AC 2011-1031: INTRODUCTORY LEVEL TEXTBOOK PROBLEMS ILLUSTRATING CONCEPTS IN PHARMACEUTICAL ENGINEERING

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Introductory level textbook problems illustrating concepts in pharmaceutical engineering

Abstract

Chemical Engineering faculty members and students from XX University are engaged in a collaborative venture with Engineering Research Center for Structured Organic Particulate Systems (C-SOPS) to create educational materials related to chemical engineering in the pharmaceutical and consumer care industries. The C-SOPS is hosted by Rutgers University and also involves Purdue University; the New Jersey Institute of Technology; and the University of Puerto Rico, Mayagüez, and it is funded by the National Science Foundation. 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. XX University has partnered as an outreach/education member institution to expand the impact of the Center through SMET education and outreach.

This paper describes problem sets for introductory chemical engineering courses such as material and energy balances. The problems emphasize concepts of unit conversions, engineering calculations, estimations, writing a process flow diagram, mass balances, safety, heat of formation, and looking up physical properties, through the application to problems related to over-the-counter medications and consumer care products. The problems and solutions are readily transferrable for use by instructors at other institutions. These problems will be pilot tested in the fall of 2011.

Introduction

XX University is an Outreach Partner for the National Science Foundation (NSF) Engineering Research Center (ERC) for Structured Organic Particulate Systems (SOPS) led by Rutgers University. The Center conducts research and technology transfer related to products and processes in the pharmaceutical, nutraceutical, and related fields. In addition to its research mission, the Center conducts and coordinates educational and outreach programs from K-12 through graduate instruction. XX University's role is to produce educational materials for K-12 through undergraduate level that support the mission of the Center.

Over the past several years, XX faculty and students have developed interactive demonstrations and course modules related to particle technology and pharmaceutical engineering. The objective is to translate organic particulate systems manufacturing concepts and research being done the Center into educational materials that can be used at various levels [1,2, 3]. The majority of the course modules (which we also refer to as problem sets) are based on pharmaceutical manufacturing or drug delivery technology suitable for integration into an introductory chemical engineering course [4, 5]. These courses are usually the first chemical engineering course in the curriculum and aretaught in either the freshman or the sophomore year. Each course module

consists of a multi-part problem statement with a link to an ERC topic/area, relevant literature references, web sites, and fully executed solution.

Problem Development

The SOPS research and applications are found in fields of health care/medicine, pharmaceuticals, nutraceuticals, consumer and personal care products and agrochemicals. This paper presents problem sets covering terminology, formulation and manufacturing techniques for consumer/personal care products and over the counter (OTC) medicines. They were developed last year by chemical engineering students, refined through peer feedback and are currently undergoing pilot testing in our courses. The problem sets described in this paper were developed for introductory chemical engineering course(s).

The formatting, layout, style and focus of the problems are based on those of the widely used text, *Elementary Principles of Chemical Processes, 3rd,* by R. Felder and R. Rousseau [6]. Courses taught with a different textbook may still use the problems since they cover topics such as units and conversions, material balances with and without reaction, single and multiphase systems, and energy balances. To allow professors to integrate easily these problems into their classes, we have "mapped" them to specific chapters/sections of the text. The next edition of the book (4th ed, Felder, Rousseau, Newell; 2012) will integrate problems from pharmaceutical and other novel engineering areas.

In the development of problems, the following general guidelines were followed:

- All problems directly relate to topics from pharmaceutical technology or related consumer products (either basic concepts related to formulation or to manufacturing)
- Each problem, has a fully executed solution
- Interesting terms (introduced in the problem) are boldfaced.
- Appropriate references and web links are provided
- All problems were designed to be reasonable, with information drawn from various texts or literature sources although the following should be considered when using them
    - The actual drug formulations may vary from manufacturer to manufacturer
    - Information may come from "research" studies and may not represent the final process as approved by FDA
    - Problems that are clearly fictitious are written that way for a student to analyze why the situation would not occur in real life.

The following examples illustrate the types of problems developed for the various topical areas. We have utilized the PharmaHUB (www.PharmaHUB.org) to post problem modules under the ERC Educational Modules resources section [7,8]. Complete problem sets can be obtained through the PharmaHUB. The problem sets have been incorporated into two easy to use documents that have the problems organized by the chapter/section of Felder and Rousseau they would be used in. If these problems are used in another course, such as a Freshman Engineering class, they can be easily integrated them by using the chapter/topic outline found in the document on PharmaHUB. The complete module sets include an introduction and table of contents with index problems and solutions. The problems and solutions are on separate pages allowing the faculty member to easily use these for homework or in-class problems. The solutions are sufficiently detailed to allow students with limited knowledge in the field to understand the concepts described in the problem statement.

The PharmaHUB provides numerous educational and training materials for topics in the pharmaceutical manufacturing field. The majority of these are related to upper division and graduate education and research topics. For example, Rutgers University has posted numerous lectures (as Powerpoint® slides) from the courses used in their M.S. in Pharmaceutical Engineering Program. Purdue, New Jersey Institute of Technology, and University of Puerto Rico-Mayaguez have also posted materials from their courses. The site also provides the user with research tools related to the field of particle science and engineering. The XX educational materials are the only ones for lower-division courses and are provided under the site title: Integrating Pharmaceutical Concepts into Introductory Chemical Engineering Courses.

Example Problems

(Problems taken from Ref 8 and 7, Farrell, S., Savelski, M., Slater, C.S., DelVecchio, C., Iftikhar, M., Kosteleski, A., McIver, K., Wilson, S., Problem sets on Pharmaceutical Engineering for Introductory Chemical Engineering Courses – Part I, www.PharmaHUB.org, posted February 2010 and Farrell, S., Savelski, M., Slater, C.S., DeDelva, V., Kostetskyy, P., McIver, K., Whitaker K., Zienowicz, K. Problem sets on Pharmaceutical Engineering for Introductory Chemical Engineering Courses - Part II, www.PharmaHUB.org, posted May 2010.)

Sunscreen Dosage Calculation[7]

(for use in F&R chapter/section 3.1)

Problem Statement[7]

Sunscreen is used to protect the skin from UV radiation. The molecules present in the sunscreen absorb the high energy ultraviolet photons through electron resonance delocalization, and are raised to a more energetic orbital state. The energy absorbed is released in the form of fluorescence or heat when the molecule returns to the ground state. After a long period of sun exposure the molecules in the sunscreen start to degrade and the sunscreen will have to be

reapplied. For an average sized adult the required amount of sunscreen needed for protection is 2 mg/cm^2. During the summer, 1 hour of sunlight is the equivalent of 10 joules per cm^2 [9].

a) An average size man is spending the day at the beach on a sunny summer day. He is wearing shorts that have dimensions of 15 cm by 82 cm. How many grams of sunscreen are needed to cover his exposed skin? (*Hint*: Look up average body surface area.)
b) How often should he reapply the sunscreen in order to get **maximum** protection?
c) What suggestions would you make to him?

Labeled SPF	Sunscreen active system	Percentage of total UV absorbance remaining after UV exposure			
		5 joule	10 joule	20 joule	30 joule
N/A	Antisolarium	100	95	86	70

Solution[7]

a) The average body surface area of a man is 16,200 cm^2.
The surface area of his shorts is (assume a square)

$$15 \text{ cm} \times 85 \text{ cm} = 1275 \text{ cm}^2$$

The area of exposed skin is

$$16{,}200 \text{ cm}^2 - 1275 \text{ cm}^2 = 14{,}925 \text{ cm}^2$$

Conversion

$$2 \text{ mg} \times \frac{1 \text{ g}}{1000 \text{ mg}} = 0.002 \text{ g}$$

The amount of sunscreen needed is

$$14{,}925 \text{ cm}^2 \times \frac{0.002 \text{ g}}{1 \text{ cm}^2} = \boxed{29.85 \text{ g}}$$

b) In 1 hour 10 joules are applied to 1 cm^2 of exposed skin. From the table we can observe that after 10 joules of UV exposure, 95% of Antisolarium remains which means the product began to degrade. So for maximum protection, the sunscreen should be reapplied every 30 minutes.

c) The man should purchase a more effective sunscreen.

This problem presents concepts in basic calculations of units and variables related to personal care products used for skin care. Students have to look up the surface are of an adult male to determine the dosage needed, then use the data provided to determine the dosage interval for effective protection against UV radiation.

Material Balance for Nail Polish Formulation[7]

(for use with F&R chapter/section 4.2)

Problem Statement[7]

Nail polishes, treatments and hardeners all contain a **film-former**, such as nitrocellulose to produce a hard and shiny surface when dried. Its excellent adhesion property to the natural nail makes it an indispensable ingredient in the nail lacquer formulation. Its other attributes are durability, toughness, solubility and quick solvent release under ambient drying conditions.[10] To make the film tough and resilient, a resin such as toluene-sulfonamide-formaldehyde resin is used. This resin has been shown to possess the necessary characteristics of gloss, hardness and resistance to household detergent solutions.[11] To prevent chips and cracks, one or more plasticizers, such as camphor and dibutyl phthalate are included. [12] Solvents, including ethyl acetate, butyl acetate and toluene, are used to help products flow smoothly. These solvents are used to dissolve other substances including nitrocellulose, the basic film-forming material in nail polish.[13] Colored polishes or products contain FDA-approved colorants or pigments which are evenly distributed in the product due to the inclusion of a suspension agent or clay, such as titanium dioxide. [14] Below is a table that breaks down the final nail polish components by weight percent.

The pigment, TD, is mixed with nitrocellulose (N) and the plasticizers, (C and DP), using a **mill** to grind the pigment to produce fine dispersion of the color. When fully milled, the mixture is removed from the mill and enters a mixer with the three solvents, EA, BA, T. Due to N's adhesive properties, 5% remains as residue in the mill as loss. At the end of the process, the material is cooled by a jacketed stream of water entering 5 GPM at 15°C and final additives such as resin, TSF, are added. There are 3000 kg/hr of nail polish being produced with the following composition.

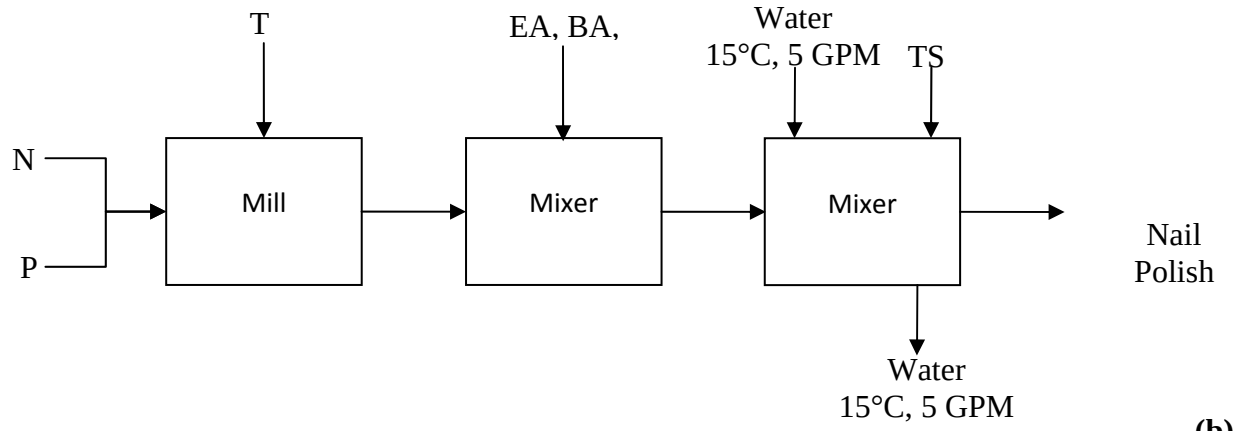
Nail Polish Formulation Component % by Weight[15]

Component	Composition (% by weight)
Nitrocellulose	13.0
Toluene-sulfonamide-formaldehyde resin	10.0
Dibutyl phthalate (plasticizer)	5.0

Camphor (plasticizer)	3.0
Ethyl acetate (solvent)	25.0
Butyl acetate (solvent)	23.5
Toluene	20.0
Titanium dioxide	0.5

a) Draw a process flow diagram of the process described above.
b) Determine the quantities of the components that must be added to produce the final 3000 kg/h of nail polish.
c) What is a problem with using Toluene-sulfonamide-formaldehyde resin? Is there an alternative?

Solution
a)



(b)

Basis: 3000 GPH
Total Mass Balance:

$$\dot{m}_N + \dot{m}_{TSF} + \dot{m}_P + \dot{m}_{EA} + \dot{m}_{BA} + \dot{m}_T + \dot{m}_{TD} = \dot{m}_{TOTAL}$$

$$\dot{m}_{\mathrm{TOTAL}} = 3000 \text{ kg/h}$$

$$x_{\mathrm{N}} + x_{\mathrm{TSF}} + x_{\mathrm{P}} + x_{\mathrm{EA}} + x_{\mathrm{BA}} + x_{\mathrm{T}} + x_{\mathrm{TD}} = 1.0$$

Components:
TSF:

$$(x_{TSF})\dot{m}_{\mathrm{TOTAL}} = \dot{m}_{\mathrm{TSF}}$$

$$\dot{m}_{\mathrm{TSF}} = (0.1)3000 \text{ kg/h} = \boxed{300 \text{ kg/h } TSF}$$

P:

$$(x_P)\dot{m}_{\mathrm{TOTAL}} = P$$

$$(0.08)3000 \text{ kg/h} = \boxed{240 \text{ kg/h } P}$$

EA:

$$(x_{EA})\dot{m}_{\mathrm{TOTAL}} = \dot{m}_{\mathrm{EA}}$$

$$(0.25)3000\ \text{kg/h} = \boxed{750\ \text{kg/h}\ EA}$$

BA:

$$(x_{BA})\dot{m}_{\text{TOTAL}} = \dot{m}_{\text{BA}}$$
$$(0.235)3000\ \text{kg/h} = \boxed{705\ \text{kg/h}\ BA}$$

T:

$$(x_T)\dot{m}_{\text{TOTAL}} = \dot{m}_{\text{T}}$$
$$(0.2)3000\ \text{kg/h} = \boxed{600\ \text{kg/h}\ T}$$

TD:

$$(x_{TD})\dot{m}_{\text{TOTAL}} = \dot{m}_{\text{TD}}$$
$$(0.005)3000\ \text{kg/h} = \boxed{15\ \text{kg/h}\ TD}$$

N:

$$(x_N)\dot{m}_{\text{TOTAL}} = \dot{m}_{\text{N}}$$
$$(0.13)3000\ \text{kg/h} = 390\ \text{kg/h}$$

5% N Loss:

You have to account for the 5% residue loss in the mill by adding 5% more N to the feed to get the proper final compositions.

$$\frac{390\ \text{kg/h}}{1 - 0.05} = \boxed{410.5\ \text{kg/h}\ N}$$

(c) Students would have to research the drawbacks of using Toluene-sulfonamide-formaldehyde resin from the web, patents, or journal articles. Acceptable answers are as follows:

Toluene-sulfonamide-formaldehyde resin is a carcinogenic formaldehyde.[16]
Many cases of allergic contact dermatitis to the toluene sulfonamide formaldehyde resin present in nail polish. [17]
The most popular resin is toluene-sulfonamide-formaldehyde, however, it is the source of allergic contact dermatitis in some nail enamels. Hypoallergenic nail enamels use polyester resin or cellulose acetate butyrate.

This problem covers the engineering principles of writing a simple process flow diagram for a multi-unit non-reactive process and performing a simple mass balance. It in introduces students to an actual case in cosmetic manufacture, the production of nail polish, and how the process uses a mill and mixers in the production operation. The problem also introduces students to the safety of raw materials used in consumer products, since the allergic reaction to the resin and its carcinogenic properties would be investigated in part 'c' of the problem and they would need to do research on possible safer alternatives.

Heat of Formation in Manufacture of Milk of Magnesia[7]

(for use with F&R chapter/section 9.3)

Problem Statement[7]

Milk of magnesia (magnesium hydroxide in aqueous solution) is an old, widely used and commonly seen **over the counter** (*OTC*) medication for constipation and **pyrosis** (heartburn). The standard heat of formation of magnesium hydroxide is[18] -924.66 kJ/mol and it is commonly produced by reaction of calcium chloride, magnesium chloride with *calcined dolomite* ($CaMgO_2$) (heat of formation: -556 kcal/mol) in water[18]. Determine the heat of formation and state whether it releases or absorbs heat (using the correct terminology).

Solution[7]

To determine the heat of formation, use Equation 9.3-1.

$$\Delta\widehat{H}_{\mathrm{r}}^{\mathrm{o}} = \sum_{\text{products}} |\nu_i|\,\Delta\widehat{H}_{fi}^{\mathrm{o}} - \sum_{\text{reactants}} |\nu_i|\,\Delta\widehat{H}_{fi}^{\mathrm{o}}$$

To use this, students must determine what the chemical reaction actually is since that information is not given. While this can be done through some basic reasoning related to the chemistry involved, it is probably best (and certainly less error prone) to just look it up[19].

$$\mathrm{CaCl_2 + MgCl_2 + CaMgO_2 + 3\ H_2O \rightarrow 2\ CaCl_2 + 2\ Mg(OH)_2 + H_2O}$$

It should be immediately obvious to the students that this equation can be simplified. Failure to do so will result in more tedious and lengthy calculations.

$$\mathrm{MgCl_2 + CaMgO_2 + 2\ H_2O \rightarrow CaCl_2 + 2\ Mg(OH)_2}$$

Looking up the heats of formation in Table B.1, students find (after converting kcal to kJ):

$$\left(\Delta\widehat{H}_{\mathrm{f}}^{\mathrm{o}}\right)_{\mathrm{CaCl_2}} = -794.96\ {}^{\mathrm{kJ}}/_{\mathrm{mol}}$$

$$\left(\Delta\widehat{H}_{\mathrm{f}}^{\mathrm{o}}\right)_{\mathrm{MgCl_2}} = -641.8\ {}^{\mathrm{kJ}}/_{\mathrm{mol}}$$

$$\left(\Delta\widehat{H}_{\mathrm{f}}^{\mathrm{o}}\right)_{\mathrm{CaMgO_2}} = 2326\ {}^{\mathrm{kJ}}/_{\mathrm{mol}}$$

$$\left(\Delta\widehat{H}_{\mathrm{f}}^{\mathrm{o}}\right)_{\mathrm{H_2O}} = -285.84\ {}^{\mathrm{kJ}}/_{\mathrm{mol}}$$

$$\left(\Delta\widehat{H}_{\mathrm{f}}^{\mathrm{o}}\right)_{\mathrm{Mg(OH)_2}} = -924.66\ {}^{\mathrm{kJ}}/_{\mathrm{mol}}$$

Note that magnesium hydroxide is not present in Table B.1, so it was taken from the NIST WebBook[20].

Now use Equation 9.3-1:

$$\Delta\hat{H}_{\mathrm{r}}^{\mathrm{o}} = \left[\left|\nu_{\mathrm{CaCl_2}}\right|\left(\Delta\hat{H}_{\mathrm{f}}^{\mathrm{o}}\right)_{\mathrm{CaCl_2}} + \left|\nu_{\mathrm{Mg(OH)_2}}\right|\left(\Delta\hat{H}_{\mathrm{f}}^{\mathrm{o}}\right)_{\mathrm{Mg(OH)_2}}\right] - \left[\left|\nu_{\mathrm{CaMgO_2}}\right|\left(\Delta\hat{H}_{\mathrm{f}}^{\mathrm{o}}\right)_{\mathrm{CaMgO_2}} + \left|\nu_{\mathrm{MgCl_2}}\right|\left(\Delta\hat{H}_{\mathrm{f}}^{\mathrm{o}}\right)_{\mathrm{MgCl_2}} + \left|\nu_{\mathrm{H_2O}}\right|\left(\Delta\hat{H}_{\mathrm{f}}^{\mathrm{o}}\right)_{\mathrm{H_2O}}\right]$$

$$\Delta\hat{H}_{\mathrm{r}}^{\mathrm{o}} = \left[1\left(\Delta\hat{H}_{\mathrm{f}}^{\mathrm{o}}\right)_{\mathrm{CaCl_2}} + 2\left(\Delta\hat{H}_{\mathrm{f}}^{\mathrm{o}}\right)_{\mathrm{Mg(OH)_2}}\right] - \left[1\left(\Delta\hat{H}_{\mathrm{f}}^{\mathrm{o}}\right)_{\mathrm{CaMgO_2}} + 1\left(\Delta\hat{H}_{\mathrm{f}}^{\mathrm{o}}\right)_{\mathrm{MgCl_2}} + 2\left(\Delta\hat{H}_{\mathrm{f}}^{\mathrm{o}}\right)_{\mathrm{H_2O}}\right]$$

$$\Delta\hat{H}_{\mathrm{r}}^{\mathrm{o}} = \{[1(-794.96) + 2(-924.66)] - [1(2326) + 1(-641.8) + 2(-285.84)]\}\,{}^{\mathrm{kJ}}/_{\mathrm{mol}}$$

$$\Delta\hat{H}_{\mathrm{r}}^{\mathrm{o}} = \{[-2644.3] - [1112.5]\}\,{}^{\mathrm{kJ}}/_{\mathrm{mol}}$$

$$\Delta\hat{H}_{\mathrm{r}}^{\mathrm{o}} = \{[-2644.3] - [1112.5]\}\,{}^{\mathrm{kJ}}/_{\mathrm{mol}}$$

$$\boxed{\Delta\hat{H}_{\mathrm{r}}^{\mathrm{o}} = -3756.8\,{}^{\mathrm{kJ}}/_{\mathrm{mol}}}$$

As the sign shows this is a “heat giving” or exothermic reaction.

This problem presents the engineering principle of heat of formation calculations for a well-known over the counter drug. It requires students to research the reaction and search appropriate physical property databases. The pharmaceutical principles that are presented relate to drug terminology (over the counter (OTC) medicine), formulation (suspension) and the differences between solid and liquid dosage forms.

Summary

Problem sets have been developed for the NSF ERC-SOPS to be used in introductory chemical engineering courses. These educational materials cover terminology, formulation and manufacturing techniques for consumer/personal care products and over the counter (OTC) medicines. All of the problem descriptions are based on realistic technology in use or in R&D stages. The objective is for students to learn the basic principles of chemical engineering while being exposed to a realistic application of consumer/personal care product technology. A detailed solution is provided with each problem for the professor to explain how to solve the problem. The solutions are written in detailed way to explain relevant engineering and consumer product concepts. The problems have been reviewed by multiple students and faculty. They are currently being evaluated in the sophomore Principles of Chemical Processes classes at XX University to get feedback from students for further improvement and assess their impact. The problem sets have been incorporated into a user –friendly document and posted on PharmaHUB for use by other universities.

Acknowledgements

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