AC 2011-1427: INTEGRATION OF PARTICLE TECHNOLOGY WITH PHARMACEUTICAL INDUSTRY APPLICATIONS IN THE CHEMICAL ENGINEERING UNDERGRADUATE CURRICULUM AND K-12 EDUCATION

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Integration of Particle Technology with Pharmaceutical Industry Applications in the Chemical Engineering Undergraduate Curriculum and K-12 Education

Abstract

Rowan University, in collaboration with the National Science Foundation (NSF) funded Engineering Research Center for Structured Organic Particulate Systems (C-SOPS), is developing teaching modules and problem sets to introduce students to engineering concepts in the particle and powder technology of pharmaceutical processing and drug delivery systems. The Center is hosted by Rutgers University and also includes Purdue University, the New Jersey Institute of Technology, and the University of Puerto Rico in Mayagüez. The goal of the Center is to become a national focal point for developing structured organic particulate systems used in pharmaceuticals and their manufacturing processes. Rowan University has partnered as an outreach/education member institution to develop teaching modules for K-12 and college level students. The Rowan University efforts have focused on mobile, hands-on teaching modules and problem sets for use in engineering courses. A pneumatic transport mobile experimental unit has been designed and constructed for use in fluid mechanics courses and for K-12 outreach activities, workshops and summer camps. The unit can be used for demonstrations and for laboratory experiments. Students can apply energy balance principles to calculate velocities and drag forces. The use of this unit in the Rowan Engineers-on-Wheels Program will be highlighted. The problem sets developed as part of this work focus on the integration of pharmaceutical technology into introductory-level chemical engineering courses. These problem set modules include topics covering terminology, formulation and manufacturing techniques for personal care products, over the counter medicines and prescription drugs. The problems are organized for use in a material and energy balance course, and cover a wide range of subjects from simple mass balances to heats of formation. The completed educational materials will be incorporated into the C-SOPS website for use by Center members and faculty at other schools. This work will serve to expand and strengthen the educational impact of the Center in the region and throughout the country.

Introduction

The NSF-sponsored Center for Structured Organic Particulate Systems (C-SOPS) is striving to become a focal point in pharmaceutical processing. The overall goals of the Engineering Research Center are coordinated through carefully planned thrust areas. The thrust areas include the major research initiatives of the Center: manufacturing science; composites structuring and characterization; and particle formation and functionalization. Three test beds based on programs developed from the thrust areas have been created at the Center. Development Program I concentrates on the continuous manufacturing of pharmaceutical tablets. Continuous tablet manufacturing processes offer significant advantages over batch processes. These advantages include an increase in tablet uniformity and stability, reduced production and labor costs and simplified scale up from experimental testing to full scale manufacturing[1]. Development Programs II and III focus on novel methods for drug delivery. Development Program II focuses on the stabilization of API (active pharmaceutical ingredient) nano-particles

in edible substrates[1, 2]. The higher surface areas of nano-particles results in higher material bioavailability. Finally, Development Program III includes a drop-on-demand system to layer API's on an edible substrate[1, 2]. The system could be portable and compact for use in third world countries and military applications. Rowan University partnered with the ERC-SOPS Center in 2008 to provide outreach and training components to support the educational mission of the Center. During the first year of the project, Rowan University worked with various constituency groups to implement certain projects that directly impact the Center's goals. This work has been expanded during the subsequent two years and additional modules and course materials have been developed.

This paper describes the progress to date. Our long term goals are to:
• train students who will be effective engineers and leaders in the manufacturing and research operations of the pharmaceutical and allied industries of the center.
• train students for roles in education and in the agencies involved in regulating food and drug manufacturing operations.
• integrate the Center´s research discoveries in engineered organic composite systems to enrich the existing engineering curriculum at both the undergraduate and graduate levels
• develop educational programs for industrial practitioners and foster alliances with industry in the education and outreach activities of the center.
• design and promote experiential programs and pedagogical material for K-12 outreach recognizing diverse student and teacher backgrounds.
• develop a suite of modular educational units for use by the various center constituents in formats that allow for efficient web-based dissemination.

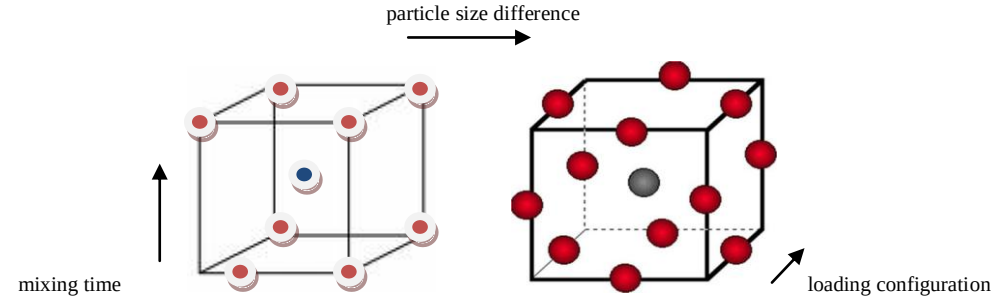
These goals are important components of the overall center vision and are an integral part of its mission to bring together cutting-edge research, technology transfer and next-generation training of the technical workforce. The outreach modules[3] and educational materials have been developed by a highly qualified College of Engineering faculty team working with undergraduate and graduate students. The following sections provide a summary of the ongoing activities in the various projects under the Rowan University / ERC-SOPS Center partnership umbrella. There are two major sections in this paper. The first section highlights the educational laboratory modules and outreach experiences, and the second section highlights the textbook problems developed as part of this work. More detailed examples of the outreach/educational materials and problems will be presented in the final poster presentation.

Educational laboratory modules and outreach experiences

Particle properties and powder mixing experiments throughout the curriculum:
A V-mixing laboratory experience[4, 5] was designed last year for students to investigate the effect of mixing time, particle size and loading configuration in a statistical design. The experiments and data analysis can be conducted over multiple class periods, and students were exposed to experimental design strategies. A 5 L constant frequency V-mixer was used for laboratory experiences in courses, projects and research. Figures 1a and b show the mixer and the loading operation for a mixing experiment.

Figures 1 a) 5 L V-mixer b) Loading mixer for experiment

Factorial and response surface Box-Behnken experimental designs are used and students assess the efficacy of experimental design strategies. Variables studied include particle size and particle size difference, mixing time and loading configuration. Figures 2 a and b are qualitative illustrations of three variable factorial and Box-Benhken experimental designs used in this work. The three variables illustrated in Figures 2 a and b are mixing time, particle size difference and loading configuration. The circles indicate experimental conditions and the vertices are the minimum and maximum values of the variables investigated. In the case of loading configuration, the experimental conditions refer to specific configurations (i.e. top/down, side by side).



Figures 2 a) Factorial Design b) Box-Behnken Design

A spectrophotometric technique was developed to measure mixing quality for these experiments[5]. Different color silica particles were used so that students could easily distinguish among different mixtures and hexane was used to dissolve a dye and carry out the spectrophotometric measurements. One color was tracked to simplify the spectrophotometric statistical analyses using variance and the Poole Index to measure mixing quality.

The V- Mixer laboratory was expanded this year to include the use of conductivity to measure mixing quality. Salt (NaCl) particles were mixed with silica particles. At the conclusion of the mixing experiment, samples were taken and placed in 25 ml of distilled deionized water. The sampling method was previously developed[5]. The conductivity of the water was measured and from a calibration curve, the sample salt content was obtained. Figure 3 shows the calibration curve obtained for this work. It compares well with literature values for the conductivity of

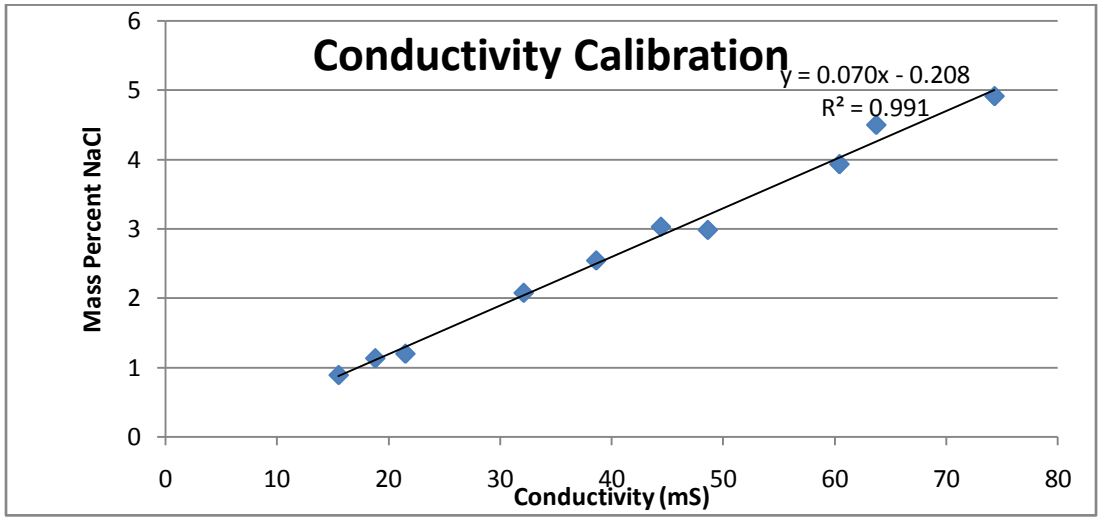


Figure 3: Conductivity meter calibration – NaCl in water

NaCl. Preliminary results were obtained by mixing equal amounts of NaCl and silica in the V-mixer for five minutes at 60Hz. At the conclusion of the experiment, the NaCl mass percent in the sample ranged from 48% to 50%. The variance of the measurements was less than 3%indicating good repeatability among measurements.

Particle density and size can impact the quality of mixing in a V- mixer. Particle characterization is an important component of overall mixing quality determination. The Stoke's terminal velocity, given by Equation 1, was used to characterize particles in this work[6]. Stoke's Law applies for Reynolds Numbers <1.

$$U_t = \frac{(\rho_s - \rho) * g * {d_p}^2}{18 * \mu} \qquad (1)$$

Where ρ_s and ρ = the density of the particle and fluid in which it falls respectively
g = the acceleration of gravity
d_p = particle diameter
μ = fluid viscosity

This particle characterization allows for a single parameter to be used as a variable in the experimental design illustrated in Figures 2. The particle size difference shown in the figure is replaced by the particle Stoke's Law terminal velocity. Particle size was measured as part of this work using a shaker. Φ_{50} values were used as estimates of average particle sizes.

Pneumatic Transport Demonstration:

A pneumatic transport demonstration was designed and constructed. This unit will be used in a process fluids transport course, and to demonstrate energy balances in a fluid mechanics course.

Figure 4 shows the unit. A more portable unit was also designed for outreach applications.

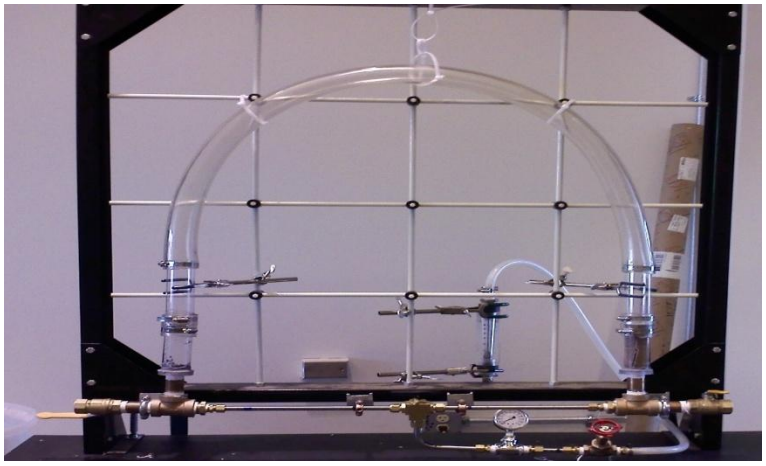


Figure 4: Pneumatic transport unit

The unit allowed for the transport of particles from one side to the other. Different shape and size particles can be used. Also, different color particles add visual appeal to the demonstration. This is especially valuable for demonstrations with younger students.

The pneumatic transport unit can be constructed from a variety of materials. The part inventory for the unit depicted in Figure 4 is listed below.

Table 1: Part Inventory For Pneumatic Transport Apparatus

ITEM	QTY.	SPECIFATION	DESCRIPTION
1	6 ft	2" ID - 2.5" OD	Tygon® PVC Tubing (0.25" wall)
2	2 ft	1.75" OD 1.5" ID	Poly-Carbonate Round Tube (clear - 0.125" wall)
3	2	1.0" NPT	Brass Ball Valve - Female Connections
4	2	1.0"	Medium-Pressure Cast Brass Threaded Pipe Fitting, TEE
5	2	1" Male X 1/2" Female	Medium-Pressure Cast Brass Threaded Pipe Fitting, Hex Bushing
6	400	0.125" DIA.	Nylon Spheres
7	4	0.5" NPTF	Std. Brass Compression Tube Fitting Adapter Male Pipe
8	1	0.5" TUBE OD	Brass Ball Valve w/ YOR-LOK Fittings Diverting 3-port Ultra High Pressure
9	6" x 6"	0.125" spacing	Std. Screen/Mesh Air Distributor
10	1	1/2" class 150	Bronze Globe Valve 1" NPT Female - Throttling Valve
11	N/A	0.5" TUBE OD	Unspecified length (can vary)
12	4	1"	Thick-wall Brass Threaded Pipe Nipple, Sch 80,11/16" Thread Length
13	1	10-60 SCFM @ STP	Rotameter/Flowmeter

Hands-on demonstrations of particle properties:

A series of demonstrations were developed last year.[5] Figures 5 through 8 show the demonstrations illustrating arching in hopper flow, the effect of particle size on segregation, compression forces generated during particle flow and the rise of a large particle in a bed of smaller particles.

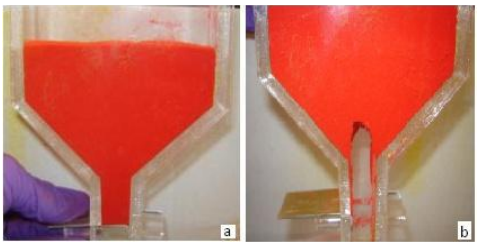


Figure 5: Arching in hopper flow


Figure 6: Tumbler apparatus for segregation demonstration

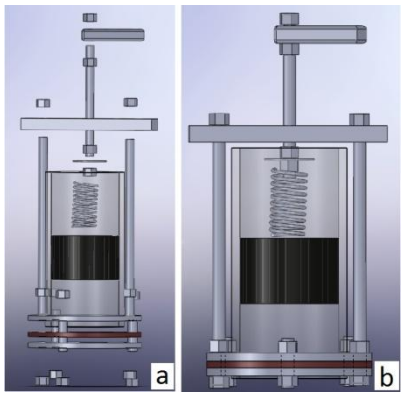


Figure 7: Compression forces generated during particle flow


Figure 8: Rise of large particle in bed of smaller particles

These demonstrations were refined this year and used in several outreach programs including summer workshops for teachers and Science, Math and Related Technology programs at Delaware Girls Inc. The demonstrations are presently being included in the Rowan Engineers on Wheels program. The demonstrations will continue to be expanded and used in courses and outreach programs.

Problem Modules for Introductory Chemical Engineering Courses

Problem sets have been developed on pharmaceutical technology for integration into introductory-level chemical engineering courses. These modules include topics covering terminology, formulation and manufacturing techniques for personal care products, over the counter (OTC) medicines and prescription drugs. The problems are organized for use in a material and energy balance course and cover a wide range of subjects from simple mass balances to heats of formation.

This component of the ERC outreach effort is the development of problem sets for use as in-class examples and homework problems for chemical engineering courses. The goal of this work is to translate organic particulate systems manufacturing concepts and research being done the Center into educational materials that can be used at various levels[5,7,8]. The problem sets are curriculum modules tailored to specific age levels by varying the technical content level of the problems. Each curriculum module consists of a multi-part problem statement with a link to an ERC area, relevant literature references, and fully executed solution.

During the last several years, the focus was on problem sets for introductory chemical engineering courses such as material and energy balances[7,8]. Concepts in drug formulation, manufacturing and delivery were integrated with the educational objectives of the course in a way that makes it easy for a professor to use. Problem sets consisting of a problem statement and fully executed solution are presented in the module organized to follow the logical sequence in an introductory course. These include problems in basic concepts in pharmaceutical technology related to unit conversions and engineering calculations. Mass and energy balance calculation problems focus on pharmaceutical engineering operations such as blenders, dryers, tablet presses, etc. Problems related to stoichiometry focus on API synthesis. Various OTC drug and consumer products are used as the basis for example problems related to single and multi-phase equilibria, heats of mixing, heat or formation and degradation.

The problems are being designed for inclusion in the next edition of the textbook Elementary Principles of Chemical Processes by Felder, Rousseau, and Newell[9]. Therefore, each problem has a designated concept/chapter/section mapping. The successful framework and concepts already started by students last year was used to produce modules that are of significant quality and suitable for inclusion into textbooks, journal papers/proceedings and web-based media. Problems are posted on the PharmaHUB (www.PharmaHUB.org) under the ERC Educational Modules resources section[7,8]. The students at Rowan who develop these problems have a close interaction with graduate student liaisons from the ERC schools for background material on research activities of the Center as well as feedback on the technical content of the educational materials.

The following examples illustrate the type of problems developed for the various topical areas. Complete problem sets can be obtained through the PharmaHUB.

Cholesterol Drug Manufacturing Process[10]:

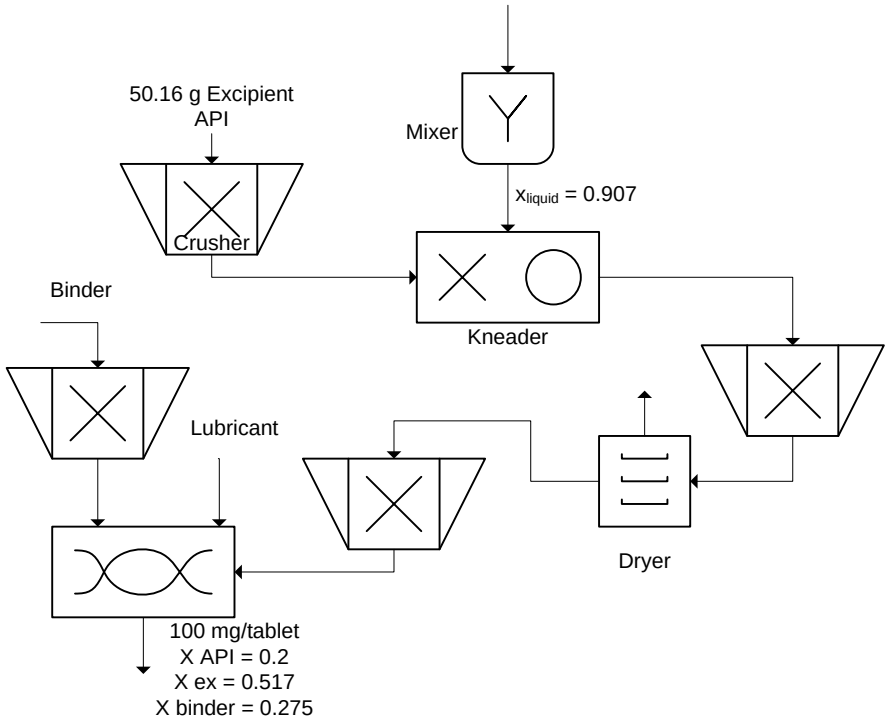
Topics covered: Material balance; Multiple unit process; Pharmaceutical manufacturing unit operations

Problem Statement:
About one in five Americans has a cholesterol level of above 200 mg/dL, this is considered to be very unhealthy[11]. A pharmaceutical company sets up a batch process in order to manufacture 1000 Cholesterol tablets used to lower the LDL and raise the HDL cholesterol[12].
The process of creating these tablets[13] is initiated by adding equal amounts of two active ingredients and 50.16 g of a filler to a kneading mixer. Once this is done another stream of

excipients consisting of 90.7% liquid by mass is added to the kneader. The resulting liquid mixture consists of two parts water and one part ethanol.

The kneading mixer produces a wet mass called a cake, which is spread over trays and kept in an oven at 45°C for eight hours. During the course of this time 17.3 wt% of the mass of the cake is evaporated. This dry substance is blended with a lubricant and a binder, it is then finally sent to be compressed into 100 mg tablets. The end product (tablets) has the following composition (% wt): 20% API, 51.7% excipients, 27.5% binder and the remaining lubricant. How much of each liquid is added to the kneader?

Problem Solution:
It is a good practice to draw the diagram with the given description.



It is known that each tablet weighs 100 mg and the process produces 1000 tablets. Based on the finished tablet formulation a calculation of the weight of 1000 tablets and its contents can be performed.

$$\frac{100\text{ mg}}{\text{tablet}}\text{ x }\frac{1\text{ g}}{1000\text{ mg}}\text{ x 1000 tablets} = 100\text{ g for 1000 tablets}$$

$$m_{\text{Binder}} = 100\text{g}(0.275) = 27.5\text{ g Binder}$$

$$m_{\text{Lubricant}} = 100\text{g}(0.008) = 0.8\text{ g Lubricant}$$

$$\left.\begin{aligned} m_{\text{APIs}} &= 100\text{ g}(0.20) = 20\text{ g API for two APIs} \\ m_{\text{excipients}} &= 100\text{ g}(0.517) = 51.7\text{ g} \end{aligned}\right\}\text{ Mass exiting from the dryer}$$

Mass leaving the dryer is equal to the mass of API and excipients

$$\text{Mass exiting the dryer} = m_{\text{API}} + m_{\text{ex}} = 20\text{ g} + 51.7\text{ g} = 71.7\text{ g}$$

The dryer evaporates 17.3 wt% of the mass entering, so 82.7 wt% of the mass is still left in the dryer which is the mass that's exiting the dryer.
Mass balance on the dryer:

$$m_{\text{in}} = m_{\text{evap}} + m_{\text{out}}$$
$$m_{\text{evap}} = 0.173 m_{\text{in}}$$
$$m_{\text{in}} = 0.173 m_{\text{in}} + m_{\text{out}} \rightarrow 0.827 m_{\text{in}} = m_{\text{out}} \rightarrow m_{\text{in}} = \frac{71.7\text{g}}{0.827} = 86.7$$
$$m_{\text{evap}} = m_{\text{in}} - m_{\text{out}} = 86.7\text{ g} - 71.7\text{ g} = 15.0\text{ g}$$

Mass entering the dryer is the same mass exiting the kneader. There are two streams entering the kneader, one with the API and excipients and the other with excipients containing 90.7 wt% liquid. It is also known that the 90.7 wt% liquid contains water and 95% ethanol, and there is twice as much water as ethanol.

The mass of the API is found to be 20.0 g in the initial steps and the problem statement gives the weight of the excipient in the stream with the API. A mass balance around the kneader can now be performed to find the contents of each stream.
Mass balance around the kneader:

$$\underset{\text{(stream with API)}}{m_1} + \underset{\text{(stream with liquid)}}{m_2} = m_3 = 86.7\text{ g}$$
$$m_1 = m_{\text{API}} + m_{\text{ex}} = 20.0\text{ g} + 50.16\text{ g} = 70.16\text{ g}$$
$$m_2 = m_3 - m_1 = 86.7\text{ g} - 70.16\text{ g} = 16.54\text{ g}$$
$$m_{\text{liquid}} = 0.907 m_2 = 0.907(16.54\text{g}) = 15.0\text{ g}$$

Using ratios of 2 parts water to 1 part ethanol, the mass of each can be calculated.

$$15\text{g} = 3x$$
$$x = \boxed{5.0\text{ g ethanol}}$$
$$2x = \boxed{10.0\text{ g water}}$$

This problem illustrates the following engineering principles: batch process calculations, multiple unit processes, solid and liquid properties. It introduces the pharmaceutical concepts of drug formulation terminology (API, binder, lubricant, etc), and pharmaceutical engineering processes (mixers, kneaders, blenders, dryers).

Through this problem, the instructor can introduce the concept of drug formulation and the role of the API and excipients. This is helpful in providing students with the terminology of the pharmaceutical industry. It uses the example of a cholesterol lowering medication, since these are among the most widely prescribed drugs on the market. Most problems in a material and energy balance course introduce students to unit operations (distillation, extraction, continuous stirred tank reactors, etc) which are prevalent in traditional chemical processing. This problem provides student with examples of pharmaceutical engineering processes such as blenders, kneading mixers, and cake dryers used in manufacturing.

Vapor Pressure of Surfactant in Medicinal Shampoo[14]:

Topics covered: Multiphase Systems, Colligative Solution Properties, OTC Pharmaceutical Formulations

Problem Statement:
Shampoos are composed principally of a surfactant (essentially soap), with various other functional (plasticizers, binders, fillers) and decorative (lather enhancers, fragrances, colors) ingredients added to suit specific regulation or marketing demands.[15] Trichologic (hair/scalp) complaints are frequently treated by the use of medicated shampoos, which contain some effective ingredient for treating the condition.

Two popular surfactants (which you may have seen on the ingredient list of shampoo) are *sodium lauryl* and *sodium laureth sulfate*. You are researching the feasibility of including *pyrithione zinc*, a common anti-dandruff medication, in the new surfactant sodium super sulfate (SSS). The solution of pyrithione zinc in SSS has a markedly lower vapor pressure than pure SSS, which is fortunate since SSS boils at a low enough temperature (80 °F) already.
If the heat of vaporization of sodium super sulfate is 15 kJ/mol determine the lowest viable molar fraction. Remember this is going to be used in hot showers as well as stored at room temperature.

Solution:
This is an exploration of colligative solution properties and an examination of possible applications of this interaction.
By reading the problem statement, students can see that they need to determine boiling point temperature as a function of composition of a solution of SSS and pyrithione zinc. A review of Felder & Rousseau Section 6.5c (colligative solution properties) gives the equation below:

$$\Delta T_{\mathrm{b}} = T_{\mathrm{bs}} - T_{\mathrm{b}0} = \frac{RT_{\mathrm{b}0}^2}{\Delta \widehat{H}_{\mathrm{v}}} x$$

Since it is necessary to find what amount of pyrithione zinc in SSS will raise the boiling temperature to a reasonable value, it makes sense to rearrange the equation:

$$T_{\mathrm{bs}} = \frac{RT_{\mathrm{b}0}^2}{\Delta \widehat{H}_{\mathrm{v}}} x + T_{\mathrm{b}0}$$

It should be obvious to students (possibly after a suggestion, if they don't like or didn't have graphical algebra) that this is slope-intercept form:

$$y = mx + b$$

Because it looks complex and takes some time to calculate, it is worth simplifying the coefficient:

$$\frac{RT_{b0}^2}{\Delta\widehat{H}_v} = 8.314\frac{\text{J}}{\text{mol}\cdot\text{K}} \times [(80+459)\ ^\circ\text{R}]^2 \times \frac{1}{15}\frac{\text{mol}}{\text{kJ}} \times \frac{1}{1.8}\frac{\text{K}}{\text{R}^\circ} \times \frac{1}{1000}\frac{\text{kJ}}{\text{J}} = 89\ \text{R}^\circ = 89\ \text{F}^\circ$$

Note the necessity of converting to an absolute temperature scale (Rankine, as shown here, or Kelvin) to match the absolute temperature scale of the gas constant. Also note the equivalency of Rankine and Fahrenheit degrees.
Putting this into the equation:

$$T_{bs} = (89x + 80)\ ^\circ\text{F}$$

The students are now faced with a practical problem: What constitutes "viable" for the purposes of this problem? What temperature range should be considered appropriate? OSHA stipulates that water should not be less than 50°C at the showerhead to prevent incubation of Legionnaire's Disease[16], however this is scalding[17]. Assuming that people won't care if their shampoo boils when they are already being scalded, take 50°C as the minimum temperature.
Converting to degrees F:

$$T(^\circ\text{F}) = 1.8T(^\circ\text{C}) + 32$$
$$T(^\circ\text{F}) = 1.8 \times 50\ ^\circ\text{C} + 32$$
$$T(^\circ\text{F}) = 122\ ^\circ\text{F}$$

And now substituting:

$$\frac{122-80}{89} = x$$
$$\boxed{x = 0.47}$$

It is left to the student to suggest that this is a rather high fraction for a solute in a solution. This problem illustrates the following engineering principles: boiling point of solution as a function of temperature, process design (temperature of water). It introduces the pharmaceutical concepts of drug formulation terminology: surfactant, API, etc, and OTC solid-liquid solution formulations.

Summary

The laboratory experiences and the textbook problems described here serve to educate students on the research and technology associated with pharmaceutical processing. The modules will be integrated into the CSOPS website for distribution to faculty within the Center and other schools. The modules will also be used in college level courses and in outreach efforts for middle and high school students and teachers. The laboratory modules illustrate a wide range of pharmaceutical technologies and operations. They can be used to show how concepts of physics, chemistry and engineering contribute to pharmaceutical manufacturing, research and development. The problems developed as part of this work are intended for use in sophomore level chemical engineering courses. Each problem introduces topics related to pharmaceutical technology and is directly related to a process, tablet formulation, drug delivery, or pharmaceutical equipment. All of the problem descriptions are based on realistic technology in use or currently under development. Students must use principles of chemical engineering they

are learning in their courses to solve the problems. Detailed solutions are provided with each problem. These solutions can be used by faculty to assist in the presentation of the problem, or distributed directly to students. The problems have been reviewed by multiple team members and faculty. They will be distributed to sophomore classes at Rowan University to obtain feedback from students in the type of course where the problems could be used. Feedback on the educational modules will be obtained as well in an effort to continuously enhance and improve the material. The goal is for students to become familiar with pharmaceutical applications of powder and particle technology, and to practice the material they are learning in class in a realistic application of pharmaceutical technology. Students will become familiar with an important technology in chemical engineering and the impact of the Center will be expanded through increased student interest in pharmaceutical engineering.

Acknowledgements

ERC-SOPS is funded by NSF grant # 0540855

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