The object of this column is to enhance our readers' collections of interesting and novel problems in chemical engineering. We request problems that can be used to motivate student learning by presenting a particular principle in a new light, can be assigned as novel home problems, are suited for a collaborative learning environment, or demonstrate a cutting-edge application or principle. Manuscripts should not exceed 14 double-spaced pages and should be accompanied by the originals of any figures or photographs. Please submit them to Dr. Daina Briedis (e-mail: briedis@egr.msu.edu), Department of Chemical Engineering and Materials Science, Michigan State University, East Lansing, MI 48824-1226.

Development of Problem Sets for K-12 and Engineering on PHARMACEUTICAL PARTICULATE SYSTEMS

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Over the past several years, there has been a significant effort to develop curricula and coursework for chemical engineers in biochemical engineering and biotechnology,[1] but little effort has been undertaken to develop courses and coursework in the pharmaceutical engineering field. This field involves the manufacture of the active pharmaceutical ingredients and drugs in the final dosage form. A successful development of curriculum materials requires a new approach to integrating concepts of batch processing, solid-liquid separation techniques, solid-solid particulate processing, and technology at the nano-scale. The interface of pharmaceutical science and chemical engineering is crucial for understanding the basis of structured organic particulate systems (SOPS), a term that describes the multicomponent organic system that comprises a drug, nutraceutical, or medicine formulation.

It might be argued that a separate curriculum (at a graduate level) is necessary for a full understanding of this technology, but one approach fostered by Rowan University and other institutions is to integrate concepts of new technologies into the traditional undergraduate chemical engineering curriculum through laboratories/demonstrations, in-class/homework problems, and case studies. Rowan faculty members have successfully incorporated the fundamentals and applications

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of green engineering into the chemical engineering curriculum and are currently working to integrate principles of pharmaceutical particulate systems.[2,3] This paper describes the first step in that process: to develop in-class and homework problems that present key principles of this field that are appropriate to K-12 through chemical engineering courses.

The NSF-sponsored Engineering Research Center for Structured Organic Particulate Systems (SOPS) led by Rutgers University (<www.ercforsops.org>) is striving to become a focal point in pharmaceutical processing. Rowan University is an outreach partner school of the Center. The work involves developing coursework that integrates fundamental concepts and research advances in SOPS into K-12 and undergraduate engineering curricula. More than 20 problem sets have been developed and will be integrated into the Center Web site for dissemination. A study by the American Association of Pharmaceutical Scientists (AAPS) found that nearly 60% of practicing industrial scientists believe that there is a lack of qualified applicants available with backgrounds in product development and pharmaceutical technology.[4] The development of educational outreach programs and course modules could increase student interest in the area of pharmaceutical engineering from basic research to manufacturing technology.

A review of the literature shows some K-12 and college-level educational activities in specific areas of pharmaceutical science and particle technology. Some experimental methods have been developed, but synthesis into coursework is not widespread. Laboratory exercises have been developed to educate lower-level engineering students on fundamentals of drug delivery.[5] Experimental methods developed by Nash illustrate the bulk density, compressibility, flowability, and other properties of cohesive and non-cohesive pharmaceutical powders.[6] Simple demonstrations of particle sampling, flow, and segregation have also been created to display the unique properties of particles.[7-9] The need for the study of particle technology in the chemical engineering curriculum has led to the development of undergraduate and graduate coursework.[10-13]

This paper presents our first steps in our educational partnership with the Center. The overall goal of this phase of the project is to develop problem sets that have both an educational objective that fits into existing coursework and also a direct link to an area of pharmaceutical research at the Center. Some of the education topics that have been covered include: converting values to fractions, decimals, and percentages; solid, liquid, or gas phase characterization; calculating molecular weight; relative standard deviation calculations; and solving simple and complex mass and energy balances involving particulate systems. The problems have also covered the following pharmaceutical processing topics: conversion from batch to continuous tableting; particle behavior and segregation; continuous mixers, granulators, and milling machines; high-pressure homogenization and characterizing nanoparticles; and drop-on-demand technology. The following section will introduce several problems that have been developed for elementary school to college-level students. All problems are available on the Resources / Educational Modules page of <www.PharmaHUB.org> along with other educational materials from the ERC.

PROBLEM 1: WHY POWDERS ARE UNIQUE

Granular materials are unique because they can display the properties of different states of matter. Particles are able to support weight, which is a property of a solid; flow from a container, which is a property of a liquid; and be in compression, which is a property of a gas. The problem presents the distinctive properties of particles and asks the student to identify the property being displayed and connect it to a physical state. The exercise emphasizes the properties of the different states of matter while introducing relevant pharmaceutical engineering concepts. The different properties of powders can apply directly to pharmaceutical engineering production techniques. The compressibility of powders is important for producing pharmaceutical tablets, where differences in compressibility could alter the ability of the tablet to dissolve in the body or cause it to be brittle and easily broken. The powder flowability is important for transportation of powders during the production process, where batches of powder must be transported throughout the pharmaceutical plant. This problem is for a middle school science class.

Problem Statement

Imagine you are walking down the beach. With each step that you take, the sand moves beneath your feet, but how is this sand unique? If sand were considered a liquid or a gas, it would not be able to support the weight of your step. As a result, in this case, sand must be classified as a solid. Now, picture building a sand castle. You push the sand down into a bucket and feel it compress into a harder powder. Are solids able to be compressed? The only form of matter that can be compressed under force is a gas. Finally, you have a bucket full of dry sand. You tip the bucket over to empty it and watch the sand pour out. If sand were a solid or a gas, it would not simply flow out of the bucket. Under this condition, the sand acts as if it were a liquid as it flows out of the bucket. Particle behavior is difficult to understand because it cannot easily be classified as a liquid, solid, or gas.[14]

Determine the state of matter with properties similar to those being displayed by particles in the following situations:

a) *You pour salt into a salt shaker.*

b) *You go to shake the salt, but it was packed into the bottom of the salt shaker when it was filled.*

c) *You jump up and down on a gravel parking lot, but your feet do not sink into the gravel.*

d) *Can you think of any other examples displaying the complex properties of powders?*

Problem Solution

The problem requires that the student have a strong knowledge of the properties of a physical state of matter. Using this knowledge, the student will classify the properties being displayed by the particulates as similar to a solid, liquid, or gas.

a) *The salt is flowing into the salt shaker, which is a property of a fluid. This property can be used during transportation of pharmaceutical powders. The flow of powders through pipes and hoppers can significantly affect processing.*

b) *The salt has been compressed into the bottom of the salt shaker. The ability to be compressed is a property of a gas. This property is used to create pharmaceutical tablets, where powders are compressed to form a solid dosage form.*

c) *The gravel can support the weight of your body. This is a property of a solid material. This understanding of the unique properties of granular materials is important in specific industrially relevant situations including powder transportation through chutes and tableting operations where powders are compressed into compact pills.*

PROBLEM 2: EXAMINING PARTICLE SEGREGATION WITH THE RSD

The active pharmaceutical ingredient (API) in a pharmaceutical tablet is often significantly smaller than the particles being used as fillers and binders. As a result, the segregation of the small API particles can detrimentally effect the production of pharmaceuticals by creating inconsistent tablet compositions. Currently, the Center is using computer simulations to determine the effects of particle properties on the segregation of granular mixtures. The relative standard deviation (RSD) is used to quantify the degree of segregation within the mixture. This problem introduces the concept of segregation in pharmaceutical engineering, while teaching students about RSD calculations. Particle technology concepts are not always incorporated into a traditional chemical engineering curriculum. A better understanding of granular behavior is important because it can greatly affect the composition and therefore the efficacy of pharmaceutical products.[4] This problem is suitable for a freshman or sophomore engineering or applied math course.

Problem Statement

When manufacturing pharmaceutical products, it is important to limit the segregation of materials to prevent differences in pharmaceutical powder concentrations. Segregation occurs when property differences between the particles cause them to demix. To illustrate segregation in powder a vibrating cylinder system containing pharmaceutical powders of differing sizes can be used (Figure 1a). This geometry is similar to the trans-

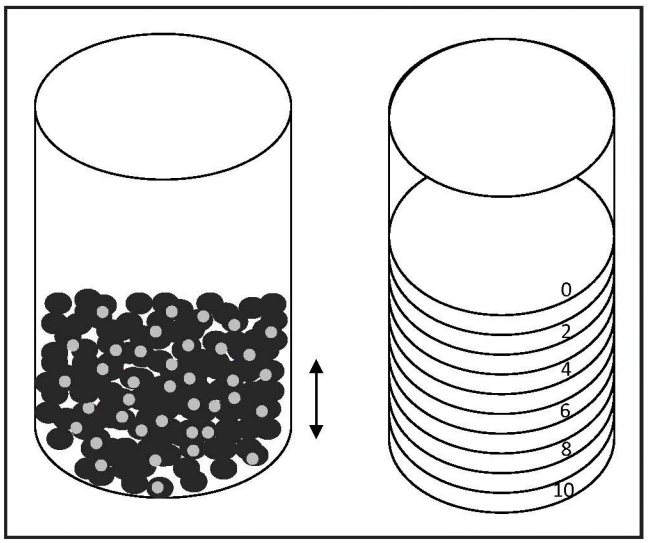

Figure 1. *Figure 1a (left) shows a diagram of vibrating cylinder system with grey API particles and black filler particles. Figure 1b (right) shows the position of the samples taken from the vibrating cylinder system.*

TABLE 1
Number of API Particles in Samples Over Time

	Time (s)						
	0	10	20	30	40	50	60
Sample Number	Number of API Particles						
1	10	3	2	0	0	0	0
2	10	6	3	1	0	0	0
3	10	8	5	2	1	0	0
4	10	8	5	3	2	3	1
5	10	9	8	5	7	5	4
6	10	10	10	12	12	11	8
7	10	12	12	15	13	14	16
8	10	15	14	17	16	17	19
9	10	12	18	20	23	24	25
10	10	17	23	25	26	26	27
Sum	100	100	100	100	100	100	100

portation of powder products in drums in the pharmaceutical industry where segregation can occur.

Students are presented with an example of a vibrating system where segregation occurs between the small gray particles that represent the API and the large black particles, that represent the binder and filler particles. By analyzing the segregation in the system over time, the behavior of the particles can be examined. One method of analyzing particle segregation is through the use of the RSD. The equation for the RSD can be seen in Equations (1), (2), and (3).

$$C = \frac{\#\text{ of API Particles in Sample}}{\text{Total \# of Particles}} \quad (1)$$

$$RSD = \frac{\sigma}{\bar{C}} \quad (2)$$

$$\sigma = \sqrt{\frac{\sum_{i=1}^{N}\left(\bar{C} - C_i\right)^2}{N-1}} \quad (3)$$

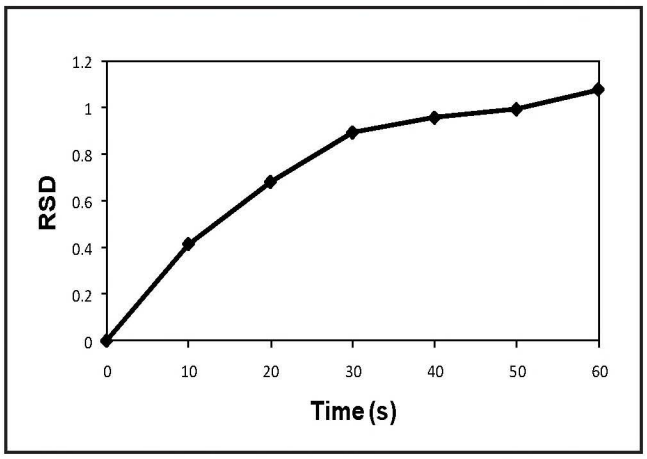

Figure 2. *RSD of the API particles showing the degree of segregation as the cylinder vibrates.*

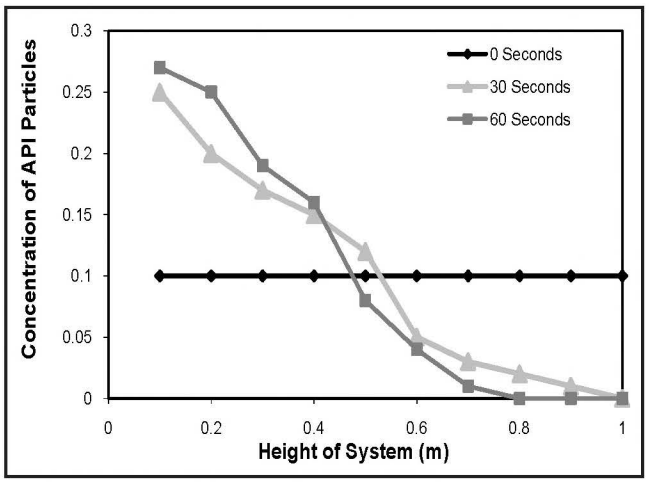

Figure 3. *Change in the distribution of API particles over the height of the vibrating cylinder.*

where $\bar{C}$ is the fully mixed concentration of API particles (time = 0), C_i is the concentration of API particles in sample i, and N is the total number of samples.

Based on the data in Table 1, produce a graph of the RSD vs. time for the cylindrical system seen in Figure 1b.

a) What does it mean when the RSD is equal to zero?

b) What do you think the chart says about the amount of segregation over time?

c) Each of the samples shown in Table 1 represents all of the particles in one disk of the cylinder, as seen in Figure 1b. If the particles reach a height of 1 m, produce a graph containing the concentration of API particles with respect to the height at 0, 30, and 60 seconds. What happens to the API particles over time?

Problem Solution

The students will convert the number of particles to the concentration of particles in each sample using Equation (1). Table 1 shows the concentration of API particles in each sample over time. The concentrations can then be used to determine the RSD using Equations (2) and (3) and can be tabulated (see Table 2, on page 57). The students can then graph the RSD value over time to determine the relationship between the RSD and the level of segregation in the drug system (Figure 2). When the RSD is equal to zero, it means that the system is perfectly mixed and the concentration of API (small particles) is equal in every sample. As time goes on, the RSD becomes higher, which means that the system is becoming segregated. Therefore, if the drugs were formulated from this mixture, they would have too little or too much API to meet specifications.

The students can then change the sample number to the height of particles in the cylinder, with each sample disk being 0.1 m in height, and further calculations can be made. The students can graph the concentration of API particles vs. the height of particles to see the distribution of particles over the height of the system (Figure 3). The graph shows that the API particles move toward the bottom of the system over time. The system starts fully mixed, but as it vibrates, the smaller particles are able to fit through the void spaces between the filler (larger particles). This type of segregation is called percolation and occurs between small APIs and larger filler and binder particles used to make pharmaceutical tablets.

Drums similar to the cylinder discussed in this problem are used to transport pharmaceutical particles from site to site in an industrial setting. It is important that the particle size distribution remains homogeneous throughout the process to prevent inconsistencies in processing. Also, when transporting pharmaceutical powders between equipment (for example from a mixer to the tablet press) this type of segregation can occur. The resulting nonhomogeneous mixture can be detrimental to the manufacturing process, therefore understanding this phenomenon is important.

The goal is to increase student interest in research and development in the pharmaceutical industry by introducing students to basic pharmaceutical engineering concepts within the framework of existing courses. Educational topics include the states of matter, unit conversions, material balances, and relative standard deviations.

PROBLEM 3: CONTINUOUS POWDER FLOW MIXING

Introductory-level chemical engineering students often learn about material balances through problems that involve gas and liquid process streams. The problem aims to emphasize material balances for multi-component solid-phase systems while introducing the pharmaceutical manufacturing concept of continuous tablet production. The problem requires the student to perform material balances around a continuous dry blender. The problem exposes introductory-level chemical engineering students to novel solids blending technologies being developed in the pharmaceutical industry. This problem can be used in an introductory sophomore material balance or process principles class.

Problem Statement

Research is under way to convert traditional batch processes to continuous-flow operation for pharmaceutical tablet production. The continuous processing techniques will decrease the costs of labor and time while increasing the uniformity of the final drug tablets. One of the research areas in pharmaceutical powder flow technologies examines the cohesive properties in continuous powder flow blending.[15] One of these experiments examines the properties of pharmaceutical formulations after they have been blended using a continuous-flow mixer.

The production of acetaminophen tablets used for pain relief requires many unit operations to process the active ingredients and excipients (other ingredients) into tablet form. One of these unit operations is a powder-blending stage in which powders are mixed together in preparation for the final tableted product. These powders include: starch, a binder; acetaminophen and codeine phosphate, the active ingredients in prescription-strength pain medicine; and Avicel microcrystalline cellulose, a filler. Three feed streams enter a continuous blender; the first contains pure starch at 28 mg/min, which is combined with a stream of pure cellulose. The third feed stream contains a mixture of acetaminophen and codeine phosphate in a 10:1 mass ratio, respectively. The output flow leaves at a rate of 9.3×10^{-4} lb/min and has a composition of 71.0 wt% acetaminophen. In the next process, magnesium stearate, a lubricant, is blended with the output mixture.

a) *What is the input flow rate of the third stream and what is its composition?*

b) *What are the compositions of the other components of the output stream?*

c) *If each tablet contains 300 mg of acetaminophen, how many tablets are being produced per hour?*

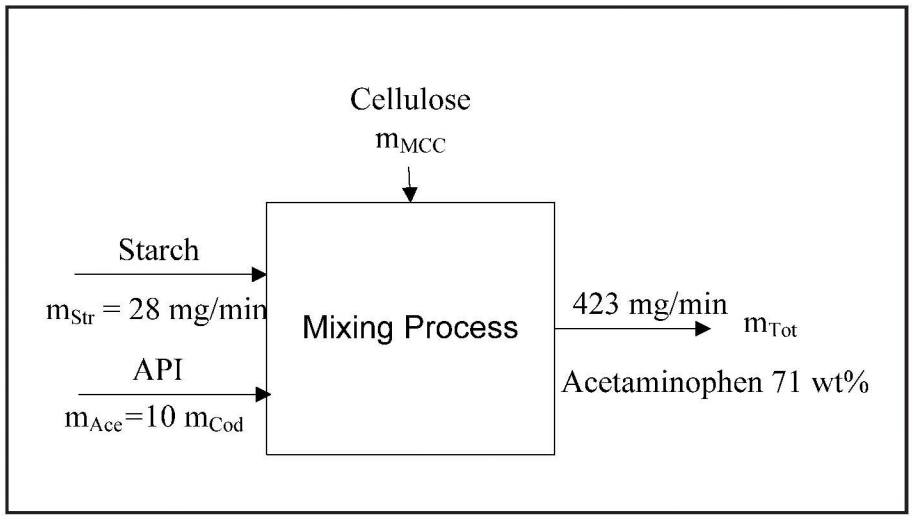

Figure 4. *Flow diagram of the continuous mixing process.*

Problem Solution

The student will need to perform a mass balance to solve for the flow rates and compositions of the inlet and outlet streams. A flow diagram of the process is shown in Figure 4. From the diagram, an overall material balance can be performed to determine the flow rate of materials in and out of the system (with appropriate unit conversions). From the problem it is known that the mass of acetaminophen to codeine is 10:1.

$$m_1 + m_2 + m_3 + m_4 = m_5 \tag{4}$$

$$28\frac{mg}{min} + m_{Ace}\left(\frac{10m_{Cod}}{m_{Ace}}\right) + m_{Cod} + m_{MCC} = 9.3\times10^{-4}\ \frac{lb}{min}\left(\frac{1g}{0.0022lb}\right) = 423\frac{mg}{min} \tag{5}$$

The output stream composition from the blender can be used to find the input stream flow rate of acetaminophen.

$$m_{Ace} = 423\frac{mg}{min}(0.71) = 300\frac{mg}{min} \tag{6}$$

$$m_{Ace} = 300\frac{mg}{min} = 10m_{Cod} \Longrightarrow\ m_{Cod} = 30\frac{mg}{min} \tag{7}$$

Using the total mass balance we can now find the input flow rate of Avicel microcrystalline cellulose.

$$28\frac{mg}{min} + 11\left(30\frac{mg}{min}\right) + m_{MCC} = 9.3\times10^{-4}\ \frac{lb}{min}\left(\frac{1g}{0.0022\ lb}\right) = 423\frac{g}{min} \tag{8}$$

$$m_{MCC} = 65\frac{mg}{min} \tag{9}$$

Now that the flow rate of each component is calculated, the composition of the output stream from the ribbon blender can be calculated and number of pills determined.

$$m_{MCC} = \frac{65\frac{mg}{min}}{423\frac{mg}{min}}\times100 = 15.4\% \tag{10}$$

$$m_{Cod} = \frac{30\frac{mg}{min}}{423\frac{mg}{min}}\times100 = 7.0\% \tag{11}$$

$$m_{Ace} = 300\frac{mg}{min}\times\frac{1\ pill}{300\ mg}\times\frac{60\ min}{hr} = 60\frac{pills}{hr} \tag{12}$$

PROBLEM 4: ACETAMINOPHEN DRYING RATE DETERMINATION

Drying is a process not normally taught in the traditional chemical engineering curriculum, but is important in pharmaceutical manufacture. In this problem, students perform material balances on a dryer and determine the time required to fully dry a pharmaceutical powder mixture. The problem can be used in material and energy balance and heat transfer classes.

Problem Statement

The pharmaceutical industry currently uses a series of batch processes in the full-scale production of tablets. In one of the initial steps in manufacturing a pain medicine, acetaminophen and hydroxypropyl cellulose are granulated to create small drug particles, which form a powder. The hydroxypropyl cellulose is a water-soluble binder that is dissolved in water prior to granulation. After granulation, the water must be removed so that only 2.0 wt % water remains in the powder.[16] Initially, the powder contains 7,560 g of acetaminophen, 247 g of hydroxypropyl cellulose, and 15.0 wt % water.[17] The water is then removed in a tray dryer, where the powder is placed on trays and hot air is circulated until only 2.0 wt % water remains.

a) Determine how much water must be removed from the powder.

b) The powder is placed on five trays that are 24 inches wide and 30 inches long. The thickness of the powder is 20 mm and the

bottom and sides of the tray are assumed to be insulated. Dry air at 75 °C (T) and 8.5% humidity flows parallel to each tray at a rate of 5 m/s. Estimate the rate of drying for the constant-rate drying period of the powder.[18]

c) What will be the minimum time required for the drying of the powder?

Problem Solution

$$\text{Total Mass} = 7{,}560\text{ g Ace} + 247\text{ g Hyd} + \text{x g Water} \tag{13}$$

To calculate the amount of water in the initial and final powder stream use the mass fraction values to calculate the grams of water.

$$\frac{x_i}{7{,}807 + x_i} = 0.15 \Longrightarrow x_i = 1{,}378\text{ g Water} \tag{14}$$

$$\frac{x_f}{7{,}807 + x_f} = 0.02 \Longrightarrow x_f = 159\text{ g Water} \tag{15}$$

$$1{,}378\text{ g water} - 159\text{ g water} = 1{,}218\text{ g water is removed} \tag{16}$$

At 8.5% humidity, it was determined that the air absolute humidity (H) is 0.010 kg H_2O/kg air, the wet bulb temperature (T_W) was found to be 40 °C, and the absolute humidity at saturation (H_W) was 0.05 kg H_2O/kg air. The humid volume of the air (ν_H) was then determined.

$$\nu_H\left[\frac{m^3}{\text{kg dry air}}\right] = \frac{22.41}{273}T[K]\left(\frac{1}{28.97} + \frac{1}{18.02}H\right) = 1.00\frac{m^3}{\text{kg dry air}} \tag{17}$$

Using the humid volume, the density (ρ) and the mass velocity (G) of the humid air were calculated.

$$\rho = \frac{1.0\text{ kg dry air} + 0.010\text{ kg water}}{1.00\dfrac{m^3}{\text{kg dry air}}} = 1.1\frac{kg}{m^3} \tag{18}$$

$$G = \nu\rho = 19{,}800\frac{kg}{hr\ m^2} \tag{19}$$

The convective heat transfer coefficient (h in W/m^2K) for parallel air flow across the tray was then calculated.

$$h = 0.0204\ G^{0.8} = 55.8\frac{W}{K\ m^2} \tag{20}$$

Using steam tables, it was determined that the latent heat of the vaporization at T_W (λ_W) was equal to 2,574.3 kJ/kg. This can then be used to find the rate of drying per unit area (R_c) during the constant-drying period.

$$R_C\left[\frac{\text{kg water}}{h\ m^2}\right] = \frac{h}{\lambda_W}\left(T - T_W[°C]\right)\frac{3600\text{ s}}{1\text{ hr}} = 2.73\frac{\text{kg water}}{h\ m^2} \tag{21}$$

The total rate can then be determined by multiplying the rate of drying per unit area by the area of all of the trays.

$$\text{Total Rate} = 2.73\left[\frac{\text{kg water}}{h\ m^2}\right]\left(5\text{ trays} \times 24\text{ in} \times \frac{1\text{ ft}}{12\text{ in}} \times \frac{0.3048\text{ m}}{1\text{ ft}} \times 30\text{ in} \times \frac{1\text{ ft}}{12\text{ in}} \times \frac{0.3048\text{ m}}{1\text{ ft}}\right) \tag{22}$$

$$\text{Total Rate} = 6.34\text{ kg } H_2O/\text{hour} \tag{23}$$

The time required for drying can be determined by

$$\text{Drying Time} = \frac{\text{Amount of Water to be Removed}}{\text{Constant Drying Rate}} \tag{24}$$

$$\text{Drying Time} = \frac{1218\text{ g } H_2O}{6.34\frac{kgH_2O}{h}} \times \frac{1\text{ kg}}{1000\text{ g}} \times \frac{60\text{ min}}{1\text{ h}} = 11.5\text{ minutes} \tag{25}$$

SUMMARY

Basic problems on particle technology and processing relevant to pharmaceutical manufacturing have been developed for integration into engineering curricula. Educational topics include the states of matter, unit conversions, material balances, and relative standard deviations. The goal is to increase student interest in research and development in the pharmaceutical industry by introducing students to basic pharmaceutical engineering concepts within the framework of existing courses.

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REFERENCES

1. P.R. Westmoreland, "Chemistry and Life Sciences in a New Vision of Chemical Engineering," *Chem. Eng. Ed.*, **35**(4), 248 (2001)
2. Slater, C.S., and R.P. Hesketh, "Incorporating Green Engineering into a Material and Energy Balance Course," *Chem. Eng. Ed.*, **38**(1), 48 (2004)
3. Slater, C.S., R.P. Hesketh, D. Fichana, J. Henry, A.M. Flynn, and M. Abraham, "Expanding the Frontiers for Chemical Engineers in Green Engineering Education," *J. Eng. Ed.*, **23**(2), 309 (2007)
4. Augsburger, L.L., "Ensuring the Supply of Highly Qualified Pharmaceutical Scientist Specialists in Product Development and Related Technologies for Present and Future Needs —Report of the 2004 PT Section Education Committee," *AAPS PharmSciTech*, **8**, p. E1 (2007)
5. Farrell, S., and R.P. Hesketh, "An Introduction to Drug Delivery for Chemical Engineers," *Chem. Eng. Ed.*, **36**(2), 198 (2002)
6. Nash, R.A., "A Laboratory Experiment in Pharmaceutics: Macro-Physical Properties of Pharmaceutical Powders," *American J. of Pharmaceutical Ed.*, **48**, 143 (1984)
7. Ross, M.R., "A Classroom Exercise in Sampling Technique," *J. Chem. Ed.*, **77**, 1015 (2000)
8. Iveson, S.M., and G.V. Franks. "Particle Technology Demonstrations," *Chem. Eng. Ed.*, **37**(4), 274 (2003)
9. Fritz, M.D., "A Demonstration of Sample Segregation," *J. Chem. Ed.*, **82**, 255 (2005)
10. Bucalá, V., and J. Piña, "Teaching Population Balances for ChE Students: Application to Granulation Processes," *Chem. Eng. Ed.*, **41**(3), 209 (2007)
11. Ehrman, S.H., P. Castellanos, V. Dwivedi, and R.B. Diemer, "A Population Balance Based Design Problem in a Particle Science and Technology Course," *Chem. Eng. Ed.*, **41**(2), 88 (2007)
12. Sinclair, J.L., "A Survey Course in Particle Technology," *Chem. Eng. Ed.*, **33**(4), 266 (1999)
13. Schmid, H., and W. Peukert, "Novel Concepts for Teaching Particle Technology," *Chem. Eng. Ed.*, **36**(4), 272 (2002)
14. Geldart, D., "Powder Processing—The Overall View," in *Principles of Powder Technology*, M.J. Rhodes, Ed. John Wiley & Sons, New York (1990)
15. Portillo, P.M., M.G. Ierapetritou, and F.J. Muzzio. "Characterization of Continuous Convective Powder Mixing Processes," *Powder Technology*, **182**, 368 (2008)
16. Uhumwangho, M.U., and R.S. Okor, "Modification of Drug Release from Acetaminophen Granules by Melt Granulation Technique—Consideration of Release Kinetcis," *Pharmaceutical Science*, **19**(1), 27 (2006)
17. Holinej, J., J.L. Johnson, and L.J. Miller, "Evaluation of Hydroxypropylcellulose as a Dry Tablet Binder in Granulation," *Pharmaceutical Technology Report*, Hercules Incorporated (2002)
18. Niazi, S., *Handbook of Pharmaceutical Manufacturing Formulations: Compressed Solid Products*, Vol 1., CRC Press, New York (2004) ❐

TABLE 2
Calculation of RSD from the concentration of API particles

	Time (s)						
	0	10	20	30	40	50	60
Sample Number	$\left(\overline{C}-C_i\right)^2$						
1	0	4.90E-03	6.40E-03	1.00E-02	1.00E-02	1.00E-02	1.00E-02
2	0	1.60E-03	4.90E-03	8.10E-03	1.00E-02	1.00E-02	1.00E-02
3	0	4.00E-04	2.50E-03	6.40E-03	8.10E-03	1.00E-02	1.00E-02
4	0	4.00E-04	2.50E-03	4.90E-03	6.40E-03	4.90E-03	8.10E-03
5	0	1.00E-04	4.00E-04	2.50E-03	9.00E-04	2.50E-03	3.60E-03
6	0	0.00E+00	0.00E+00	4.00E-04	4.00E-04	1.00E-04	4.00E-04
7	0	4.00E-04	4.00E-04	2.50E-03	9.00E-04	1.60E-03	3.60E-03
8	0	2.50E-03	1.60E-03	4.90E-03	3.60E-03	4.90E-03	8.10E-03
9	0	4.00E-04	6.40E-03	1.00E-02	1.69E-02	1.96E-02	2.25E-02
10	0	4.90E-03	1.69E-02	2.25E-02	2.56E-02	2.56E-02	2.89E-02
$\Sigma\left(\overline{C}-C_i\right)^2=\text{Sum}$	0	1.56E-02	4.20E-02	7.22E-02	8.28E-02	8.92E-02	1.05E-01
Sum/(N-1)	0	1.73E-03	4.67E-03	8.02E-03	9.20E-03	9.91E-03	1.17E-02
$[\text{Sum}/(N-1)]^{1/2}=\sigma$	0	4.16E-02	6.83E-02	8.96E-02	9.59E-02	9.96E-02	1.08E-01
$\sigma/\overline{C}=\text{RSD}$	0	4.16E-01	6.83E-01	8.96E-01	9.59E-01	9.96E-01	1.08E+00