of pharmaceutical engineering education. These experiments introduce students to the basic principles of pharmaceutical engineering; such as quality management, drug delivery devices, and solids transport. General educational objectives were also incorporated in each experiment; such as the ability to gather and interpret data; understand and apply core science and mathematical principles; and working individually and in teams to identify and solve problems [18]. These experiments were designed to meet typical undergraduate safety standards, be

relatively cost-friendly, not rely on highly specialized equipment, and take roughly two hours to complete. Of the experiments that were developed, the three that will be discussed are the Tablet Statistical Analysis Lab, the Creation of Dissolvable Strips Lab, and the Fluidization of Pharmaceutical Excipients Lab. These experiments, and other experimental write-ups, are available on the pharmaceutical engineering resource website, PharmaHUB.org. More information on the Fluidization of Pharmaceutical Excipients Lab and the Tablet Statistical Analysis Lab can be found in a previous publication by the authors [15].

Experiments

Fluidization of Pharmaceutical Excipients Lab

The pharmaceutical industry has used fluidized beds in processing applications for many years. Indeed, fluidization technology has been used for several decades for granulation, in which powders with small particulate diameters are gathered and made into larger particles to improve powder properties [19]. This unit operation is also used for coating operations, which are often used to mask tastes and provide a controlled release [20]. Fluidized beds can also be used for drying particulates. Recent work has been investigating the effect of solid mixtures on drying behavior in fluidized beds [21].

One of the reasons for the fluidized bed's popularity is that it can be run as a continuous process [22]. With this in mind, a lab was designed to introduce students to this unit process and the basic theory behind it. The Fluidization of Pharmaceutical Ingredients Lab was designed for this purpose [15]. This lab had students analyze the fluidization of a pharmaceutical excipient and measure fluid and particle properties. In the first part of this experiment, students conduct a gravimetric analysis on two excipients; kaolin (white clay powder) and Avicel® PH 200 (microcrystalline cellulose, or MCC, that is specifically designed for use in fluidized beds). In this gravimetric analysis, students use a graduated cylinder and water in order to determine three particle properties; bulk density, particle density, and bed porosity [15]. Sample data for this portion can be seen in Table 1.

Table 1. Sample data for the gravimetric analysis in the Fluidization of Pharmaceutical Excipients Lab.

Measurement	Kaolin	Avicel® PH 200
Mass of substance (g)	61.5	63.67
Volume of substance (mL)	220	177
Bulk density (g/cm3)	0.2795	0.3597
Volume of water (mL)	850	700
Volume of mixture (mL)	875	740
Volume of particles (mL)	25	40
Mass of substance (g)	61.25	63.40
Particle density (g/cm3)	2.450	1.585

The second part of this experiment focuses on the fluidization phenomenon. In this portion of the lab, students are tasked with determining fluidization regimes and determining the effect of process parameters on the fluidization process. Using the fluidized bed setup (Figure 1), students measure the bed height and the pressure drop across the bed as a function of air flow rate [15]. Students then take this data, and make graphs of these correlations. Through these graphs, students should recognize that at a certain point (denoted by a change in the slope of the lines), the bed goes from packed bed behavior to fluidized bed behavior.

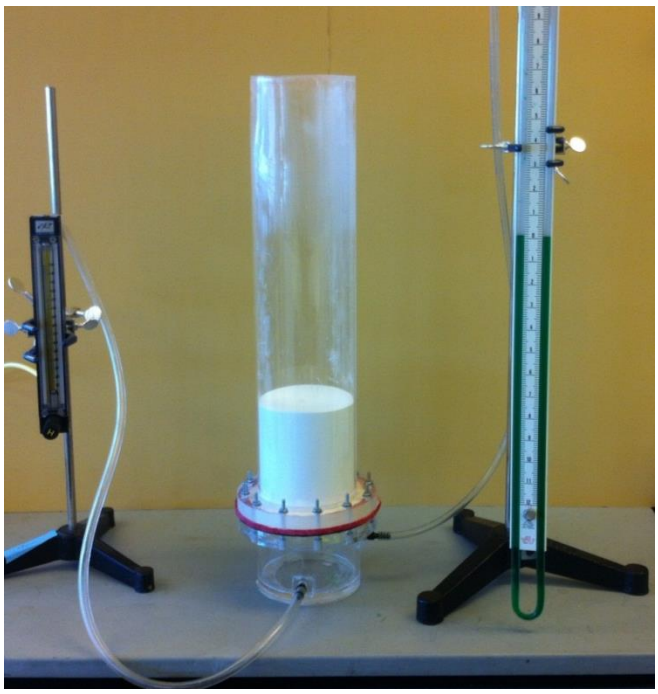

Figure 1. The fluidized bed apparatus used for the Fluidization of Pharmaceutical Excipients Lab. The fluid used is pressurized air, and the excipient shown is Avicel® PH 200.

To show how particle properties affect the fluidization process, an exercise was given that had students compare the Reynolds Number at minimum fluidization (Re_{mf}) for the two substances used in the gravimetric analysis portion of the lab [15]. The primary reason Re_{mf} is different between these two values is that the average particle size between the two powders is vastly different (1.4 µm for kaolin and 180 µm for Avicel® PH 200). The students also use a design equation to predict Re_{mf} and then compare that value to the Re_{mf} found during experimentation. The design equation, and the supplemental governing equations, were adapted from Kunil and Levenspiel, and is shown through Equations 1 through 4 [23].

$$Re_{mf} = \sqrt{(C_1^2 + C_2 Ar)} - C_1 \quad (1)$$

With:

$$Ar = \frac{Dp^3 \, \rho_g \left(\rho_s - \rho_g\right) g}{\mu^2} \quad (2)$$

$$C_1 = \frac{300(1-\varepsilon_{mf})}{7} \quad (3)$$

$$C_2 = \frac{\varepsilon_{mf}^3}{1.75} \quad (4)$$

Where ε_{mf} is the void fraction at minimum fluidization; Dp is the diameter of the particle; ρ_g is the density of the fluid; ρ_s is the particle density of the solid; and μ is the viscosity of the fluid. For this experiment, Avicel® PH 200 was found to have an Re_{mf} of 19.10, while the design equation predicted a value of 19.36. The difference comes out to 1.4%, well within the range of error.

Creation of Dissolvable Strips Lab

While developing new drugs has often been the main focus of the pharmaceutical industry, research has also been placed on developing new methods of drug delivery. In some ways, developing these new drug delivery devices may be more economically viable. For example, drug delivery systems cost significantly less and take about half the time to develop as opposed to discovering a novel drug [24]. This research has led to many drug delivery mechanisms, but the one the most recent is orally dissolving thin films, or strip films [25]. These fast dissolving films were first used for confection purposes (e.g. breath strips or vitamins), but are now starting to be used in over-the-counter medications, such as cold/flu medications, anti-gas medications, and oral pain relief products [26]. Currently, researchers are looking for ways to incorporate this drug delivery device in prescription drugs. For example, oral thin films were investigated for delivering anti-vomiting medication to patients undergoing chemotherapy [27].

What may push this drug delivery device to be incorporated into more pharmaceutical products is that it can be manufactured in a continuous way. The solvent-casting method, shown in Figure 2, is often used by pharmaceutical manufacturers. Since there have been advances in thin film research, it is important that engineers working in the pharmaceutical industry have an understanding of this drug delivery technique. The Creation of Dissolvable Strips Lab was designed to introduce students to this manufacturing method, along with some of the quality testing methods that are used on dissolvable strips.

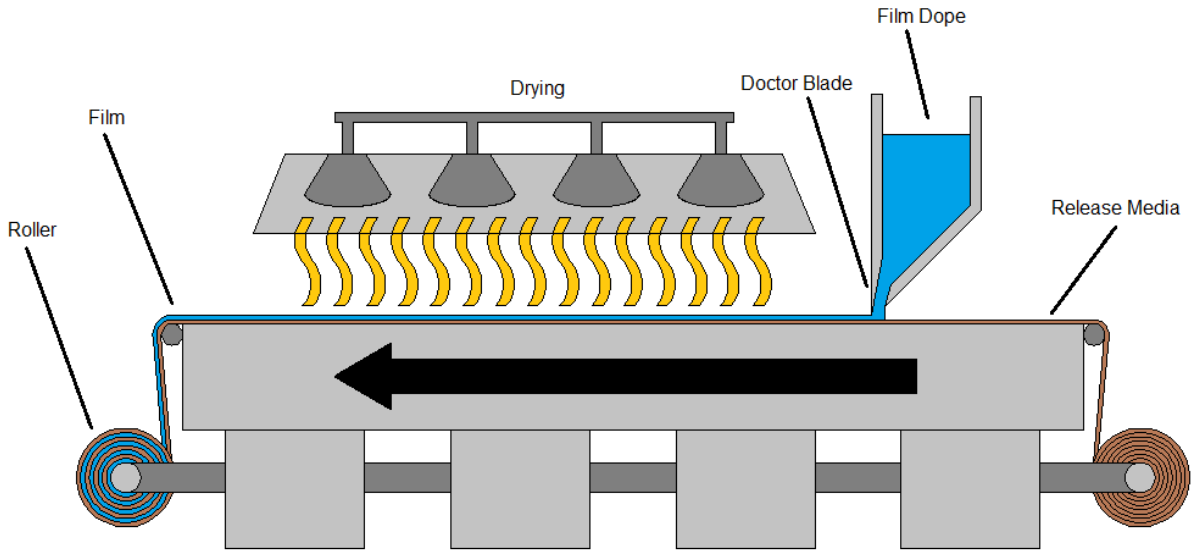

Figure 2. A diagram of a solvent-casting system used for manufacturing pharmaceutical thin films.

In this lab, students were given a formula for making strips. These strips were made with water, a polymer (carboxymethylcellulose, or CMC), a surfactant (sodium lauryl sulfate), a plasticizer (glycerol), a sweetener (sucrose), and a saliva stimulator (citric acid). Students were allowed to choose what color or flavor to make their strips to add customization to the lab. These items were added to the water kept between 80 to 90 °C and at a vigorous stir. Students then place their solution under vacuum to remove any air bubbles trapped in the solution. Once this is completed, students place their solution in a special casting tray made specifically for this lab (Figure 3). The solution was allowed to sit for approximately 4 days, giving the solution time to dry and form dissolvable strips.

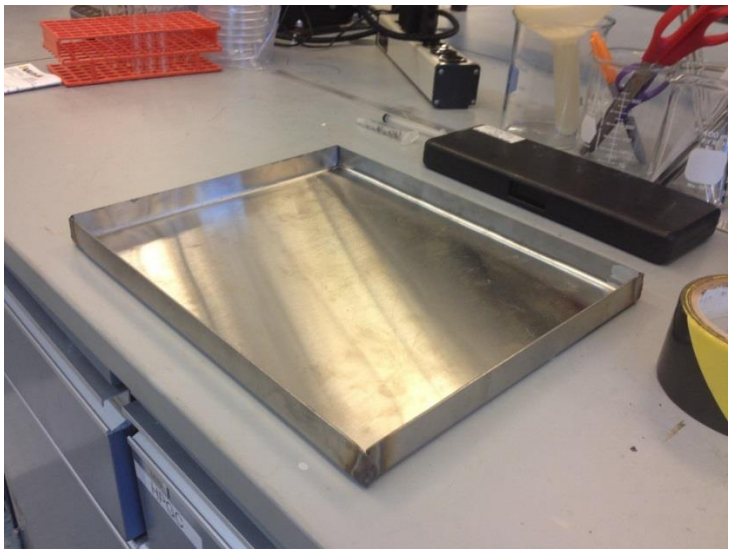

Figure 3. The casting tray made specifically for the Creation of Dissolvable Strips Lab.

Once the films are dried, students cut out four sample strips. These strips have the dimensions of 1 in. by 1.5 in. These strips are then used in three quality analysis tests; thickness measurements, folding endurance, and surface pH. These tests were chosen from the literature due to their ease of setup and lack of any specialty equipment [28]. Thickness measurements were taken on each side of the sample using a caliper. The folding endurance was found by folding a strip in half repeatedly until the film breaks in half. Surface pH was determined by dropping one drop of water unto the surface of a sample, and then placing litmus paper on the wet surface. The mean and range of each quality test was then calculated. Sample data for these quality tests can be found in Table 2. The students are then asked to comment about their results: For example; what are the dangers of large variances in strip thickness; how does the folding endurance found compare to that of a commercial brand strip; and is the surface pH acceptable for human consumption?

Table 2. Sample data for the quality tests used in the Creation of Dissolvable Strips Lab.

Sample	Thickness (mm)	Folds endured	Surface pH
1	0.08	32	5.0
2	0.10	28	5.5
3	0.12	39	5.5
4	0.07	23	6.0
Average	0.09	30.5	5.5

Tablet Statistical Analysis Lab

In regards to pharmaceutical manufacturing, it is important for engineers to understand good manufacturing practices (GMP's). GMP's are the guidelines that pharmaceutical companies follow when developing products. If these guidelines are not followed, regulatory actions can be implemented [29]. GMP's cover many aspects of the industry, such as personnel training, building and facility requirements, and process controls. These can also cover acceptable active pharmaceutical ingredient (API) variances and methods for quality testing [30]. This is how statistics play a vital role in the pharmaceutical industry. As such, it is important that future engineers in the pharmaceutical industry have a solid understanding of statistics and statistical tests. The Tablet Statistical Analysis Lab introduces students to basic statistical analyses of ibuprofen tablets [15].

In this lab, students take mass measurements of two types of ibuprofen tablets; Advil® brand tablets and a generic brand. Students were given ten of each tablet, and measured the mass of each tablet using a bench scale. When all the measurements were taken, students were to find the average ($\bar{x}$), variance (s), and standard deviation (σ) for each of the brands [15]. The students then conduct their first statistical test; an F-test. This test is used to determine if the two sets of data are statistically different from one another. The equation for the F-test, and a sample

calculation, is shown in Equation 5. The F-critical value was found in the Montgomery, Runger, and Hubele statistics text to be 3.18 [31]. Since the F-experimental value is greater than the F-critical value, the two brands are considered statistically different.

$$F_{exp} = \frac{s_1^2}{s_2^2} = \frac{(9.726 \cdot 10^{-5})^2}{(1.526 \cdot 10^{-5})^2} = 40.63 \quad (5)$$

The second statistical test performed by the students was a T-test. The T-test was used to determine if the two sets of data were statistically different from a known value. For this test, students use the theoretical mass of an ibuprofen tablet (μ_0). This theoretical mass given was obtained from the Handbook of Pharmaceutical Manufacturing Formulations [32]. The T-test equation, and the sample calculations for the Advil® and the generic brand, is shown in equations 6 and 7, respectively. The T-critical value was also found in the Montgomery, Runger, and Hubele statistics text [31]. This value, 2.262, is larger than the T-experimental value for the Advil® brand. This means that the average mass of the Advil® brand is not statistically different from the known value. On the other hand, the T-critical value is smaller than the T-experimental value for the generic brand. This shows that the average mass of the generic brand was statistically different than that of the known value [15].

$$t_{exp} = \left| \frac{\bar{x} - \mu_0}{\frac{\sigma}{\sqrt{n}}} \right| = \left| \frac{0.4867 - 0.4800}{\frac{0.00986}{\sqrt{10}}} \right| = 2.136 \quad (6)$$

$$t_{exp} = \left| \frac{\overline{x} - \mu_o}{\frac{\sigma}{\sqrt{n}}} \right| = \left| \frac{0.3320 - 0.4800}{\frac{0.00391}{\sqrt{10}}} \right| = 119.8 \quad (7)$$

This lab was also an introductory experiment to the pharmaceutical industry. As such, it contained information regarding pharmaceutical terminology. This included definitions for API and several different excipients (e.g. filler, binder, glidant, etc.). In addition, this lab had students identify the first three excipients in both brands, and determine what type of excipient they would be classified as. This lab also included an exercise to introduce process flow diagrams [15]. In this exercise, students are given a procedure for making coated ibuprofen tablets obtained from the Handbook of Pharmaceutical Manufacturing Formulations [32]. This information is given in list form. Students are to convert this information into a process flow diagram. The solution to this exercise is shown in Figure 4.

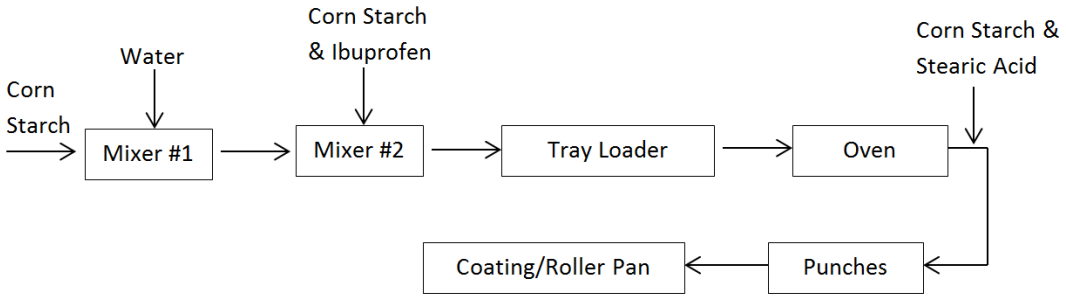

Figure 4. The solution to the process flow diagram exercise in the Tablet Statistical Analysis Lab.

Conclusions

Laboratory experiments were developed to introduce students to the pharmaceutical industry. Specific interest was placed on developing labs that could be tied to continuous manufacturing. The Fluidization of Pharmaceutical Excipients Lab introduces students to the fluidized bed unit process and the underlying theory behind the phenomena. The Creation of Dissolvable Strips Lab has students investigate a novel method of drug delivery and perform quality analysis measurements. Lastly, the Tablet Statistical Analysis Lab has students perform statistical tests on ibuprofen tablets, while also introducing them to pharmaceutical terminology. Future endeavors for this work include obtaining assessment results for the experiments. This would include pre- and post- lab tests in order to determine student learning and a Likert-scale assessment in order to determine student opinions. Lab write-ups for the experiments described in this paper, and others not mentioned, can be obtained through PharmaHUB.org. More information, including preliminary assessment data, can be found in a previous publication of the authors [15].

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