AC 2010-176: INTRODUCTORY LEVEL TEXTBOOK PROBLEMS ILLUSTRATING CONCEPTS IN STRUCTURED ORGANIC PARTUCULATE SYSTEMS

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Introductory level textbook problems illustrating concepts in Structured Organic Particulate Systems

Abstract

The National Science Foundation (NSF) Engineering Research Center for Structured Organic Particulate Systems (ERC-SOPS) conducts research related to pharmaceutical technology. Rowan University is one of the Center's Outreach Partners responsible for developing educational materials related to the Center's area of study. Textbook style problems introducing pharmaceutical topics at the level of an introductory chemical engineering course have been created, along with detailed solutions. The problems illustrate subjects and skills students would learn and use if they were to pursue a career in pharmaceutical engineering. The procedure and rationale followed in the development of the problems is outlined, and representative problems with solutions are shown.

Introduction

Rowan University is an Outreach Partner for the National Science Foundation's (NSF) Engineering Research Center for Structured Organic Particulate Systems (ERC-SOPS) led by Rutgers University. The Center conducts research related to pharmaceutical technology and coordinates educational outreach programs with member schools. Rowan University's role is to produce educational materials related to the pharmaceutical industry to be used by the ERC in education and outreach programs.

At Rowan University, student teams take a 2-credit course during each academic term in which they work on various projects under the direction of faculty members. Professors Savelski, Farrell, and Slater are the local contacts for the ERC and have overseen student teams working on ERC projects for several terms. The purposes of the projects to date have been the creation of in-class and homework (textbook) problems focusing on pharmaceutical aspects of science and engineering. Previous teams have focused on the production of problems for students ranging in educational level from late middle school to the second year of a baccalaureate degree. The teams this semester have been focused solely on the revision of old problems and production of new problems for students of introductory chemical engineering courses, usually taught during the freshman or sophomore year.

This paper presents the problems developed during this semester for use in these courses. The formatting, layout, style and focus of the problems are based on those of Felder and Rousseau's Elementary Principles of Chemical Processes[1], a widely-used textbook for these types of courses. Courses taught with a different textbook may still use the problems developed since they cover topics such as units and conversions, material balances with and without reaction, single and multiphase systems, and energy balances.

Problem development

As detailed above, the purpose of these problems is to expose chemical engineering students to topics associated with the pharmaceutical industry at an early stage in their engineering education. To do this, the problems were written to include and explain terminology, processes and issues unique to the pharmaceutical field. By illustrating the field at the level of the course, students are shown practical industrial and research applications of the subjects they are being taught. They are also informed of the existence of the specialization of pharmaceutical chemical engineering as a possible career path after graduation. Many of the problem statements are written using second-person narrative to encourage the students to see themselves involved in the process.

Development of problems was done solely by the members of the student teams. These students examined published literature of every description, such as patents, textbooks, handbooks and reference works, on the subjects of pharmaceutical design, manufacturing and engineering. Ideas for problems were individually integrated into problems, using Felder and Rousseau as a guide to determine the allowable rigor of problem solutions. Felder and Rousseau was also used as a guide for the selection of concepts and subjects to be covered in new problem development. The pharmaceutical literature served to ensure the process and values described in the problems are reasonable.

Once a problem had been developed to the satisfaction of the student developing it, the individual student submitted it at a regularly scheduled weekly meeting for feedback. All participants were equally entitled to submit corrections and revisions in hard copy and electronically. The student who designed the problem was free to incorporate or reject shared suggestions and resubmit the problem at the next meeting. This cycle continued until the professor required submission of a final version or the student was satisfied with its development.

Once complete the problems will be publicly distributed on the PharmaHUB website[2] for professors at Rowan University and others to use in their courses. Feedback from these professors and their students will be received to make adjustments and issue improved versions. More problems will be created in later semesters to round out coverage of all chapters in Felder and Rousseau.

Example problems

Emulsification system

In this problem students are exposed the process of emulsification and one method of performing it. Additionally the relationship between the pressure and velocity of a fluid is illustrated. The problem provides an early introduction to Bernoulli's equation which will prove helpful when students later encounter it in fluid mechanics courses.

The problem statement is as follows:

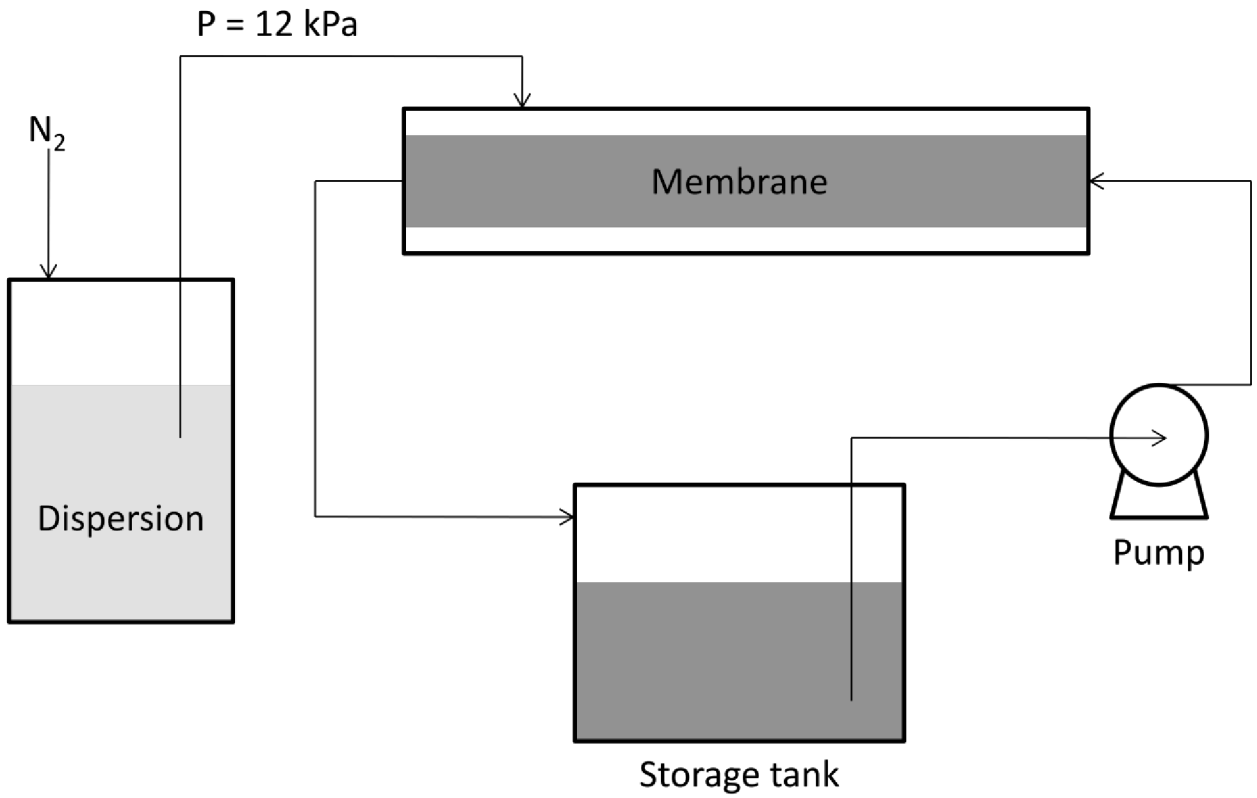

Figure 1. Membrane emulsification process

The Shirasu Porous Glass (SPG) membrane system is used to create an **emulsion** or suspension of small globules of a liquid in a second immiscible liquid. Before being emulsified, the mixture is stored in the dispersion storage tank under constant pressure of nitrogen at 12 kPa. The emulsification takes place in a membrane through which the liquid is forced by constant pressure. After passing through the membrane the emulsion is sent to the storage tank. Additional information: ρ = 1261 kg/m^3, ID pipe = 10 mm

(a) Use the Bernoulli equation to find the velocity of the liquid leaving the dispersion tank.

(b) If the recirculation pump is turned off, how long would it take for 100 L to accumulate in the storage tank?

The solution is as follows:

(a) Using the Bernoulli equation

$$\frac{\Delta P}{\rho} + \frac{\Delta u^2}{2} + g\Delta z = 0$$

$$g\Delta z \xrightarrow{assume} 0$$

$$\frac{\Delta P}{\rho} + \frac{\Delta u^2}{2} = 0$$

$$P_2, u_1 \xrightarrow{assume} 0$$

$$P_1 = \frac{\rho u_2^2}{2}$$

$$u_2^2 = \frac{2P_1}{\rho}$$

$$u^2 = 2 \times (1.2 \times 10^4)\ \text{Pa} \times \frac{\text{N}}{\text{Pa} \cdot \text{m}^2} \times \frac{\text{kg} \cdot \text{m}}{\text{N} \cdot \text{s}^2} \times \frac{\text{m}^3}{1261\ \text{kg}}$$

$$u^2 = 19.03\ {}^{\text{m}^2}/_{\text{s}^2}$$

$$\sqrt{u^2} = 4.36\ {}^{\text{m}}/_{\text{s}}$$

(b) Finding the radius in meters

$$r = \frac{D}{2}$$

$$r = \frac{10\ \text{mm}}{2} \times \frac{1\ \text{m}}{1000\ \text{mm}} = 0.005\ \text{m}$$

Finding the cross sectional area of the pipe

$$A = \pi r^2$$

$$A = \pi(0.005\ \text{m})^2 = 7.85\ \times 10^{-5}\ \text{m}^2$$

Finding the volumetric flow rate

$$V = Av$$

$$V = 7.85 \times 10^{-5}\ \text{m}^2 \times 3.084 \frac{\text{m}^3}{\text{s}} = 2.420 \times 10^{-4} \frac{\text{m}^3}{\text{s}}$$

Converting to L/s

$$V = 2.420 \times 10^{-3}\ \frac{\text{m}^3}{\text{s}} \times \frac{1000\ \text{L}}{1\ \text{m}^3} = 0.242 \frac{\text{L}}{\text{s}}$$

Finding how long would it take to reach the 100 L mark

$$t = \frac{1\text{ s}}{0.252\text{ L}} \times 100\text{ L} = 413\text{ s} \times \frac{1\text{ min}}{60\text{ s}} = \boxed{6.88\text{ min}}$$

Microsphere production

This problem tests the ability of the students to do mass balances on multiple unit and stream processes. It also introduces a method for drug delivery, microspheres, and a method for their production. The final part of the problem is a purely conceptual break from algebraic operations into engineering reasoning and brainstorming.

The problem statement is as follows:

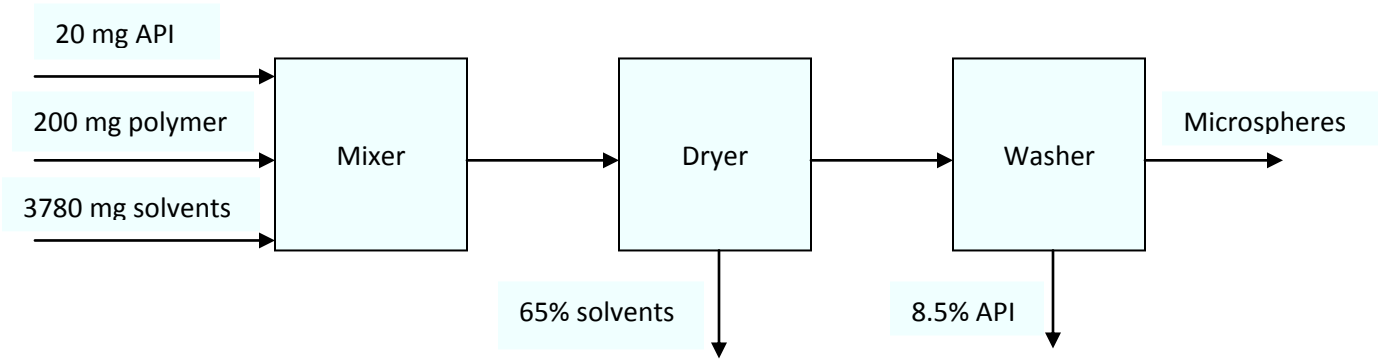

Figure 2. Polymeric microsphere production process

Prednisolone the **active pharmaceutical ingredient** (API) is a corticosteroid drug that is useful for the treatment of inflammatory and auto-immune conditions such as asthma, uveitis, multiple sclerosis, and other conditions. To effectively treat these conditions, **controlled release** over a long time is needed. Highly porous polymer spheres impregnated with API called microspheres fulfill this requirement by degrading in a predictable manner, releasing the API.

To manufacture the drug, the prednisolone, polymers and solvents are introduced to the mixer and are blended. The liquid phase is then sent to the dryer where 65% of the solvents are removed. The products from the dryer are transferred to the washer where 8.5 % of the prednisolone is lost in the washing operation.

(a) Find the mass percent of each component coming out of the dryer
(b) Present some realistic ways to cut down on the wasted API.

The solutions is as follows:

(a) Finding how much solvent is left

$$3780 \text{ mg} \times (1 - 0.65) = 1323 \text{ mg}$$

Percent of API

$$\frac{20 \text{ mg}}{(20 + 200 + 1323) \text{ mg}} \times 100\% = \boxed{1.29\%}$$

Percent polymer

$$\frac{200 \text{ mg}}{(20 + 200 + 1323) \text{ mg}} \times 100\% = \boxed{13\%}$$

Percent of solvent

$$100\% - (12.96\% + 1.29\%) = \boxed{85.71\%}$$

(b) Improve the washing process so no API is lost during that step.
Change the polymers used so that they biodegrade completely within 7 days.

Reaction stoichiometry

Reaction stoichiometry is an important concept in introductory chemical engineering courses as evident by the coverage in Felder and Rousseau, (sections of chapter Four). This problem is designed to illustrate the final reaction step in the production of a pharmaceutical ingredient.

The problem statement is as follows:

> Acetaminophen is used to treat many conditions such as headaches, arthritis, backache, toothaches, colds, and fever[3]. To produce Acetaminophen, p-aminophenol and acetic anhydride in dichloromethane (**reaction medium**) are fed to the reactor in the presence of $NaHSO_4 \cdot SiO_2$ as a **heterogeneous** catalyst[4]. The reaction stoichiometry is given below:
>
> $$\underset{p-\text{aminophenol}}{C_6H_7NO} + \underset{\text{Acetic anhydride}}{C_4H_6O_3} \rightarrow \underset{\text{Acetaminophen}}{C_8H_9NO_2} + \underset{\text{Acetic acid}}{C_2H_4O_2}$$
>
> The feed to the reactor contains 45.5 mole % p-aminophenol and the remainder acetic anhydride. For a 48.18 kg feed of reactants and a fractional conversion of 95% of the limiting reactant, find the following:
> **(a)** Limiting reactant
> **(b)** The percentage by which it is in excess
> **(c)** How many kg of acetaminophen are produced

The solution is as follows:

Heterogeneous catalytic process involves more than one phase. The catalyst is usually in a solid form while the reactants and the products are in either gaseous or liquid form[5]. Dichloromethane (l) serves as the medium in which the reaction takes place. After the completion of reaction the mixture is separated to obtain solid Acetaminophen.

$$\underset{p-\text{aminophenol}}{C_6H_7NO} + \underset{\text{Acetic anhydride}}{C_4H_6O_3} \rightarrow \underset{\text{Acetaminophen}}{C_8H_9NO_2} + \underset{\text{Acetic acid}}{C_2H_4O_2}$$

A = p-aminophenol (M = 109.13)
B = Acetic anhydride (M = 102.09)
C = Acetaminophen
D = Acetic acid

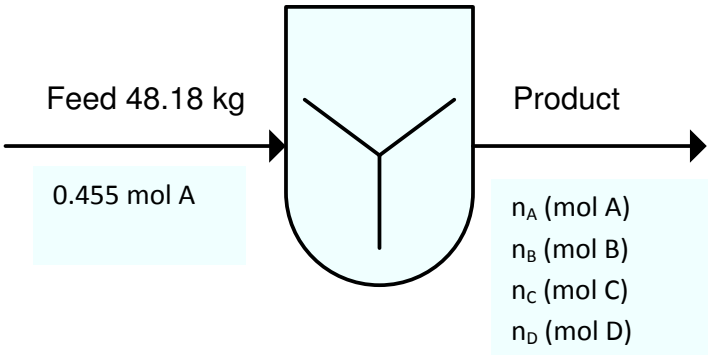

Figure 3. Acetominophen production in a stirred tank reactor.

(a) First, the average molecular weight of the feed needs to be determined and the feed calculated in terms of a molar flow. Then the moles of each reactant need to be determined so the limiting reactant can be calculated from the stoichiometric coefficients (ratios).The reaction as written is balanced and all reactants and products have stoichiometric coefficients of 1.

$$\bar{M}_{\text{reactants}} = \left(0.455\ \frac{\text{mol A}}{\text{mol}} \times \frac{109.13\ \text{kg}}{\text{mol A}}\right) + \left(0.545\ \frac{\text{mol B}}{\text{mol}} \times \frac{102.09\ \text{kg}}{\text{mol B}}\right) = 105.29\ \frac{\text{kg}}{\text{mol}}$$

$$n_{\text{reactants}} = 48.18\ \text{kg} \times \frac{\text{mol}}{105.29\ \text{kg}} \times = 0.4576\ \text{mol}$$

$$(n_A)_0 = 0.455 \times 0.4576\ \text{mol} = 0.208\ \text{mol}$$

$$(n_B)_0 = 0.545 \times 0.4576\ \text{mol} = 0.249\ \text{mol}$$

$$\Downarrow$$

$$\left.\begin{matrix}(n_B/n_A)_0 = 249.4/208.2 = 1.20 \\ (n_B/n_A)_{\text{stoich}} = 1/1 = 1.0\end{matrix}\right\} \text{Acetic anhydride is in excess } (1.20 > 1)$$

$$\boxed{p-\text{aminophenol is the limiting reactant}}$$

(b) Percent excess

$$(\%\ excess)_{\mathrm{B}} = \frac{n_{\mathrm{B}_0} - n_{\mathrm{B}_{\mathrm{stoich}}}}{n_{\mathrm{B}_{\mathrm{stoich}}}} \times 100\% = \frac{249.4 - 208.2}{208.2} \times 100\% = \boxed{20\ \%}$$

(c) To determine how much acetaminophen is produced, we need to calculate the extent of reaction to find the moles of acetaminophen ($C_8H_9NO_2$, M = 151.17) produced.

Fractional conversion of p-aminophenol is 95%, then

$$n_{\mathrm{A}_{\mathrm{out}}} = 0.05(n_{\mathrm{A}})_0 = 0.05(208.2\ \mathrm{mol}) = 10.4\ \mathrm{mol\ A}$$

$$\xi = n_{\mathrm{A}_0} - n_{\mathrm{A}_{\mathrm{out}}} = 208.2\ \mathrm{mol} - 10.4\ \mathrm{mol} = 198.5\ \mathrm{mol}$$

$$n_B = 249.4\ \mathrm{mol} - \xi = 50.9\ \mathrm{mol}$$

$$n_C = \xi = \boxed{198.5\ \mathrm{mol}}$$

$$n_D = \xi = 198.5\ \mathrm{mol}$$

Convert moles to mass of acetaminophen.

$$m_{\mathrm{A}} = nM_{\mathrm{A}} = 197.79\ \mathrm{mol} \times \left(\frac{151.17\ \mathrm{g}}{\mathrm{mol}}\right) \times \left(\frac{1\ \mathrm{kg}}{1000\mathrm{g}}\right) = \boxed{30\ \mathrm{kg}}$$

API production process

One of the most important principles in chemical engineering is the conservation of mass and the calculations which it allows to be performed on a system. Chapter four in Felder and Rousseau is entirely devoted to this subject. Industrial processes are rarely a single step process, rather multi-step process are applied. In a multi-step or multi-unit process, different ingredients are added throughout the process. In an attempt to illustrate the importance of comprehending a problem statement and drawing the process, a mass balance problem has been put together for a pharmaceutical formulation.

The problem statement is as follows:

> The second most widespread cause of cancerous death among women is breast cancer. This cancer involves the rapid intensification of cells that originate in the breast tissue. Tamoxifen is a medication used in the treatment of hormone-receptive breast cancers. Tamoxifen interferes with the activity of the hormone estrogen, which feeds the growth of these cancers. The manufacturing of Tamoxifen has been proposed as a multi-step process in which active and inactive ingredients are first granulated and then mixed with water. This mixture is sent to a dryer. The mixture is dried to 1% water[6] by mass and the final excipients are blended to form tablets (final step). In order to produce a hundred thousand tablets, 176.78 kg of final material is required containing 8.65 mass % Tamoxifen, 1.98 mass % PVP K30 (binder), and 2.12 mass % of final excipients. The stream to the granulator contains 9.12 mass % API and remaining are excipients. The

granulated material is sent to a mixer containing PVP K30 and water. What is the mass and composition entering the dryer if the dryer evaporates 94.23% of water?

The solution is as follows:

This is a rather complicated process due to multiple steps, so it is important to draw an accurate diagram and carefully label the streams and the information provided. We know that blending is the final step and granulation is the first step. The problem statement also mentions the moisture content of the mixture after drying and before entering the blender. Water was added to a mixture before putting the wet mass in the dryer. Using this information, a diagram is drawn and labeled.

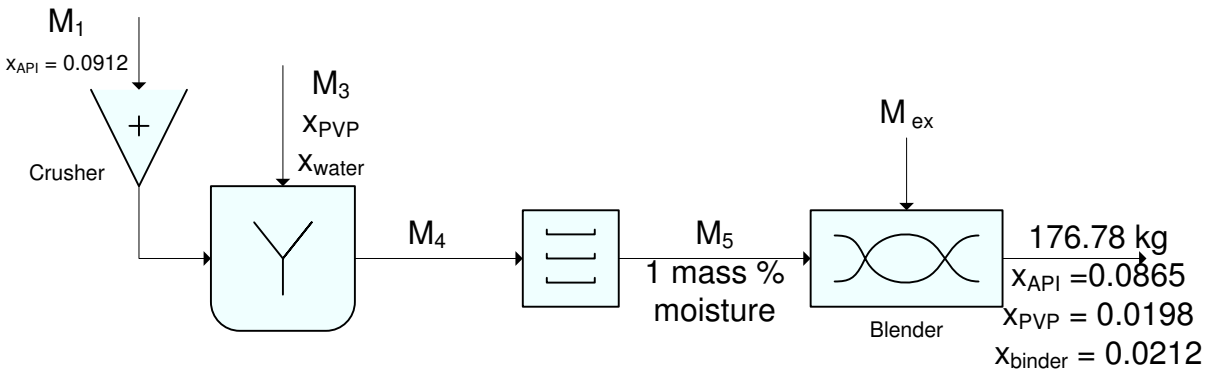

Figure 4. Multistep process for Tamixofen production.

From here it can be assumed that the system is at steady state. From the outlet stream, the mass of the API, binder, and the final set of excipients are calculated.

$$m_{\text{API}} = 176.78\ \text{kg} \times (x_{\text{API}}) = \ 176.78\ \text{kg} \times (0.0865) = \ 15.3\ \text{kg}$$
$$m_{\text{PVP}} = 176.78\ \text{kg} \times (x_{\text{PVP}}) = \ 176.78\ \text{kg} \times (0.0198) = \ 3.5\ \text{kg}$$
$$m_{\text{ex 2}} = 176.78\ \text{kg} \times (x_{\text{ex 2}}) = \ 176.78\ \text{kg} \times (0.0212) = \ 3.75\ \text{kg}$$

A mass balance around the blender will result in m_5. Here it is important to note that 94.23 mass % of the water entering is evaporated and only 5.77% remains with the dried granules.

$$m_5 = 176.78\ \text{kg} - 3.75\ \text{kg} = 173.03\ \text{kg}$$

$$\frac{5.77\ \%}{100\ \%} = \frac{(0.01) \times 173.03\ \text{kg}}{m_{\text{water}}} \rightarrow m_{\text{water}} = 30.0\ \text{kg water entering the dryer}$$

Now we can calculate the mass of excipients entering the granulator with the API and the stream entering the dryer to get the composition.

$$m_1 = \frac{m_{\text{API}}}{x_{\text{API}}} = \frac{15.3\text{ kg}}{0.0912} = 167.8\text{ kg}$$

$$m_{\text{ex}} = m_1 x_{\text{ex}} = 167.8\text{ kg} \times (1 - 0.0912) = 152.5\text{ kg}$$

$$m_4 = m_1 + m_3 = 167.8\text{ kg} + 33.5\text{ kg} = \boxed{201.3\text{ kg}}$$

Composition of each material is calculated by taking the mass of each material found and dividing it by the total mass entering the dryer.

$$x_{\text{API}} = \frac{15.3\text{ kg}}{201.3\text{ kg}} = \boxed{0.076}$$

$$x_{\text{PVP}} = \frac{3.5\text{ kg}}{201.3\text{ kg}} = \boxed{0.0174}$$

$$x_{\text{ex 1}} = \frac{152.5\text{ kg}}{201.3\text{ kg}} = \boxed{0.758}$$

$$x_{\text{water}} = 1 - (x_{\text{API}} + x_{\text{PVP}} + x_{\text{ex}}) = 1 - (0.076 + 0.0174 + 0.758) = \boxed{0.1486}$$

Pressurized propellant in a metered-dose inhaler

Gas-phase behavior and modeling is an important subject in chemical engineering and therefore in chemical engineering education; most sophomore-level material and energy courses devote significant time to these subjects. A commonly used text book for these courses, Felder and Rousseau's Elementary Principles of Chemical Processes, devotes the greater part of a chapter (Five) to the ideal gas law and other, higher order, equations of state (EOS).

This problem was developed to illustrate the use of a more complex quadratic EOS, the truncated virial equation of state, in a unique setting. The choice of a common and easily understood medical device, the respiratory inhaler, as the system is intended to show the application of apparently abstract chemical engineering models to familiar, concrete objects. The universal knowledge of inhalers among students and professors from personal use, observation of others' use of them and advertisements makes them particularly useful objects for study since basic knowledge of their operation and function can be assumed. This allows a professor to extend the problem with information or demonstrations of his or her own, such as displaying a sample inhaler and documentation. The choice of propellant, which comprises the realistic background to the problem, references the environmental ("green") and sustainability issues present in the pharmaceutical engineering industry.

The problem statement is as follows:

> In a **metered-dose inhaler** (MDI), such as those used for asthma medication, the medicine is delivered by a pressurized **propellant**, similar in idea to a can of spray paint. When the inhaler is activated, a set amount of the medicine is expelled from the mouthpiece to be inhaled. In the past, chlorofluorocarbons (CFCs) were used as propellants; however because of their reactivity with the Earth's ozone layer they have been suppressed. The new propellants, hydrofluorocarbons (HFCs), are considered "greener" because they do not react with the ozone layer.

You are assigned to calculate the amount of substance required to meet specifications of an MDI. The original propellant, CFC 12, has been replaced by HFC 227ea. Both inhalers contain 100 mL of propellant under 80 psia. Because of the pressurization of the cylinder the use of the truncated virial equation of state is specified. Because of the increased computational effort required to use the virial equation of state (You'll see when you try it), you should test the ideal gas law equation of state to see if it is close enough to use instead.

The solution is as follows:

This is a blatant attempt to get students to use something OTHER than the ideal gas law.

In setting up the problem an assumption of temperature must be made. The most logical is standard temperature (25 °C / 298 K) since inhalers are commonly used at room temperature.

We then need to look up the values needed for these compounds, specifically critical temperature (T_c), critical pressure (P_c) and the acentric factor (ω). To do this we consult sources. An expected part of this is the discovery of what CFC 12 and HFC 227ea really are: dichlorodifluoromethane and 1,1,1,2,3,3,3-heptafluoropropane. What reference is chosen is immaterial, since all legitimate references should give very similar values.

Using the 2nd edition of Knovel Critical Tables (available through the AiCHe Elibrary[7]) for the critical constants and two papers for the acentric factors:

	T_c (K)	P_c (atm)	ω
CFC 12	384.95	40.71	0.180
HFC 227ea	374.83	28.74	0.356

Now the hard part is done and the calculations may be performed.

Since, like all advanced equations of state, the constants are obtained from the solution to earlier equations, we should examine the equations to determine the order of the equations and where to start:

$$(\text{Start})\ T_\text{r} \rightarrow (B_0, B_1) \rightarrow B \rightarrow \hat{V}$$

The first step is to calculate the reduced temperature, which we will do for CFC 12:

$$T_\text{r} = \frac{T}{T_\text{c}}$$

$$T_\text{r} = \frac{298\ \text{K}}{384.95\ \text{K}} = 0.774$$

Substituting this into the equations for B_0 and B_1:

$$B_0 = 0.083 - \frac{0.422}{T_\mathrm{r}^{1.6}}$$

$$B_0 = 0.083 - \frac{0.422}{0.774^{1.6}} = -0.553$$

$$B_1 = 0.139 - \frac{0.172}{T_\mathrm{r}^{4.2}}$$

$$B_1 = 0.139 - \frac{0.172}{0.774^{4.2}} = -0.365$$

We now substitute these values into the formula for B:

$$B = \frac{RT_\mathrm{c}}{P_\mathrm{c}}(B_0 + \omega B_1)$$

$$B = 0.08206\ \frac{\mathrm{L \cdot atm}}{\mathrm{mol \cdot K}} \times \frac{384.95\ \mathrm{K}}{40.71\ \mathrm{atm}}(-0.553 + 0.180[-0.365])$$

$$B = -0.480\ {}^{\mathrm{L}}/_{\mathrm{mol}}$$

Inserting this and other values into the viral equation:

$$\frac{P\hat{V}}{RT} = 1 + \frac{B}{\hat{V}}$$

$$80\ \mathrm{psi} \times \frac{1}{14.696}\frac{\mathrm{atm}}{\mathrm{psi}} \times \hat{V} \times \frac{1}{0.08206}\frac{\mathrm{mol \cdot K}}{\mathrm{L \cdot atm}} \times \frac{1}{298\ K} = 1 + \left(-0.480\ \frac{\mathrm{L}}{\mathrm{mol}} \times \frac{1}{\hat{V}}\right)$$

$$0.122\frac{\mathrm{mol}}{\mathrm{L}} \times \hat{V} = 1 - 0.480\ \frac{\mathrm{L}}{\mathrm{mol}} \times \frac{1}{\hat{V}}$$

There are two solutions (roots) to any quadratic equation. This may be solved with an equation solver, such as Wolfram Mathematica, a spreadsheet "goalseek" function, or the quadratic formula. In any case, two answers are found:

$$\hat{V} = (3.944, 0.546)\ {}^{\mathrm{L}}/_{\mathrm{mol}}$$

The obvious question now is how to make a choice. A possible choice is to compare the two values to an already known molar volume, such as a compressed gas in a similar circumstance. An easier and more reasonable way (That is also suggested by the book) is to use the ideal gas law and pick the value that is closer it to its solution.

To use the ideal gas law here, we simply rearrange Equation 5.2-2:

$$P\hat{V} = RT$$

$$\hat{V} = \frac{RT}{P}$$

Substituting and solving:

$$\hat{V} = \frac{0.08206\ \text{L} \cdot \text{atm}}{\text{mol} \cdot \text{K}} \times 298\ \text{K} \times \frac{1}{80\ \text{psi}} \times 14.696 \frac{\text{psi}}{\text{atm}} = 4.50\ {}^{\text{L}}/_{\text{mol}}$$

This suggests that 3.944 is the correct solution to the quadratic equation of state.

Remembering that this is a 40 mL cylinder, we determine the amount of substance:

$$n = \frac{V}{\hat{V}} = \frac{0.100\ \text{L}}{3.944\ \frac{\text{L}}{\text{mol}}}$$

$$\boxed{n_{\text{CFC 12}} = 0.0254\ \text{mol CFC 12}}$$

Doing the same thing for HFC 227ea gives us:

$$\boxed{n_{\text{HFC 227ea}} = 0.0274\ \text{mol HFC 227ea}}$$

To test the ideal gas law, we simply divide 40 mL by the specific molar volume found before:

$$n = \frac{V}{\hat{V}} = \frac{0.100\ \text{L}}{4.50\ \frac{\text{L}}{\text{mol}}} = 0.0223\ \text{mol}$$

To calculate the percent error we substitute in:

$$\epsilon_{\text{CFC 12}} = \left|\frac{0.0254 - 0.0233}{0.0254}\right| \times 100\%$$

$$\boxed{\epsilon_{\text{CFC 12}} = 12.2\%}$$

$$\boxed{\epsilon_{\text{HFC 227ea}} = 18.7\%}$$

The ideal gas law is not completely incorrect, but is noticeably deviate from the virial value. Since this subject concerns medicine, a difference of this magnitude is unacceptable.

Students should be warned not to attempt to use the ideal gas law and divide by a correction factor determined from these percent errors instead of using the more

accurate EOS. The correct way to save time is to do this all in a spreadsheet that will automatically redo the calculations when any conditions are changed.

In solving the problem, the student is required to: perform independent research to discover the necessary physical property constants, understand the use of critical properties, cascading calculations, solution of non-obvious quadratic equations, determination of the root of physical significance, calculation of error, and drawing the requested conclusions from the data.

Diethylene glycol poisoning

A common concern of all engineering and therefore engineering education is safety. Engineering curricula include safety training in laboratories and explanation of safety concepts in lectures and reading. In common with other branches of engineering, pharmaceutical engineering safety violations 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, to the extent of being able to kill them.

This problem was written to allow more advanced topics in pharmaceutical engineering safety, such as toxicology and solvent evaluation, to be introduced at an earlier time in the curriculum. Numerous problems in introductory textbooks, such as Felder and Rousseau's Elementary Principles of Chemical Processes, include problems related to other disasters or imaginary situations of safety violations. The pharmaceutical focus of provided by this "applied disaster" improves the coverage of safety when included in a course by extending it to this field. In addition, the problem relates some of the history of chemical engineering by entertaining storytelling, introduces some toxicology terminology and calculations and involves some uncommon unit conversions.

The problem statement is as follows:

> 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 requested his **research and development** scientists to find a way to fill this market segment. The **active pharmaceutical ingredient** (API) of his proposed medicine, sulfanilamide, was widely accepted; its high insolubility in water or any other common pharmaceutical **diluent** had prevented a liquid dose form being made already.
>
> The chief researcher at the firm approached this as the main problem to be solved. After some laboratory research, he found that the substance dissolved satisfactorily in diethylene glycol (DEG). Unfortunately, they did no testing whatever, made up some batches of it (240 gallons in total), and sold it. After a madcap 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 this corresponds to for the dosage given.
(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.

The solution is as follows:

This problem is a disguised use of the Elixir Sulfanilamide disaster to teach some unit conversions, pharmacy terminology, mathematic reasoning and caution.

The company in question was S. E. Massengill of Bristol, Tennessee. The citations provided give a good illustration of the actual events.

In dealing with poison and toxicology, it is common practice to assume the highest dose/worst case scenario. All calculations and assumptions are based on this.

(a) First we need to make assumptions about how many doses were taken per day by a patient. While there are 6 four hour periods in one calendar day, it is unlikely a patient would wake up at 4 in the morning to take a dose. If a person was awake for 16 hours, they would take, at most, 4 doses (Waking, mid-day, before sleep). At this point we know that the patient would take:

$$V_\mathrm{d} = 4\ \text{doses} \times \frac{3\ \mathrm{t}}{\text{dose}} = 12\ \mathrm{t}$$

Now we need a conversion to a useful unit of volume. The volume of a teaspoon from 1937 may have been slightly less rigorously defined, but we will go by the current definition from the NIST's Weights and Measures: 5 mL/t.

$$V_\mathrm{d} = 12\ \mathrm{t} \times 5\frac{\mathrm{mL}}{\mathrm{t}} = 60\ \mathrm{mL}$$

Also, note that common kitchen measures like teaspoons are strongly discouraged in modern pharmacy

Now we need a density to obtain the mass of DEG. Consulting Knovel Critical Tables[8] we find it is 1.119 g/cm^3.

$$m_\mathrm{d} = 60\ \mathrm{mL} \times 1.119\frac{\mathrm{g}}{\mathrm{cm}^3} \times 1\frac{\mathrm{cm}^3}{\mathrm{mL}}$$

$$\boxed{m_\mathrm{d} = 67.14\ \mathrm{g\ DEG}}$$

(b) To determine the human weight this corresponds to, we take the ratio:

$$m_{\mathrm{h}} = 67.14\ \mathrm{g\ DEG} \times \frac{1}{0.5} \frac{\mathrm{kg\ weight}}{\mathrm{g\ DEG}}$$

$$\boxed{m_{\mathrm{h}} = 134.3\ \mathrm{kg} = 295.\ \mathrm{lb_m}}$$

Anyone under ~300 $\mathrm{lb_m}$ would be fatally poisoned. 5 g/kg was the other limit, which produced 13.43 kg or 29.5 $\mathrm{lb_m}$, however the worst case scenario is again assumed.

(c) The most immediately occurring answer is that a highly poisonous substance should not be taken even if the quantities are supposedly below a lethal level. Glycol (antifreeze) poisoning is attended with severe symptoms even if death is not the ultimate result.

The more mathematical answer is that the toxic dose range covers a huge range.

(d) To do this, we simply divide the total volume produced by the dose volume from the initial calculation:

$$N_{\mathrm{p}} = \frac{V}{V_{\mathrm{d}}} = \frac{240\ \mathrm{gal}}{60\ \mathrm{mL}} \times \frac{10^6}{264.17} \frac{\mathrm{mL}}{\mathrm{gal}}$$

$$\boxed{N_{\mathrm{p}} = 15141}$$

(e) This is best presented in a table to show the flow from first, on:

Error	Correction	Effect of correction
Veterinary medicine company decides to produce drug for human use	Check if the company knew what it was getting into; the two are vastly different fields	Ensured that the proper physical plant and mindset existed to do this work
Research chemist does lab research with, apparently, no library research.	May have turned up a possible alternate solvent. Definitely would have discovered DEG's poisonous qualities.	Almost certainly would have prevented the use of a toxic solvent
Product made with almost nonexistent testing	Testing for effectiveness, quality, storage life, toxicity, etc.	Would have prevented the poisoning and otherwise improved the product
Product released unrestricted without initial field testing	Send out a test batch or two and see what the results are	Dangerous quality would be immediately discovered

Note that two of the five questions are reasoning based rather than research or calculation based in order to give the problem a strong focus on the "moral" of the story. The calculational questions are relatively simple and intended as "speed bumps" to prevent the student from slapping something together as sometimes occurs with purely verbal answer questions.

In working through this problem, the student will primarily deal with simple unit conversions and ratios. It is intended that their main focus (and interest!) will be in the story itself and the intentionally rather obvious morals they are asked to draw.

Hypothermia treatment

Mass and energy balances are common topics covered in introductory chemical engineering courses. The following problem uses two different hypothermia treatments to illustrate these concepts. In addition to simply using mass and energy balances, this problem was designed to force students to use additional materials to obtain the data they need to complete the balances. For example, the first part of the problem requires using the steam tables to find the initial and final internal energies associated with a closed system energy balance. The second part of the problem requires the use of the psychrometric charts to complete the material balance needed to solve the problem.

The problem statement is as follows:

(a) As a way of replacing fluid volume lost during respiration[9], hypothermia patients are sometimes given an IV of saline solution warmed to 40-42 °C (104-108 °F)[10]. Saline solution is a mixture of sodium chloride and sterile water; the sodium chloride content in normal saline solution is 0.9%[11]. Calculate the energy required (kJ) to heat a 1 L bag of saline solution from 25 °C to 40 °C.

(b) Administering humidified oxygen or air, which has been heated to 42 °C (108 °F), is used as a noninvasive way to raise a hypothermia patient's core body temperature and is used as a first response treatment[2].

A hypothermia patient in Alaska is being transported to the hospital. The EMT uses a device which takes air from inside the ambulance, heats it to 42 °C, and humidifies it to its saturation point. The air from inside the ambulance enters the device at 21 °C and 71% relative humidity. The device holds 70 mL of water, which is used to humidify the air. The humidified air is delivered to the patient at a rate of 15 L/min. Calculate the mass flow rate (kg/min) of dry air entering the device, the rate (kg H_2O/min) water is being added to the air inside the device, and the length of time (h) the device can run at these conditions.

The solution is as follows:

(a)

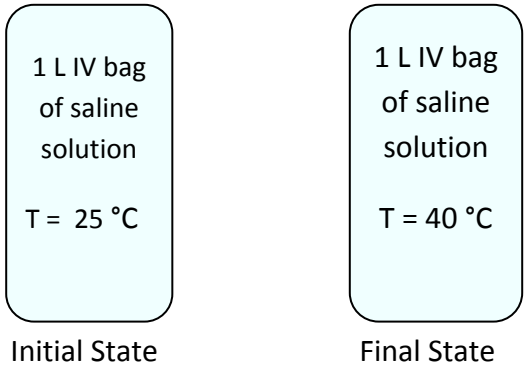

Figure 5. Heating of saline solution for treatment of hypothermia.

To solve this problem, use a closed system energy balance.

$$\Delta U + \Delta E_k + \Delta E_p = Q - W$$

No work is being done by or on the system: W = 0. The system is not in motion: $\Delta E_k = 0$. There is no change in the height of the system, so there is no potential energy change: $\Delta E_p = 0$. Therefore, the energy balance reduces to:

$$\Delta U = Q$$

$$m\hat{U}_F - m\hat{U}_I = Q$$

$$m\left(\hat{U}_F - \hat{U}_I\right) = Q$$

Because it is a dilute solution, assume it has the properties of water. Look up the initial and final internal energies in the steam tables (Table B.5 in Felder and Rousseau).

$$\hat{U}_I = 104.8 \ \frac{\text{kJ}}{\text{kg}}$$

$$\hat{U}_F = 167.4 \ \frac{\text{kJ}}{\text{kg}}$$

$$Q = \left[(1 \ \cancel{\text{L}})\left(\frac{1 \ \cancel{\text{kg}}}{\cancel{\text{L}}}\right)\right]\left[\left(167.4 \frac{\text{kJ}}{\cancel{\text{kg}}}\right)\left(104.8 \frac{\text{kJ}}{\cancel{\text{kg}}}\right)\right] = \boxed{62.6 \text{ kJ}}$$

(b)

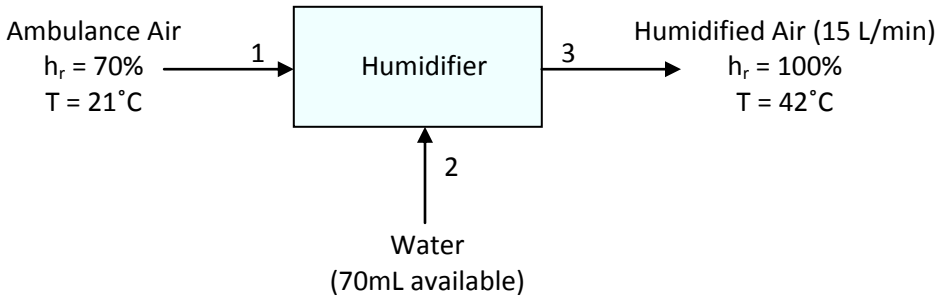

Figure 6. Humidification and heating of air for hypothermia treatment.

Calculate the volume of dry air (DA) entering the device:

$$\dot{m}_{\text{DA in}} = \dot{m}_{\text{DA out}}$$

From the psychrometric chart, $\hat{V}_{\text{H out}} = 0.941 \frac{\text{m}^3}{\text{kg DA}}$

$$\dot{m}_{\text{DA out}} = \left(15 \frac{\cancel{\text{L}}}{\text{min}}\right)\left(\frac{\text{kg DA}}{0.941\ \cancel{\text{m}^3}}\right)\left(\frac{\cancel{\text{m}^3}}{1000\ \cancel{\text{L}}}\right) = 0.0159 \frac{\text{kg DA}}{\text{min}}$$

$$\dot{m}_{\text{DA out}} = \dot{m}_{\text{DA in}} = \boxed{0.0159 \frac{\text{kg DA}}{\text{min}}}$$

Calculate the rate at which water is being added to the air entering the device:

Material balance on water:

$$\dot{m}_{1\ \text{H}_2\text{O}} + \dot{m}_2 = \dot{m}_{3\ \text{H}_2\text{O}}$$

From the psychrometric chart:

$$h_{\text{a in}} = 0.0108\ \frac{\text{kg H}_2\text{O}}{\text{kg DA}}$$

$$h_{\text{a out}} = 0.0330\ \frac{\text{kg H}_2\text{O}}{\text{kg DA}}$$

Solve for $\dot{m}_{2\ \text{H}_2\text{O}}$, the rate of water being added.

$$\dot{m}_2 = \dot{m}_{3\ \text{H}_2\text{O}} - \dot{m}_{1\ \text{H}_2\text{O}}$$

$$\dot{m}_2 = \left(0.033 \frac{\text{kg H}_2\text{O}}{\cancel{\text{kg DA}}}\right)\left(0.0159 \frac{\cancel{\text{kg DA}}}{\text{min}}\right) - \left(0.0108 \frac{\text{kg H}_2\text{O}}{\cancel{\text{kg DA}}}\right)\left(0.0159 \frac{\cancel{\text{kg DA}}}{\text{min}}\right) = \boxed{3.53 \times 10^{-4} \frac{\text{kg H}_2\text{O}}{\text{min}}}$$

Calculate the length of time the device can run:

$$\dot{V}_2 = \left(3.53 \times 10^{-4} \frac{\text{kg } H_2O}{\text{min}}\right)\left(\frac{1 \text{ L}}{\text{kg}}\right)\left(\frac{1000 \text{ mL}}{\text{L}}\right) = 0.353 \frac{\text{mL } H_2O}{\text{min}}$$

$$t = (70 \text{ mL})\left(\frac{1 \text{ min}}{0.353 \text{ mL } H_2O}\right)\left(\frac{1 \text{ h}}{60 \text{ min}}\right) = \boxed{3.3 \text{ h}}$$

Tablet production

The solution to the following problem requires the students to perform multiple material balances to calculate the desired quantities. However, rather than simply giving the students a diagram with the information needed to solve the problem, the problem was developed around the production of metoclopramide tablets. In general, the procedure for producing the metoclopramide tablets is simple because the ingredients just need to be added together. 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. They students must use their knowledge of moisture content to complete the calculations successfully.

The problem statement is as follows:

> Metoclopramide is an **active pharmaceutical ingredient (API)** used to treat heartburn[12]. Making the formulation that gets compressed into metoclopramide tablets is a multistep process[7]. For a process designed to make a batch of 1000 tablets, the required amounts of metoclopramide (Stream 1), preglatinized starch (Stream 2), and lactose (Stream 3) are mixed with 15 mL of water. The resulting mixture contains 11.38% water 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 (Stream 11), 0.76 g of magnesium stearate (Stream 12), and dried maize starch (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 the final product.

Figure 7 multistep process for metoclopramide tablet production.

(a) Calculate m_2.

Mass balance (M.B.) around the mixer:

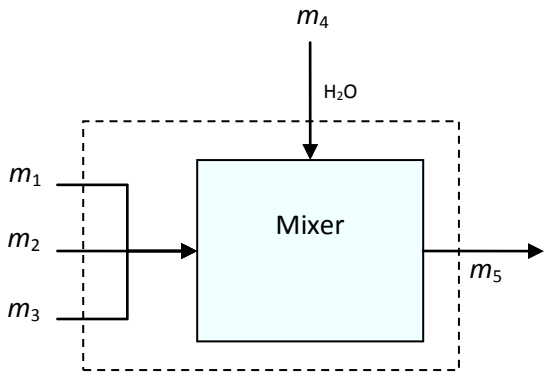

Figure 8. Mass balance around the mixer in metoclopramide tablet production.

$$m_1 + m_2 + m_3 + m_4 = m_5$$

m_1 is the only source of the API into the process so

$$m_1 = m_{\text{API in}} = m_{\text{API out}} = 10.54 \text{ g}$$

m_3 is the only source of lactose. There are 101.24 mg lactose per tablet and this process makes 1000 tablets per batch, so

$$m_3 = \left(101.24 \frac{\cancel{\text{mg}}}{\cancel{\text{tablet}}}\right)(1000\ \cancel{\text{tablets}})\left(\frac{1\ \text{g}}{1000\ \cancel{\text{mg}}}\right) = 101.24\ \text{g}$$

m_4 is the water being added to the mixer which is given as a volume in the problem statement. Convert volume to mass using the density of water:

$$\text{m}_4 = (15\ \cancel{\text{mL}})\left(\frac{1\ \text{g}}{\cancel{\text{mL}}}\right) = 15\ \text{g}$$

m_5 can be calculated using the given percentage of water in the stream (11.82%). All of the water added from m_4 will be added into m_5.

$$m_5 = \frac{m_{5\,\text{H}_2\text{O}}}{x_{5\,\text{H}_2\text{O}}} = \frac{\text{Mass of H}_2\text{O in stream 5}}{\text{Total mass of stream 5}}$$

$$m_5 = \frac{15\ \text{g}}{0.1138} = 131.81\ \text{g}$$

Plug back into M.B.:

$$m_2 = m_5 - m_1 - m_3 - m_4$$

$$m_2 = 131.81\ \text{g} - 10.54\ \text{g} - 101.24\ \text{g} - 15\ \text{g} = \boxed{5.03\ \text{g}}$$

(b) Calculate m_6

Component M.B. on water around tray dryer:

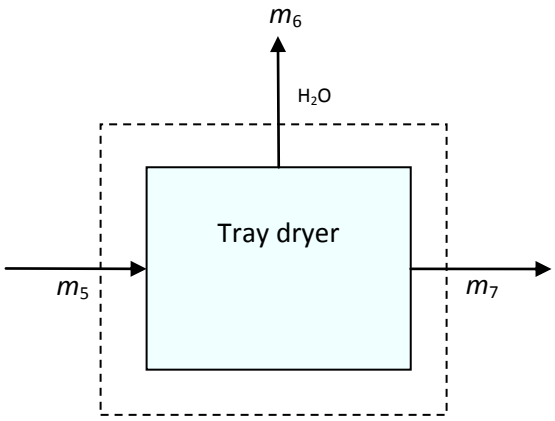

Figure 9. Mass balance around the tray dryer in metoclopramide tablet production

$$m_{5\,\text{H}_2\text{O}} = m_{6\,\text{H}_2\text{O}} + m_{7\,\text{H}_2\text{O}}$$

Need to calculate $\text{m}_{7,\text{H}_2\text{O}}$:

$$\text{Moisture Content} = x_{7\,H_2O} = \frac{m_{7\,H_2O}}{m_{7\,H_2O} + m_{7\,\text{dry solids}}}$$

Component M.B. on dry solids (D.S.):

$$m_{5\,\text{D.S.}} = m_{7\,\text{D.S.}} = (1 - 0.1138) \times (131.81\ \text{g}) = 116.81\ \text{g D.S.}$$

Plug into equation for moisture content:

$$0.052 = \frac{m_{7\,H_2O}}{m_{7\,H_2O} + 116.81\ \text{g}}$$

$$m_{7\,H_2O} = 7.23\ \text{g}$$

Plug back into M.B.:

$$m_6 = m_{6\,H_2O} = m_{5\,H_2O} - m_{7\,H_2O} = 15\ \text{g} - 7.23\ \text{g} = \boxed{7.77\ \text{g}}$$

(c) Calculate m_{13}

M.B. around Blender:

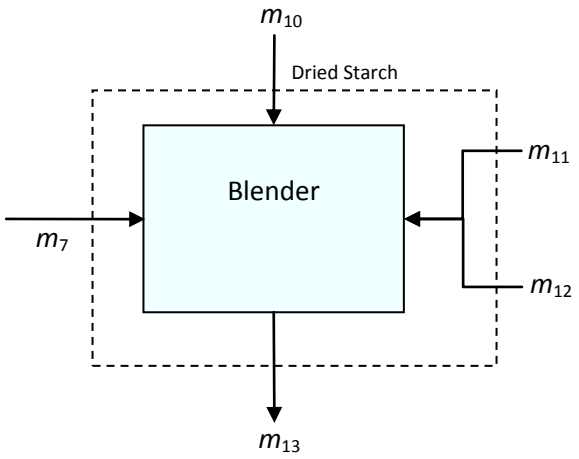

Figure 10. Mass balance around the blender in metoclopramide tablet production

$$m_7 + m_{10} + m_{11} + m_{12} = m_{13}$$

From the problem statement:

$$m_{11} = 1\ \text{g}$$

$$m_{12} = 0.76\ \text{g}$$

m_7 can be calculated from values found in part (b):

$$m_7 = m_{7\ H_2O} + m_{7\,\text{D.S.}} = 7.23\ \text{g} + 116.81\ \text{g}$$

$$m_7 = 124.04\ \text{g}$$

m_{10} can be calculated using the information given about the dried starch stream coming out of the dryer. However, first the mass entering the dryer, m_8 must be calculated:

$$\%\text{ change in mass of starch} = \frac{m_8 - m_{10}}{m_8} \times 100\% = \frac{\Delta m_{\text{drying}}}{m_8} \times 100\%$$

Δm_{drying} is from the water lost from the stream, therefore

$$\Delta m_{\text{drying}} = m_9 = 0.128$$

Solve for m_8:

$$m_8 = \frac{m_9}{\%\text{ change in mass of starch} \times 100\%} = \frac{0.128\text{ g}}{1.8 \times 100\%} = 7.11\text{ g}$$

Now compute a M.B. around the dryer:

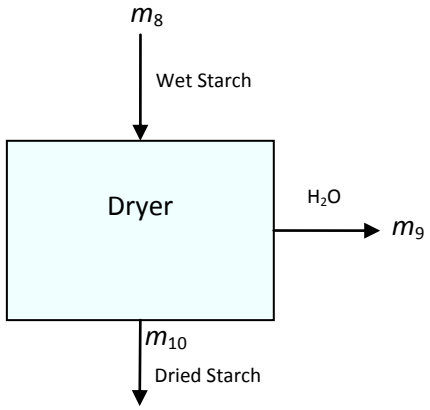

Figure 11. Mass Balance around the dryer in metoclopramide tablet production

$$m_8 = m_9 + m_{10}$$

$$m_{10} = m_8 - m_9 = 7.11\text{ g} - 0.128\text{ g} = 132.78\text{ g}$$

Now all of the values for the blender material balance are known and m_{13} can be solved for:

$$m_{13} = 124.04\text{ g} + 6.98\text{ g} + 1.0\text{ g} + 0.76\text{ g} = \boxed{132.78\text{ g}}$$

Conclusions

The problems developed for the NSF ERC-SOPS are intended to be used in sophomore level chemical engineering courses. Each problem introduces topics related to pharmaceutical technology. Each problem is 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 being researched. The students must use the principles of chemical engineering they are learning in their courses to solve the problems. A detailed solution is provided with each problem for the professor to explain how to solve the problem. The solutions are written so that they could be given directly to the students without any additional instruction from the professor. The problems have been reviewed by multiple team members and faculty. They will be distributed to sophomore classes at Rowan University to get feedback from students in the type of course where the problems could be used. The goal is for students to practice the subjects they are learning in class while being exposed to a realistic application of pharmaceutical technology.

Acknowledgements

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