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Introductory Level Problems Illustrating Concepts in Pharmaceutical Engineering

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ABSTRACT

Textbook style problems including detailed solutions introducing pharmaceutical topics at the level of an introductory chemical engineering course have been created. The problems illustrate and teach subjects which students would learn if they were to pursue a career in pharmaceutical engineering, including the unique terminology of the field, common unit operations, calculations pertaining to drug manufacturing, and some of the specific concerns of the industry such as regulations and testing. Over seventy problems have been created; selected problems have been administered to students and their impact evaluated. Students demonstrated significant gains in knowledge of pharmaceutical engineering topics.

Keywords: Pharmaceutical engineering, drug manufacture, problem sets

INTRODUCTION

The American Society of Engineering Education (ASEE) recommended in 1994[1] that engineering programs should relate to the needs of its community, including the industries in which its graduates are employed. Graduates of Chemical Engineering programs have traditionally been employed in oil, commodity chemical or specialty chemical industries, but in recent years chemical engineers have emerged as essential contributors with an expanding role in other industries such as biotechnology

and pharmaceuticals [2], [3]. A 2005 survey for Chemical Engineering Progress [4] showed the pharmaceutical industry as one of the top five employers of chemical engineers. In the United States, the pharmaceutical industry employs one eighth of all chemical engineers, second only to the chemical process industry [4]. The pharmaceutical industry has traditionally focused heavily on research and development, but with fewer marketable drugs being discovered, there has been a shift to the optimization of existing production processes [5]. The role of chemical engineering in pharmaceutical production has therefore expanded requiring the inclusion of pharmaceutical engineering concepts in chemical engineering courses [3]. Attempts to add pharmaceutical engineering to the chemical engineering curriculum have commonly been made in the form of new upper-level and graduate courses specific to the pharmaceutical industry, such as pharmaceutical process development [6], or by teaching lessons specifically related to pharmaceutical topics. Graduate-level educational materials (lecture-based slides sets) have been published on the pharmaHUB website [6] and are related to unit operations used in pharmaceutical processes, solid-liquid separation techniques, nanopharmaceutical materials, or liquid-liquid and liquid-solid mixing equipment. These materials serve as lectures on specific segments of the pharmaceutical industry within an upper-level or graduate chemical engineering course.

Therefore, it is educationally useful and desirable to expose chemical engineering students to the field in early foundation courses such as their introductory material and energy balance course. Creating a pharmaceutically-oriented problem set that covers all of the topics in an introductory material and energy balance course allows for an integrated approach to exposing students to the pharmaceutical industry. Students will become familiar with pharmaceutical unit operations and terminology over the course of a semester instead of a short glimpse of it in one single lesson. This approach requires no additional curriculum modifications such as new courses, and problem sets can be readily integrated allowing for easy implementation by faculty.

Generally, material and energy balance courses introduce the engineering thought processes, teach units and their conversions, measurement of process values, use of mass balance equations, liquid and gas phases and their interactions, energy balance equations, basic thermodynamics, and stoichiometry. The subject matter in these introductory courses allows for the incorporation of problems related to pharmaceutical concepts because the areas of focus in the course can be found in many aspects of the pharmaceutical industry.

The pharmaceutical industry uses unique aspects of chemical engineering principles which are not always the primary focus of introductory courses. For example, mixing phases of gases, liquids, and solids to study the properties of homogeneous solutions is a common topic in introductory courses. However, using a pharmaceutical perspective allows for studying mixing of solid-solid mixtures and solid-liquid mixtures which can be found in final drug formulations and at different

stages of a pharmaceutical production process. For this topic, studying two-phase heterogeneous mixtures lends itself well to the pharmaceutical industry.

Many introductory courses use common unit operations such as distillation to teach the principles of mass and energy balances. By writing material and energy balance problems related to unit operations, students are given the opportunity to practice chemical engineering principles while learning about the equipment used in the industry. The pharmaceutical industry has unit operations specific to the industry, such as mixers, blenders, dryers, tablet presses, and milling machines. Mass and energy balance problems have been developed pertaining to these specific unit operations to give students the practice performing mass and energy balances and learn about pharmaceutical process equipment.

Introductory courses also tend to have a heavy focus on steady state continuous flow processes common to the chemical and petrochemical industries. However, the pharmaceutical industry is heavily batch-based; therefore examples of batch calculations are important in pharmaceutical processes and have been incorporated into our educational materials.

Finally, as with all fields, pharmacy and pharmaceutical engineering have unique jargon which must be mastered before any more advanced material can be understood. The most obvious example of this is in the names and classification of the raw materials used, such as "active pharmaceutical ingredient (API)" (the active ingredient) and "excipient" (inactive ingredient) and drug delivery method (parenteral, oral, etc.). These terms have been incorporated in many problems developed. The unique pharmaceutical term appears in bold-faced font in the problem statement and is followed by a definition.

Rowan University is an Outreach Partner for the National Science Foundation's (NSF) Engineering Research Center (ERC) for Structured Organic Particulate Systems (ERC-SOPS), which is led by Rutgers University. While the Center conducts research related to pharmaceutical technology, Rowan University's role is to produce educational materials related to the pharmaceutical industry. Rowan University's initial goal was to create problems related to the pharmaceutical industry which could supplement K-12 and engineering courses [7], and we have focused our current activities on introductory chemical engineering courses. The problem sets described in this paper can be used as in-class examples and cooperative learning exercises or as homework assignments.

This paper presents some of the problems resulting from the work being completed at Rowan University. The formatting, layout, style, and focus of the problems are based on those used in Felder and Rousseau's *Elementary Principles of Chemical Processes* [8], a widely-used textbook for these types of courses. Because of the common focus of introductory chemical engineering courses, those using a different textbook will not encounter any obstacles using these problems.

Table 1 displays the pharmaceutical topics that are explored in the problems, and how each topic is integrated into a particular chapter of Felder and Rousseau's book. The more universally applicable

Pharmaceutical Engineering Topic [9]	Course Subject (Follows Felder and Rousseau [8])	Number of Problems Created for Each Chapter
Existence of pharmaceutical engineering as a specialization of chemical engineering.	Chapter 1: What Some Chemical Engineers Do for a Living	1
Unit conversions related to drug formulations and dosage forms/delivery systems * Units specific to the pharmaceutical field (e.g. toxicology units, apothecary system) Physician prescription nomenclature Pharmaceutical terminology (e.g. API, excipient, binder, filler, lubricant, glidant)* Government regulations related to pharmaceutical development and manufacture Drug development timeline (discovery, clinical testing, scale-up, manufacture)	Chapter 2: Introduction to Engineering Calculations	12
Batch formulation calculations based on desired drug dose or production amount and raw materials Estimating parameters in drug delivery systems (dosage, human surface area for transdermal delivery, etc.)	Chapter 3: Process and Process Variables	18
Balances around continuous and batch pharmaceutical processes (mills, grinders, granulators, pill presses, kneaders, V-mixers) Production of pharmaceutical process flowsheets from process descriptions and incorporating unique unit operations	Chapter 4: Fundamentals of Material Balances	17
Analysis of metered dose inhalers (MDIs) Calculating liquid and solid dose drug formulation mixture densities	Chapter 5: Single Phase Systems	2
Use of Cox charts to estimate solvent evaporation Reading triangle phase diagrams to determine state of liquid-liquid mixture in a manufacturing or purification process Consideration of lowering vapor pressure caused by colligative properties in a liquid drug	Chapter 6: Multiphase Systems	5
Heat/energy duties in pharmaceutical processes Use of steam for heating and sterilization Use of Bernoulli's equation to determine necessary fluid velocities for suspension or homogenization	Chapter 7: Energy and Energy Balances	3
Calculation of heat of solution of a mixture used to provide cooling (e.g. cold packs) Use of mixture enthalpy chart in product manufacture Dissolution and precipitation in drug delivery	Chapter 8: Balances on Nonreactive Processes	10
Energy released and required in formation and degradation of pharmaceutical substances	Chapter 9: Balances on Reactive Processes	3
Calculation of batch reaction time Rate of release from a controlled drug delivery system Pharmacokinetic modeling	Chapter 11: Balances on Transient Processes	4

*Indicates a topic incorporated into every problem.

Table 1: Topics in Pharmaceutical Engineering and their Integration into a Material and Energy Balance Course.

topics of importance to the industry, such as regulation, safety, health, and environmental concerns, are not tied to a specific topic or chapter in a book and may be incorporated into any problem in any chapter. Additionally, concepts underlying pharmaceutical engineering such as units, conversions and terminology are incorporated or referenced in every problem.

PROBLEM DEVELOPMENT

Instead of trying to find room in the undergraduate curriculum for a separate introductory course specifically related to pharmaceutical engineering, the goal is to integrate pharmaceutical concepts into the existing framework of a material and energy balance course. Integrating in-class and homework problems is a time-efficient way to incorporate pharmaceutical topics while simultaneously covering essential course objectives. This concept has been used successfully at Rowan University and other schools for integrating green engineering and sustainability into existing chemical engineering courses [10], [11]. Since each problem is identified with a particular chapter and section in Felder and Rousseau it is easy for the professor to select problems appropriate for parts of an existing course. The problems can be used as in-class examples, cooperative learning exercises, or homework problems at the professor's discretion.

To expose chemical engineering students to topics associated with the pharmaceutical industry early in the curriculum, problems were written to include and explain terminology, processes, and issues unique to the pharmaceutical field. Students are shown practical industrial and research applications of the pharmaceutical field while learning the basic principles of chemical engineering. They are also informed of the existence of the specialization of pharmaceutical chemical engineering as a possible career path. Many of the problem statements are written using second-person narrative to encourage the students to envision themselves being involved in the process.

The problems are meant to model realistic situations and use quantities and conditions that may be encountered in an industrial process. Published literature, such as patents, textbooks (Martin [12], Ansel [13]), handbooks (Niazi [14], [15]) and reference works on the subjects of pharmaceutical design, manufacturing and engineering were studied to ensure the processes and operating conditions described in the problems were realistic representations of the pharmaceutical industry.

The problem statements are used to introduce pharmaceutical processes, topics, and equipment. They are written using terminology unique to the pharmaceutical industry with explanations of the phrases which may be new to the students. In the problem statements, new terminology is easily identified using bold font. The problem statements also usually contain interesting facts and

comparisons to catch the students' interest, such as amounts produced per year, side effects of certain drugs, or historic background of the problem subject.

The solutions focus on the chemical engineering principles that need to be taught in a material and energy balance course. Some of the problem solutions also emphasize the pharmaceutical industry by asking the students to research safety guidelines specific to the pharmaceutical industry; this gives the students the opportunity to conduct research outside of the given textbook. Other solutions require the students to research information needed to solve the problems, such as the average weight of an adult male or the average size of an organ. The objective of having students perform this research is to familiarize the students with the pharmaceutical literature. It forces the students to discern which are credible sources and extract the needed information from them. At the end of some of the problems, students are often asked to give suggestions on how to change, fix, or improve a pharmaceutical process. This simulates the thinking and brainstorming that they will have to do in the field if they do follow a career in the pharmaceutical industry.

Several programs have developed material for integration of diverse science, mathematics and engineering topics into a current curriculum. At San Jose State University, the BioEMB project performs work similar to ERC SOPS by creating problems that facilitate the application of engineering principles to biological problems [16], [17]. Compilations of student problems have been developed for thermodynamics and related subjects [18], [19] and green engineering [20]. ConcepTests provides clicker-based questions and video ScreenCasts for a variety of chemical engineering core courses [21]. The SCALE-UP project has developed classroom and curricular materials in physics, chemistry and biology designed to establish a collaborative, hands-on learning environment for large-enrollment classes. These materials have been used in engineering and science courses to improve student understanding of subjects [22].

EXAMPLE PROBLEMS

To date, over seventy problems and solutions have been developed. The goal is to create problems with a pharmaceutical basis to cover all subjects taught in an introductory course. The problems are publicly distributed on the pharmaHUB website [6] for professors to use in their courses. Feedback from these professors and their students will be used to make adjustments and issue improved versions.

Problem Statement: DEG Poisoning Problem (Chapter 2;Units and Professional Responsibility)

In 1937, a veterinary pharmaceutical company in Tennessee decided to produce an oral **liquid dose form** of a popular (human) drug that to date had only been administered as an injection or

pill. Knowing the existence of a large market of people who preferred liquid doses, the head of the company had his **research and development** scientists find a way to fill this market segment. The **active pharmaceutical ingredient** (API) of his proposed medicine, sulfanilamide, was widely accepted. However, a liquid dose form of the API had not been made because it is highly insoluble in water or any other common pharmaceutical **dilutant**.

The chief researcher at the firm wanted to address this problem. After some laboratory research, he found that the substance dissolved satisfactorily in diethylene glycol (*DEG*). Unfortunately, no testing was performed and some batches (240 gallons in total) were made and sold. After a chase by nearly the entire FDA staff, most of the distribution was collected on a legal technicality and about 100 people had died of taking it.

(a) The dosage instructions for the preparation were "...2 to 3 teaspoonsful [sic] in water every four hours...". Assume each teaspoon was pure DEG and calculate the mass of diethylene glycol a patient would have ingested in a day.

(b) The probable oral **lethal dose** of diethylene glycol is 0.5 g/kg weight. Determine the human weight for which this dose would be fatal.

(c) Explain why this would be dangerous even if the patient was well above this weight.

(d) If the total distribution had been consumed according to the quoted dosage guidelines, how many people would have been poisoned?

(e) Develop a chronological list showing the error(s), the corrections to them that were not applied, and how the corrections would have prevented this.

Commentary: Safety violations in engineering risk personal injury, equipment wreckage and public health or environmental damage. Because of the end use of the final product, pharmaceutical safety violations that alter the final product affect all consumers of the product and can even be fatal. This problem introduces topics in pharmaceutical engineering safety, such as toxicology and solvent evaluation. Numerous existing problems in textbooks describe other disasters or imaginary situations of safety violations; this problem expands those concepts to the pharmaceutical industry. It also illustrates the need for basic testing for toxic effects and a reason for regulation by the government. The problem also introduces some terminology, calculations, and involves some less common unit conversions. However its primary intent is to educate the student about a concern unique to the pharmaceutical industry. This problem is based on the Elixir Sulfanilamide disaster [23], which the FDA considers seminal in its history [24].

Problem Statement: General Batch Calculations (Chapter 3; Mass and Mole Fractions)

In pharmaceutical production, medicine is composed of **active pharmaceutical ingredients** (APIs) and inert materials called **excipients**.

(a) What are the mass fractions of API and excipients in a batch produced from 829 moles of acetaminophen (M = 151) and 62.1 kg excipients?

(b) Excipients are principally **fillers** and **binders**. The former are bulk forming materials while the latter act as a kind of 'glue' to retain the form of the pill. If the ratio of filler to binder is 2:1, what is the percent by mass of binder in the tablets?

(c) How many 750 mg tablets will this batch make?

(d) If these are to be taken twice a day for 10 days, how many prescriptions will this fill?

Commentary: In this problem, the use of basic chemistry and chemical engineering measurements is applied to pharmaceutical production. At the same time, new terminology (APIs, excipients, fillers and binders) is introduced and explained for the students. A common generic pain killing API, acetaminophen, is mentioned. The problem is deliberately sparse to focus on the new definitions and the simplicity of the calculations to be performed.

Problem Statement: Metoclopramide Tablet Production Process (Chapter 4; Mass Balances)

Metoclopramide is an **active pharmaceutical ingredient (API)** in medicines used to treat acid indigestion [25]. Making the formulation that is compressed into metoclopramide tablets is a multistep process [14], which is shown in Figure 1. For a process designed to produce a batch of 1000 tablets, the required quantities of metoclopramide (**API**) in Stream 1, preglatinized starch (**binder** to hold particles together after tablet compression) in Stream 2, and lactose (**binder**) in Stream 3 are mixed with 15 mL of water. The resulting mixture contains 11.38% water by mass and is sent to a tray dryer where the moisture content is reduced to 5.2%. The dried mixture is sent to a blender where it is combined with 1 g of silicon dioxide (**glidant** to increase the fluidity of the powder before compression) from Stream 11, 0.76 g of magnesium stearate (**lubricant** to prevent the tablet from sticking to the tablet press) from Stream 12, and dried maize starch (**binder**) from Stream 10. The dried starch is produced by removing 0.128 g of water from wet starch, reducing the mass of the wet starch by 1.8%. The final product (Stream 13) contains 10.54 g of the API, and each tablet contains 101.24 mg lactose.

(a) Calculate the mass (g) of pregelatinized starch added to the mixer.

(b) Calculate the mass (g) of water removed from the tray dryer.

(c) Calculate the total mass (g) of thefinal product.

Commentary: Rather than simply giving the students a diagram with the information needed to solve a material balance, this problem was developed around the production of metoclopramide tablets. The problem statement provides a description of the composition of an individual tablet and an overview of the tablet production process, which is a multistep batch process for these tablets. Additionally, the problem statement introduced pharmaceutical terminology associated with the

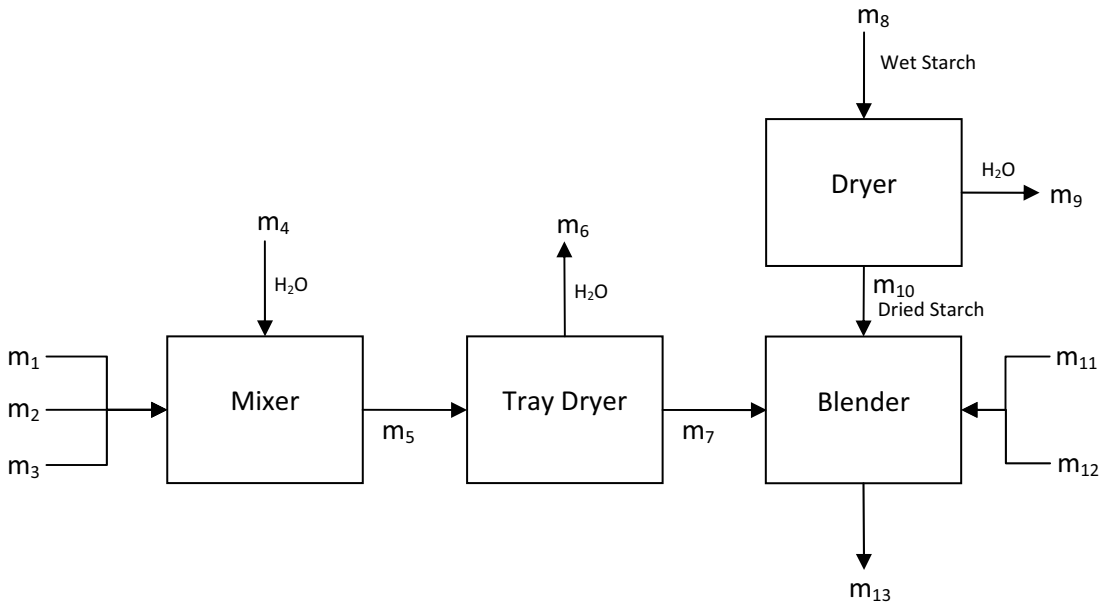

Figure 1. Metoclopramide Tablet Production Process.

types of ingredients, called excipients, used in tablets, such as binders, glidants, and lubricants. The solution to the problem requires the students to perform multiple material balances to calculate the desired quantities. The production process is simple and consists of a series of steps for addition of the ingredients. Each step illustrates pharmaceutical manufacturing unit operations for powder processing: solids blenders and tray dryers. However, the mixture must be dried to a specified moisture content at a certain stage in the process. This adds an extra level of complexity for the students while they are solving the problem. The students must use their knowledge of moisture content to complete the calculations successfully. This example of an industrial process demonstrates that the mixture of tablet ingredients must be combined under very specific conditions. The problem would be used in a course during the first introduction of material balances.

Problem Statement: Mouthwash Formulation (Chapter 5; Density of Homogeneous Solutions)

Table 2 lists a possible formulation [15] for an over-the-counter (OTC) mouthwash. The α-bisabolol is an antibacterial agent [26], cremophor RH 40 is a **solubilizer** [27], glycerol and saccharin salts are used as sweeteners [28], and the ethanol is the **bulk liquid**. To form the product, a mixture of items 1–3 are heated to approximately 60 °C and then added to a mixture of items 4–6.

Item #	Material	Quantity(g/L mouthwash)
1	α-Bisabolol, racemic	10
2	Flavor	100
3	Cremophor RH 40	60
4	Glycerol	10
5	Saccharin Sodium	2
6	Ethanol (96%)	818

Table 2: Mouthwash Formulation.

(a) Assuming additive volume, calculate the density of the solution of glycerol and ethanol before the saccharin sodium is added.

(b) Calculate the density of the same solution by taking the average of the pure component densities.

Commentary: This problem introduces pharmaceutical terminology describing components of a liquid formulation and shows students an actual product formulation list. The students can see that the formulation is given in concentrations which can be scaled to a desired batch size. The problem statement intentionally includes more information than is necessary to answer the question being asked in the problem because the additional description gives a larger view of the production process. However, the solution only requires estimating the density of the single phase mixture of multiple components at a specific stage of the process. The problem could be used in an introductory course to practice estimating the density of mixtures and discussing how properties of mixtures are different than the individual components.

Problem Statement: Effervescence Problem (Chapter 5; Ideal Gas Law)

Alka-Seltzer® is an over-the-counter (OTC) medicine used to treat acid indigestion, sour stomach, and heartburn with headache, body aches and pain. The **active pharmaceutical ingredients (API)** in each Alka-Seltzer® tablet are aspirin (325 mg), citric acid (1916 mg), and sodium bicarbonate (1000 mg) [29]. For a single dose, two Alka-Seltzer® tablets are dissolved in 4 ounces of water. When placed in water, the following reaction occurs:

$$\mathbf{C_6H_8O_7(aq) + 3NaHCO_3(aq) \rightarrow 3H_2O\ (l) + 3H_2O\ (g) + Na_3C_6H_5O_7(aq)}$$

Citric acid	Sodium bicarbonate (baking soda)	Sodium citrate

(a) What volume of CO_2 gas would be produced by a normal dose of Alka-Seltzer® dissolved in 4 ounces of water at 25°C and 1 atm? Assume the reaction goes to completion.

(b) You wake up feeling miserable before your chemical engineering final, but you know you can't miss it. You grab some Alka-Seltzer® and an 11oz bottle of water. You drink just enough water to leave exactly 4 fl oz left in the bottle (you've had lots of practice with this). Then you drop in the two tablets, cram the lid onto the bottle, and rush out the door. Assume the temperature remains constant at 25°C. Calculate the pressure inside the bottle. Neglect the volume of the tablets.

(c) Determine the reasonability of assuming ideal gas behavior in parts (a) and (b).

Commentary: This problem deals with the end use of a particular product rather than a production or process calculation. A common pharmaceutical product demonstrates an application of the ideal gas law equation of state. The solution focuses on the basic chemical engineering principles being reinforced by this problem. However, the problem statement is used to introduce pharmaceutical terminology, such as active pharmaceutical ingredient. It also draws attention to the chemistry taking place during the use of a common household product. The problem could be used in a course when students are learning about the ideal gas law and other equations of state. It also provides an opportunity for the professor to discuss when the ideal gas law will result in a reasonable estimation of a system's conditions.

Problem Statement: Acetone Evaporation (Chapter 6; Vapor Pressure)

Acetone is a common solvent in pharmaceutical synthesis operations (crystallizations, filtrations, etc.) and in vessel cleaning. As you may remember from your organic chemistry lab, a little spill of acetone on a paper towel or desk tends to evaporate very quickly.

(a) Use the Cox chart to estimate the vapor pressure of acetone in your organic laboratory.

(b) Determine the level of acetone in the air immediately above the surface of the acetone in the beaker.

(c) Safety requires that the air in a location holding chemicals is completely refreshed within a certain time, or (equivalently) that the air be changed so often within a set time. The latter, defined as the **air change rate**, is the commonly used unit of measure. Assume your laboratory uses the conventional [30]5 *air changes per hour* (ACH) and determine the amount of time required for your acetone to completely evaporate from the beaker.

(d) Some other common solvents used for various purposes in pharmaceutical manufacturing are methanol, ethanol, hexane and toluene. Find the vapor pressures of these compounds at room temperature and explain their desirability. Show all the considerations you used in making the list.

(e) Briefly speculate on

(i) Why pharmaceutical operations (and many others as well) are usually cooled well below the normal room temperature of 72 °F.

(ii) The physical significance of the slopes of the lines on the Cox chart.

Commentary: This problem shows a practical engineering application of the Cox chart, as well as Raoult's Law, making necessary assumptions and some simple mass equations. It utilizes the student's laboratory experiences with acetone to make a connection to the pharmaceutical industry. After analyzing the basic physical properties of acetone, the students must consider what solvent properties are most significant when selecting a solvent for a pharmaceutical process. They must consider the industrial environment in which solvents are used and how it could potentially affect the production process, the final product, or the consumer. The students must think about the physical properties of a solvent and the safety issues associated with choosing any compound to be used in a pharmaceutical process.

Problem Statement: Shirasu Porous Glass Membrane (Chapter 7; Bernoulli)

The Shirasu Porous Glass membrane system, shown in Figure 2, is used to create an emulsion of immiscible compounds. An **emulsion** is a suspension of small globules of one liquid phase immiscible in a second liquid phase. In this case, the mixture consists of monomers, diluents, oil soluble initiators, and water insoluble reagents. The emulsification takes place in a membrane through which the liquid is forced under constant pressure. The mixture is stored in the dispersion storage tank, where it is pumped by a nitrogen gas at 1.2×10^4 Pa to the membrane. After passing through the membrane the emulsion is sent to an emulsion storage tank from which it may be recirculated by a pump. Mixture density is 1261 kg/m^3 and pipe diameter 10 mm.

(a) Use a truncated version of the Bernoulli equation to find the velocity of the liquid leaving the first tank.

(b) With no recirculation, how long would it take for 100 L to accumulate in the tank?

Commentary: Students are introduced to an emulsification method for production of microspheres usable in drug delivery [31]. This particular method uses pressure to force the immiscible mixture through a membrane where the mixture will be emulsified. The students are asked to find the velocity of the liquid using the Bernoulli equation. The first part of the problem is designed to familiarize the students with the use of the Bernoulli equation, so the calculations were kept simple. The next

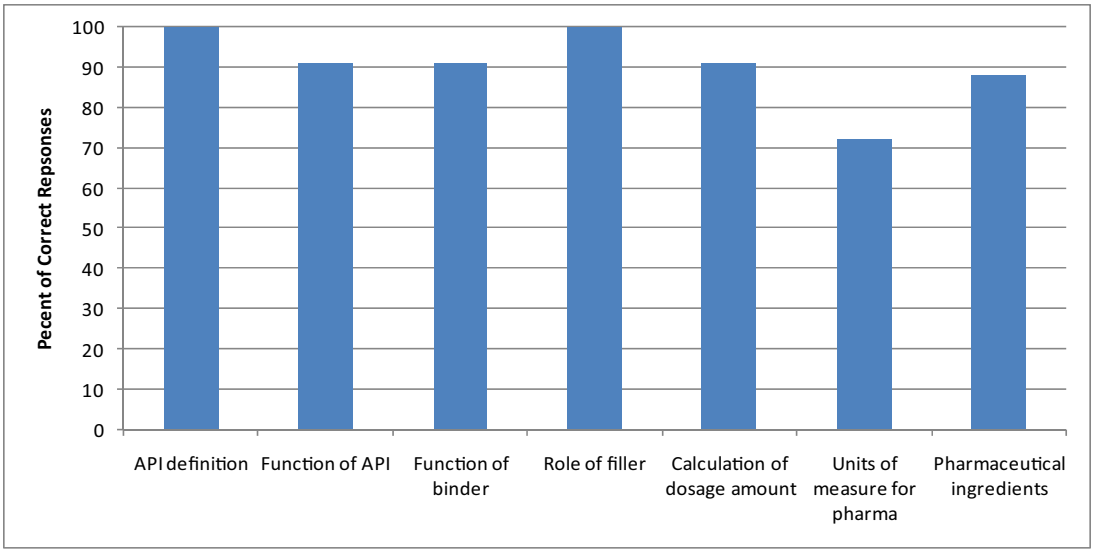

Figure 2. Drug terminology and formulation concept questions. (N = 32 students tested)

part asks them to solve for the time required to reach the 100 liters mark. This next question is more challenging, and the students must show understanding of the relationship between velocity, pipe size, and volumetric flow rate. This problem gives a concise description of a pharmaceutical production process and relates it to some fundamental engineering principles.

Problem Statement: Heat of Solution in Instant Cold Packs (Chapter 8; Heat of solution)

Instant cold packs are used for first aid when ice packs are not available. The cooling is caused by the endothermic dissolution of ammonium nitrate (NH_4NO_3) in water:

$$NH_4NO_3\ (s) \rightarrow NH_4^+\ (aq) + NO_3^-\ (aq)$$

The ammonium nitrate is kept separated from the water in a small pouch until the pouch is broken, forcing the ammonium nitrate and water to mix. A cold pack containing 200 mL water and 200 g NH_4NO_3 was activated at room temperature (25˚C). The cold pack reached a final temperature of -2°C. For NH_4NO_3 and water, the heat of solution at infinite dilution is –25.69 kJ/mol at 25°C [25].

(a) Calculate the heat of solution $\Delta\hat{H}_S$ for the solution with the composition given in the cold pack. (Hint: Use Kopp's Rule to estimate the heat capacity of NH_4NO_3.)

(b) What would be the final temperature of a pack containing 300 mL of water and the same ratio of moles of solvent per mole of solute?

Commentary: The focus of this problem is a medical product which operates effectively due to the use of an endothermic chemical reaction. It is an example of how a chemical engineering thermodynamic principle can be applied to a pharmaceutical product. The students must calculate the heat consumed by the system in order to determine the heat of solution. The problem is meant to make students more aware of the chemistry taking place in a commonly used product and recognize its connection to the chemical engineering principles they are learning in class. The problem is meant to be used when teaching students about heats of solution. It also makes the connection between determining whether a process is endothermic or exothermic by using enthalpy calculations.

Problem Statement: Production of EDTA (Chapter 9; Heat of Reaction)

Many metals have highly toxic effects when present in the bloodstream. To remove them, **chelating agents** are supplied (usually by injection) to bind to the metal molecules and **sequester** them. Ethylenediaminetetraacetic acid (universally called **EDTA**) is a commonly used **chelating agent** (or also **chelator**) in medicine, especially in the case of lead poisoning. EDTA is produced in highly pure form by the following three liquid phase reactions:

$$\mathbf{H_2NCH_2CH_2NH_2} + \mathbf{4\ H_2CO} + \mathbf{4HCN} \rightarrow \textit{EDTN} + \mathbf{4\ H_2O}$$

$$\textit{EDTN} + 4\ \mathbf{NaOH} + \mathbf{4\ H_2O} \rightarrow \text{Na}\textit{EDTA} + \mathbf{4\ NH_3}$$

$$\text{Na}\mathbf{}\textit{EDTA} + 4\ \mathbf{HCl} \rightarrow \textit{EDTA} + \mathbf{4\ NaCl}$$

Note that sometimes the sodium salt of EDTA is taken as the final product, omitting the third reaction. EDTN is an initial form that is not commonly used except as a **precursor**.

(a) Determine the overall standard heat of reaction (*Data*: Standard heat of formation of EDTA is –1759.5 kJ/mol, ethylene diamine is –63.0 kJ/mol [32]).

(b) If the heat of the first reaction is –1739 kJ/mol, determine the standard heat of formation of EDTN.

(c) Using -582 kJ/mol as the heat of formation of the EDTA salt, determine the standards heats of the last two reactions

(d) Check your solutions(*Hint*: Recall Hess's Law)

Commentary: This problem statement is written to introduce specialized medical and pharmaceutical terminology, such as chelating agents, sequestration, and precursor. The solution requires lengthy calculations of heats of reaction and heats of formation for the steps of the EDTA synthesis and specified intermediate species and would be used in teaching the principles of heat of reactions.

RESULTS

The first draft of the problem sets was evaluated by small groups of students in parallel with the problem development. Feedback was provided to improve problems and correct mistakes in both the statement and solution. The problem sets were further reviewed by graduate students from one of the ERC research partner institutions to provide additional insight into their linkage to ERC-related topic area or relevance to pharmaceutical engineering. After final editing by Rowan faculty, the problems were posted on PharmaHUB.

Problems from this set were then pilot tested in The Principles of Chemical Engineering I course at Rowan University, and preliminary assessment was conducted. Students were surveyed at the beginning and the end of the course to assess the impact of the problem sets on their general knowledge and awareness about topics related to pharmaceutical engineering. In addition, students were surveyed at the conclusion of the course to evaluate their knowledge of specific pharmaceutical engineering content.

The results of these evaluations have been organized into three graphs to show results of concept-oriented questions from the assessment instruments. Figure 2 provides results of questions related to drug terminology and formulation. The graph shows responses (percent correct based on a student population of 32) for representative concept questions. The majority of students understand the basic pharmaceutical terminology and formulation. As an example, the question listed “function of binder” was worded as:

A binder is:

a) Equipment to make pills stick together

b) A substance to make components of a drug formulation adhere to each other

c) An device to keep two pieces of equipment attached to each other

d) A substance to ensure the drug is used correctly in the body

The question, “calculation of dosage amount,” relates to their knowledge on the relative concentration of API in a formulation, requiring a simple mass balance. The question that got the lowest score, “unit of measure for pharmaceutical engineers” was a multiple-answer-multiple-choice question, so we chose to report only those students who answered with all three of the correct responses. 100% of the students were able to provide at least one correct response and 87.5% were able to identify at least two correct answers.

Figure 3 shows the responses to questions related to drug manufacture and delivery. For example the wording of the question, “role of tablet press” was:

The purpose of a tablet press in drug manufacture is to

a) Fill the bottle with a specific number of pills

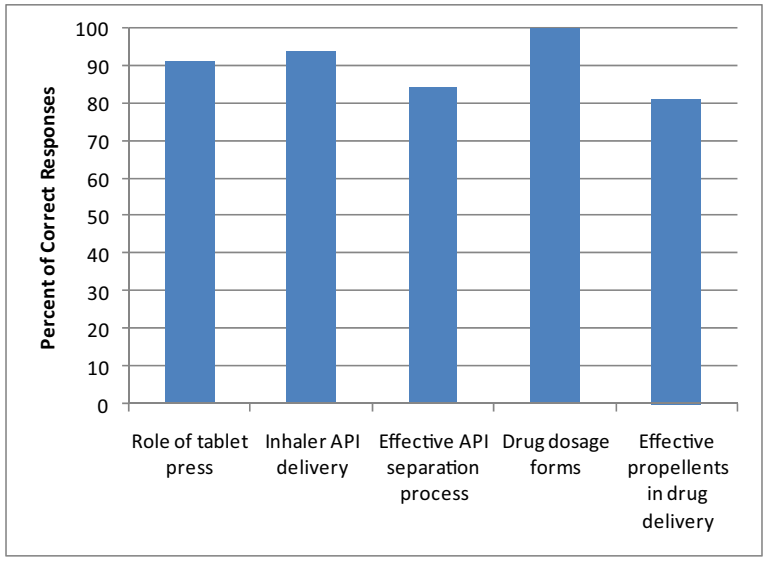

Figure 3. Drug manufacture and delivery concept questions. (N = 32 students)

b) Compress powders into a specific size and shape

c) Change the P-V-T relationship of a drug compound

d) Remove moisture from a drug powder

The assessment also shows good uptake of knowledge about pharmaceutical manufacturing and drug delivery. Students demonstrated excellent mastery of these concepts, ranging from 81% correct responses to 100% correct responses. While students were most challenged by the question related to propellants used in inhaled drug delivery devices, other questions related to methods of drug delivery and pharmaceutical manufacture showed very high percent of correct responses.

Figure 4 shows a comparison of survey results for general awareness and knowledge of pharmaceutical engineering topics before and after the problem sets. Before the problem sets, only 12.5% of the students demonstrated any knowledge of the role of a pharmaceutical engineer (although, interestingly, 50% of the students indicated an interest in a career as a pharmaceutical engineer). After the pharmaceutical problem sets, 93% of the students understood the role of a pharmaceutical engineer. For other topics such as the role of excipients, drug delivery methods, and pharmaceutical process equipment, students also showed significant increases in knowledge.

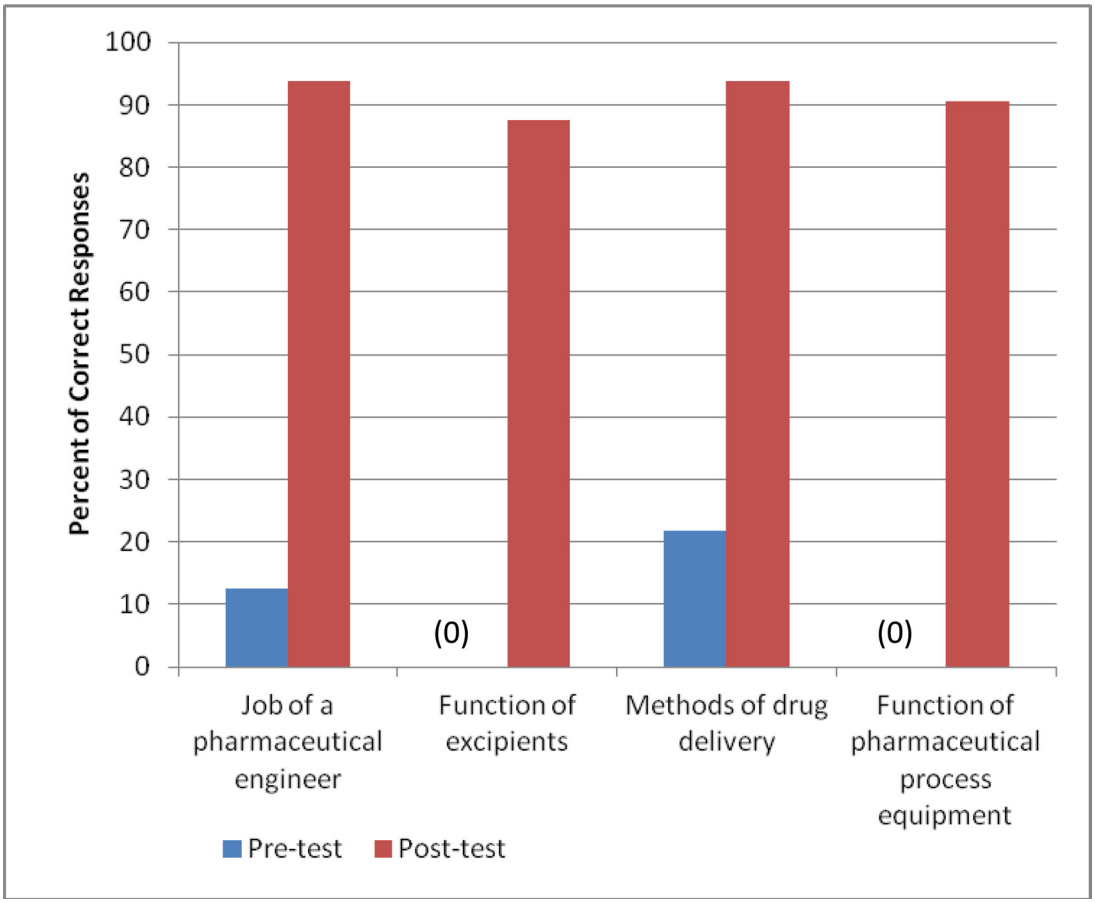

Figure 4. Change in general awareness of Pharmaceutical Engineering: before and after comparison. Note that zero (out of 32) students initially understood the function of excipients or pharmaceutical process equipment.

CONCLUSION

Pharmaceutical engineering problem sets developed are intended to be used in homework assignments or lecture examples in introductory material and energy balance chemical engineering courses. Each problem introduces topics related to pharmaceutical technology, and is related to a process, substance, unit operation, or term used in pharmaceutical engineering. All problems are based on technology in use or currently being developed for the pharmaceutical industry. The students learn the principles of chemical engineering such as mass and energy calculations within the context of solving pharmaceutical engineering problems. A detailed solution is provided with

each problem for the course instructor to explain how to solve the problem and the fundamental principles behind each problem. The solutions are written and formatted so that they can be given directly to the students without any additional instruction from the professor. The goal is for students to reinforce the theoretical material they are learning in class while being exposed to the concepts of pharmaceutical engineering. The problem sets were reviewed by graduate students at the ERC-host institution, Rutgers University, and feedback incorporated into refining the problems. The problem sets were pilot-tested in the Principles of Chemical Processes course at Rowan University. Students' knowledge of key pharmaceutical concepts before and after course integration was evaluated, and students demonstrated a significance increase in knowledge of pharmaceutical concepts. The problems are publicly available online to faculty through pharmaHUB.org (http://pharmahub.org/resources/389).

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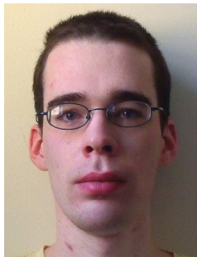
AUTHORS



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(Endnotes