

Problem sets on Pharmaceutical Engineering for Introductory Chemical Engineering Courses

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Developed for the ERC as part of the educational component under the direction of

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Instructor's Guide

The following problem sets (problems and solutions) are designed to be used in introductory chemical engineering courses involving basic engineering calculations and material and energy balances. A majority of these courses use the topics and text by Felder and Rousseau, *Elementary Principles of Chemical Processes*, 3rd edition, 2005, John Wiley & Sons. Therefore, to allow the instructor to easily integrate these problems into their classes, we have “mapped” them to the current edition of that text. The next edition of the book will integrate problems from pharmaceutical and other novel engineering areas, so we recommend you look for the 4th edition of the text when it is published.

- In the development of problems, the following general concepts were followed:
 - All problems directly relate to topics from pharmaceutical technology (either basic concepts related to drug systems 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. 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 drug 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.
- Problems are nominally assigned to chapters according to the Felder and Rousseau text topics in our Table of Contents. If you use these problems in another course, such as a Freshman Engineering class you can easily integrate them by using the following chapter/topic outline.

Material and Energy Balance Course

(Felder & Rousseau, 3rd)

Chapter 1: What Some Chemical Engineers Do for a Living

Chapter 2: Introduction to Engineering Calculations

Chapter 3: Process and Process Variables

Chapter 4. Fundamentals of Material Balances

Chapter 5. Single Phase Systems

Chapter 6. Multiphase Systems

Chapter 7. Energy and Energy Balances

Chapter 8. Balances on Nonreactive Processes

Chapter 9. Balances on Reactive Processes

Chapter 10. Computer-Aided Calculations

Chapter 11. Balances on Transient Processes

Chapter 12-14. Case Studies

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Chapters and problems

Chapter 1

Chapter 1 is an introduction chapter and has no problems associated with it. Possibly some content might be added to the text, but that is not the subject of this paper.

Chapter 2

F&R 2.2 KM-6 (Ethics in drug development and production)

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 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 **dilutant** 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 total¹), and sold it. After a madcap chase by nearly the entire FDA staff, most of the distribution was collected on a legal technicality and about² 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...”³. 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**⁴ 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.

¹ <<http://www.fda.gov/AboutFDA/WhatWeDo/History/ProductRegulation/SulfanilamideDisaster/default.htm>>

² According to the FDA, 107: <<http://www.fda.gov/AboutFDA/WhatWeDo/History/Milestones/ucm128305.htm>>

³ <<http://www.time.com/time/magazine/article/0,9171,882914,00.html>> Time Magazine. November 1, 1937

⁴ [Gosselin, R.E., H.C. Hodge, R.P. Smith, and M.N. Gleason. Clinical Toxicology of Commercial Products. 4th ed. Baltimore: Williams and Wilkins, 1976., p. II-119] Obtained from HSDB of the NLM, NIH, DH&HS.

Solution

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:

$$V_d = 4 \text{ doses} \times \frac{3 \text{ t}}{\text{dose}} = 12 \text{ t}$$

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 Measures¹: 5 mL/t.

$$V_d = 12 \text{ t} \times 5 \frac{\text{mL}}{\text{t}} = 60 \text{ mL}$$

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 (2^d Edition², supplied online by AiChE) we find it is 1.119 g/cm³.

$$m_d = 60 \text{ mL} \times 1.119 \frac{\text{g}}{\text{cm}^3} \times 1 \frac{\text{cm}^3}{\text{mL}}$$

$$\boxed{m_d = 67.14 \text{ g DEG}}$$

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

$$m_h = 67.14 \text{ g DEG} \times \frac{1 \text{ kg weight}}{0.5 \text{ g DEG}}$$

¹ <http://ts.nist.gov/WeightsAndMeasures/Metric/upload/Houshold_WM.pdf>

² E-ISBN: 978-1-59124-550-61

$$m_h = 134.3 \text{ kg} = 295. \text{lb}_m$$

Anyone under ~300 lb_m would be fatally poisoned. 5 g/kg was the other limit, which produced 13.43 kg or 29.5 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:

$$N_p = \frac{V}{V_d} = \frac{240 \text{ gal}}{60 \text{ mL}} \times \frac{10^6 \text{ mL}}{264.17 \text{ gal}}$$

$$N_p = 15141$$

- (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

F&R 2.3 TB1.03 (What is a “nano”?)

What units (American Engineering and SI) would be appropriate in reporting the following measurements?

- (a)** The thickness of a piece of paper
- (b)** The length of your foot
- (c)** The size (diameter) of a single drug molecule
- (d)** A pebble
- (e)** The size of a germ
- (f)** The diameter of your wrist

Solution

In this exercise, students should become capable of determining which prefix/unit is most appropriate for a certain length. The only “curveball” is that some objects have NO appropriate measurement in American Engineering.

- (a) Millimeters, inches (Both the accepted units for this¹)
- (b) Centimeters, inches
- (c) Nanometers, no appropriate Am. Eng. unit
- (d) Centimeters, inches
- (e) Micrometers, no appropriate Am. Eng. unit
- (f) Centimeters, inches

¹ For instance, <<http://www.paper-paper.com/weight.html>> gives thicknesses in inches and millimeters. A more reliable source may need to be found in the library.

F&R 2.5b KM-3 (Illegitimate pharmaceutical engineering)

Before the universal metricization of the sciences, pharmacists used an entirely different set of units similar on American Engineering units. In the **Apothecary system** there were twenty **grains** (gr.) in one **scruple** (ϑ), three scruples in one **drachm** (ʒ), eight drachms in one **(apothecary) ounce** (℥), and 12 ounces in an **(apothecary) pound** (℔). There are 7000 grains in a normal (**Avoirdupois**) pound, lb_m. Making matters more confusing, the amount would be written *after* the symbol in *lowercase Roman numerals* (So ϑmdcccclxxxvij represents 1988 scruples). Finally, note that the ending “i” is written with the letter “j”.

You are working as an engineering liaison in a pharmaceutical research lab when the director gives you a badly written prescription his great grandfather used to prescribe, and asks you to “do what you engineers do” with it.

R¹. Common falt, ϥij

Iron-nail ruft, ϑvj

Antimonical falts, gr. viiiiiiij (“He would keep upping the dose until something happened”)

Spanifh-mofs boil^d down, ϥxxvij

Train-oil, ℔ij

North-Caroline tarr, ℔xv

Make mix. Write: Take 1 pound [lb_m] daily for a year.

Setting aside your initial feeling on reading this, you set to work...

- (a) Convert the prescription into metric, and determine how many individual doses (“daily”) this makes.
- (b) Assemble a list to submit to purchasing, showing the amounts necessary for an initial test run of 20 dosing regimens (“for a year”), assuming 5% waste. North Carolina has not converted to metric yet, so you will have to specify the “tarr” in American Engineering.
- (c) Because of the unnatural nature of this request, you have no data on what the likely testing and evaluation needs are. You decide to be safe and **overdesign** a mixing vessel by 20% (this is the design equivalent of wastage allowance in raw material orders). Make assumptions and look up values to determine the size mixer should be specified.
- (d) Is this likely to be at all worthwhile? Is anything useful likely to come from this? Make a short list of reasons why this would never actually happen.

¹ This was completely fabricated

Solution

This is an interesting unit and conversion problem with a little conceptual work at the end.

(a) We first convert the units into more readable style:

ζij = 3 apothecary ounces

ϑvj = 6 scruples

gr. viiiiiiij = 24 grains (The Roman numerals are deliberately miswritten)

ϗxvij = 27 drachms

ībij = 3 apothecary pounds

ībxv = 15 apothecary pounds

The conversion factors are given in the problem statement. These can either be converted all at once or as needed. For ease of presentation, the former is preferred.

$$1 = \frac{1 \text{ kg}}{2.2 \text{ lb}_m} \times \frac{1 \text{ lb}_m}{7000 \text{ gr}} \times 20 \frac{\text{gr}}{\vartheta} \times 3 \frac{\vartheta}{\zeta} \times 8 \frac{\zeta}{\text{lb}} \times 12 \frac{\text{lb}}{\text{lb}} = 0.374 \frac{\text{kg}}{\text{lb}}$$

$$1 = \frac{1 \text{ kg}}{2.2 \text{ lb}_m} \times \frac{1 \text{ lb}_m}{7000 \text{ gr}} \times 20 \frac{\text{gr}}{\vartheta} \times 3 \frac{\vartheta}{\zeta} \times 8 \frac{\zeta}{\text{lb}} = 0.0312 \frac{\text{kg}}{\zeta}$$

$$1 = \frac{1 \text{ kg}}{2.2 \text{ lb}_m} \times \frac{1 \text{ lb}_m}{7000 \text{ gr}} \times 20 \frac{\text{gr}}{\vartheta} \times 3 \frac{\vartheta}{\zeta} = 0.00390 \frac{\text{kg}}{\zeta}$$

$$1 = \frac{1 \text{ kg}}{2.2 \text{ lb}_m} \times \frac{1 \text{ lb}_m}{7000 \text{ gr}} \times 20 \frac{\text{gr}}{\vartheta} = 0.00130 \frac{\text{kg}}{\vartheta}$$

$$1 = \frac{1 \text{ kg}}{2.2 \text{ lb}_m} \times \frac{1 \text{ lb}_m}{7000 \text{ gr}} = 0.0000649 \frac{\text{kg}}{\text{gr}}$$

We will need to convert back to lb_m at times, however using metric as our standard for this problem is reasonable. Students should not be penalized for using different system.

Also, note the units of the fifth conversion factor in the first equation: $8 \frac{\zeta}{\text{lb}}$. Hopefully the pharmacists had good handwriting or you were off dose by a factor of eight!

Applying the relevant conversion factors:

$$3 \zeta \times 0.0312 \frac{\text{kg}}{\zeta} = 0.0936 \text{ kg} = 93.6 \text{ g}$$

$$6 \vartheta \times 0.00130 \frac{\text{kg}}{\vartheta} = 0.0078 \text{ kg} = 7.8 \text{ g}$$

$$24 \text{ grains} \times 0.0000649 \frac{\text{kg}}{\text{gr}} = 0.00156 \text{ kg} = 1.56 \text{ g}$$

$$27 \text{ } \mathfrak{z} \times 0.00390 \frac{\text{kg}}{\mathfrak{z}} = 0.1053 \text{ kg} = 105 \text{ g}$$

$$3 \text{ } \mathfrak{lb} \times 0.374 \frac{\text{kg}}{\mathfrak{lb}} = 1.122 \text{ kg} = 1122 \text{ g}$$

$$15 \text{ } \mathfrak{lb} \times 0.374 \frac{\text{kg}}{\mathfrak{lb}} = 5.61 \text{ kg} = 5610 \text{ g}$$

We therefore have our revised prescription:

R. Common salt, 93.6 g

Iron nail rust, 7.8 g

Antimonial salts, 1.56 g

Spanish moss (boiled down), 105 g

Train oil, 1122 g

North Carolina tar, 5610 g

Note that, while it would be easy to change “Common salt” to “Sodium chloride” in our modernization, it is entirely possible the “Common salt” of the past was being used in the prescription because of some foreign agent that is now purified out (cf. The powder Dr. Jekyll used). To maintain strict accuracy, the original names should be kept. Units of the past (Especially the grain) were rarely equivalent over large distances or jurisdictional changes, so even the purely mathematical unit switching is not completely free of changes.

Finally, we sum the quantities and convert back to lb_m to answer the question.

$$(0.0936 + 0.0078 + 0.0016 + 0.105 + 1.122 + 5.61) \text{ kg} = 6.94 \text{ kg}$$

$$6.94 \text{ kg} \times 2.2 \frac{\text{lb}_m}{\text{kg}} = 15.3 \text{ lb}_m$$

$$N_d = 15.3 \text{ lb}_m \times 1 \frac{\text{dose}}{\text{lb}_m} = 15.3 \text{ doses}$$

$$\boxed{N_d \approx 15 \text{ (daily) doses}}$$

Note we rounded down because doses are logically reported in whole numbers, unless it is noted that fractional doses are used.

(b) This is a very simple problem with ratios. The values found in the previous problem are divided by the number of doses they provide, multiplied by the number of days per year, then by the “wastage factor”. The wastage factor is obtained by adding the

percent waste (5%) to the existing draft of materials (100%), resulting in a factor of 1.05 (100% + 5% = 105% = 1.05)

$$m_{\text{yr}} = \frac{m}{N_d} \times 365 \left(\frac{\text{day}}{\text{yr}} \right) \times 1.05$$

Important assumption: We don't care about leap years.

Applying the equation above gives:

$$2.35 \text{ kg} = \frac{93.6 \text{ g}}{15.3} \times 365 \times 1.05$$

$$195 \text{ g} = \frac{7.8 \text{ g}}{15.3} \times 365 \times 1.05$$

$$6.51 \text{ g} = \frac{260 \text{ mg}}{15.3} \times 365 \times 1.05$$

$$2.63 \text{ kg} = \frac{105 \text{ g}}{15.3} \times 365 \times 1.05$$

$$28.1 \text{ kg} = \frac{1.12 \text{ kg}}{15.3} \times 365 \times 1.05$$

$$141 \text{ kg} = \frac{5.61 \text{ g}}{15.3} \times 365 \times 1.05$$

To determine the amounts needed for 20 dosage regimens, we multiply the amounts by the number of subjects (20):

$$2.35 \text{ kg} \times 20 = 47 \text{ kg}$$

$$195 \text{ g} \times 20 = 3900 \text{ g} = 3.9 \text{ kg}$$

$$6.51 \text{ g} \times 20 = 130 \text{ g}$$

$$2.63 \text{ kg} \times 20 = 52.6 \text{ kg}$$

$$28.1 \text{ kg} \times 20 = 562 \text{ kg}$$

$$141 \text{ kg} \times 20 = 2820 \text{ kg}$$

Now we convert the tar weight to pounds:

$$2820 \text{ kg} \times 2.2 \frac{\text{lb}_m}{\text{kg}} = 6204 \text{ lb}_m$$

Since this is such a large quantity, "shipping units" are appropriate here:

$$6204 \text{ lb}_m \times \frac{1 \text{ ton}}{2000 \text{ lb}_m} = 3.102 \text{ tons} = 3 \frac{1}{10} \text{ ton}$$

Our final request would look something like this (Student creativity should be encouraged here, if you have a real form for situations like this, use it and have them fill it out):

Material request form		
Common salt	47	kg
Iron nail rust	3.9	kg
Antimonial salts	130	g
Spanish moss (boiled down)	52.6	kg
Train oil	562	kg
North Carolina tar	3 1/10	ton

- (c) Examining the masses of ingredients, it is obvious that tar and train oil together make up a significant portion of the total mixture (97% by mass). We assume that we only need to take these two ingredients into account. Unfortunately, “North Carolina tar” is not a very precise term. Any reasonable assumption should be accepted here, to show a solution the specific gravity of tar¹ will be 1.05. “Train oil” denotes² whale oil, which has³ a specific gravity of 0.9214. We now apply Equation 3.1-1 to calculate:

$$SG = \frac{\rho}{\rho_{ref}} \Rightarrow \rho = SG\rho_{ref}$$

$$\rho_{oil} = 0.9214 \times 1000 \frac{\text{kg}}{\text{m}^3} = 921.4 \frac{\text{kg}}{\text{m}^3}$$

$$\rho_{tar} = 1.05 \times 1000 \frac{\text{kg}}{\text{m}^3} = 1050 \frac{\text{kg}}{\text{m}^3}$$

We assume that the volumes are additive ($V_f = V_1 + V_2 + V_3 + \dots + V_n$), which is not a minor assumption, but which must be made at this level of engineering knowledge.

$$V = V_{tar} + V_{oil}$$

¹ <<http://www.maritime.org/conf/conf-kaye-tar.htm>>

² <<http://www.britannica.com/EBchecked/topic/641432/whale-oil>>

³ <<http://books.google.com/books?id=OoUBrj6s6jwC&pg=PA408>>

$$V = \frac{m_{\text{tar}}}{\rho_{\text{tar}}} + \frac{m_{\text{tar}}}{\rho_{\text{tar}}}$$

$$V = 2820 \text{ kg} \times \frac{1 \text{ m}^3}{1050 \text{ kg}} + 562 \text{ kg} \times \frac{1 \text{ m}^3}{921.4 \text{ kg}}$$

$$V = (2.69 + 0.610) \text{ m}^3$$

Finally we apply our overdesign factor (The overdesign is simply an addition to the default 100%. In this case it is 20%, so 100% + 20% = 120% = 1.20):

$$V = 3.3 \text{ m}^3 \times 1.20$$

$$\boxed{V = 3.96 \text{ m}^3 \approx 4 \text{ m}^3}$$

(d) The most obvious reason is that no drug company (or likely any company) would allow anyone to waste time on something absolutely untested. Before any engineering is done on a new compound or production, chemists will study the proposition and administer clinical tests to determine if it has merit. The first round of tests on any prospective drug (Called *Phase 1 tests*) are toxicological tests to ensure that the preparation is not deleterious. Tests will also be conducted for beneficial effect, administration method, dosage, the method by which it acts, and many other attributes that are essential to a drug. If this preparation were approved, it certainly wouldn't be presented to engineering in such a ridiculously outdated and carelessly explained manner.

Secondly, the tests described in part (b) would never be allowed by either the company or government regulators. Legitimate testing requires a rigid protocol to be drawn up, submitted and approved before testing on humans is allowed. Some jurisdictions do not have or enforce these requirements, but they should not be encouraged.

The lack of data for design in part (c) is a dead giveaway that this project is, as stated, unnatural and therefore suspect and probably dangerous. Antimony (a poisonous substance) could never be requisitioned without the necessary background described above.

Finally, you (the student/reader) would (and should) certainly not waste your time on something this blatantly illegitimate. The lab manager should know better and, if not, be told or referred to the proper authorities. Every one has the responsibility not only to practice good chemistry and engineering, but to prevent anyone else from engaging in dangerous wildcat science.

Additional reasons can easily be imagined by creative students and should be allowed.

F&R 2.5d *TB1.08 (Examining segregation with RSD)

The first step in the production of pharmaceuticals is the mixing of various components prior to their processing (into pills, patches, etc.) into a uniform compound. Mixed powders may **demix** (Settle out because of density) in transport. You are a research engineer assigned to study particle settling behavior of *ZOGoliaft*, the **active pharmaceutical ingredient** (API) in a new performance enhancing drug for competitive statisticians.

To test the settling characteristics, you make up a batch of 50 wt% coarsely ground *ZOGoliaft* with 50 wt% of the **filler** used to add volume and put it in a tester which shakes stacked 10 trays up and down, causing heavier particles (Here, the API) to settle. Your summer intern does all the dirty work of counting the particles in each of the 10 trays every 10 seconds, but is a liberal arts major with no knowledge of statistics. You'll have to do this one on your own...

To analyze the settling of the particles, a statistical measure called the *relative standard deviation*¹ or *RSD* is used. RSD here is the standard deviation divided by the fully mixed concentration. The standard deviation is:

$$\sigma = \sqrt{\frac{\sum_{j=1}^N (\bar{C} - C_j)^2}{N - 1}}$$

where \bar{C} is the fully mixed concentration (In your case, at time = 0), C_j is the concentration in tray j and N is the total number of trays. Your intern's data (in particles of API per tray) is contained the following table:

j	0 s	10 s	20 s	30 s	40 s	50 s	60 s
1	10	3	2	0	0	0	0
2	10	6	3	1	0	0	0
3	10	8	5	2	1	0	0
4	10	8	5	3	2	3	1
5	10	9	8	5	7	5	4
6	10	10	10	12	12	11	8
7	10	12	12	15	13	14	16
8	10	15	14	17	16	17	19
9	10	12	18	20	23	24	25
10	10	17	23	25	26	26	27

- (a) Produce a graph of the RSD v. time based on the data
- (b) What does RSD = 0 mean? (*Hint*: Recall the definition of standard deviation)
- (c) Intelligently describe what the charted data describes in terms of the demixing of the powder
- (d) If the entire tray assembly is 1 meter tall, determine and graph the concentration of particles with respect to height at the start, half way through, and at the end of the test

¹ Portillo, Patricia M., Marianthi G. Ierapetritou, Fernando J. Muzzio. "Characterization of continuous convective mixing processes." *Powder Technology* 182(2008): 368-378.

Solution

This problem requires the student to be able to both follow the logical path from data given to answer, but also apply it to a table of data. This is intended to be done in a spreadsheet application, such as Microsoft Office Excel, OpenOffice.org Calc, etc..

- (a) Following the order of the equations, we must obtain the RSD. To obtain the RSD, we must obtain the standard deviation. To obtain the standard deviation, we must obtain the variables it depends on. Mathematically,

$$RSD = f\left(\sigma = f(\bar{C} = f(C_j), C_j)\right)$$

First, the concentrations must be found. In this problem, concentration is easily found by dividing the number of particle in each sample by the total number of them (100), like this (numbers are for $j = 10$, $t = 60$ s):

$$C = \frac{N_p}{N_{p_t}} = \frac{27}{100} = 0.27$$

Doing this with a spreadsheet allows us to easily calculate the concentrations for the entire set of values:

j	0 s	10 s	20 s	30 s	40 s	50 s	60 s
1	0.10	0.03	0.02	0	0	0	0
2	0.10	0.06	0.03	0.01	0	0	0
3	0.10	0.08	0.05	0.02	0.01	0	0
4	0.10	0.08	0.05	0.03	0.02	0.03	0.01
5	0.10	0.09	0.08	0.05	0.07	0.05	0.04
6	0.10	0.10	0.10	0.12	0.12	0.11	0.08
7	0.10	0.12	0.12	0.15	0.13	0.14	0.16
8	0.10	0.15	0.14	0.17	0.16	0.17	0.19
9	0.10	0.12	0.18	0.20	0.23	0.24	0.25
10	0.10	0.17	0.23	0.25	0.26	0.26	0.27

Now that the specific concentrations are known, the average concentration (\bar{C}) is easily found by use of Equation 2.5-1:

$$\bar{X} = \frac{1}{N} \sum_{j=1}^N X_j$$

Substituting our variable of interest for "X":

$$\bar{C} = \frac{1}{N} \sum_{j=1}^N C_j$$

$$\bar{C} = \frac{1}{10} (0.10 + 0.10 + 0.10 + \dots + 0.10 + 0.10 + 0.10)$$

$$\bar{C} = \frac{1}{10} (1) = 0.10$$

Now, possessing all needed values for concentration, the standard deviation may be calculated. This is almost impossible without a spreadsheet, however a sample is gone over below, for $j = 10$.

$$\sigma = \sqrt{\frac{\sum_{j=1}^N (\bar{C} - C_j)^2}{N - 1}}$$

$$\sigma = \sqrt{\frac{(0.10 - 0)^2 + (0.10 - 0)^2 + \dots + (0.10 - 0.25)^2 + (0.10 - 0.27)^2}{10 - 1}}$$

Terms in the middle are omitted for printing convenience.

$$\sigma = \sqrt{\frac{0.1052}{9}}$$

$$\sigma = \sqrt{0.0116888} = 0.1081$$

Below is a spreadsheet calculating the summation terms for each 10 second interval.

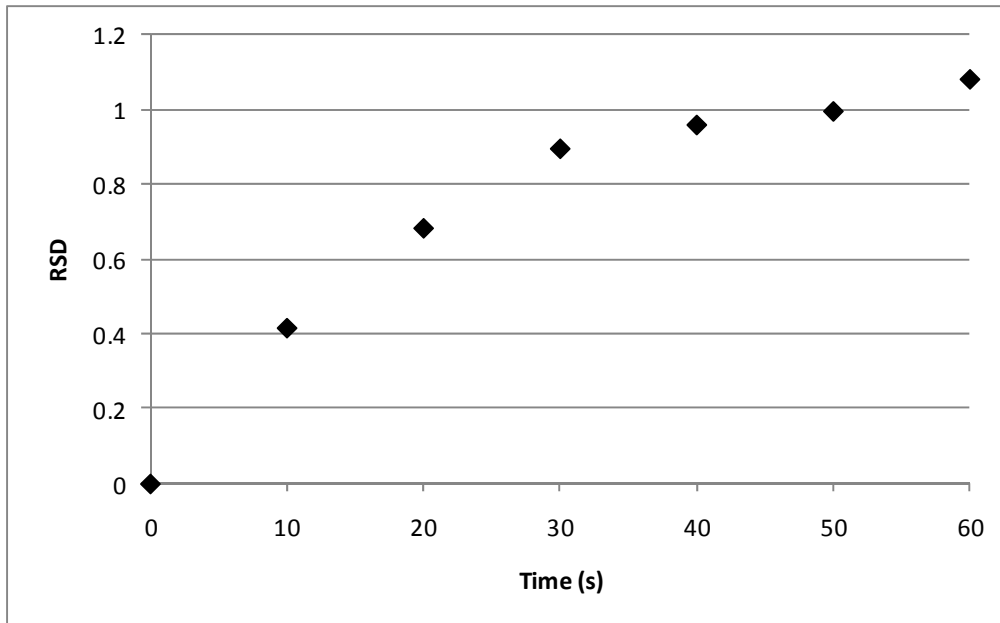
The numbers in the body of the table represent the $(\bar{C} - C_j)^2$ terms.

j	0 s	10 s	20 s	30 s	40 s	50 s	60 s
1	0	0.0049	0.0064	0.0100	0.0100	0.0100	0.0100
2	0	0.0016	0.0049	0.0081	0.0100	0.0100	0.0100
3	0	0.0004	0.0025	0.0064	0.0081	0.0100	0.0100
4	0	0.0004	0.0025	0.0049	0.0064	0.0049	0.0081
5	0	0.0001	0.0004	0.0025	0.0009	0.0025	0.0036
6	0	0.0000	0.0000	0.0004	0.0004	0.0001	0.0004
7	0	0.0004	0.0004	0.0025	0.0009	0.0016	0.0036
8	0	0.0025	0.0016	0.0049	0.0036	0.0049	0.0081
9	0	0.0004	0.0064	0.0100	0.0169	0.0196	0.0225
10	0	0.0049	0.0169	0.0225	0.0256	0.0256	0.0289
Σ	0	0.0156	0.0420	0.0722	0.0828	0.0892	0.1052

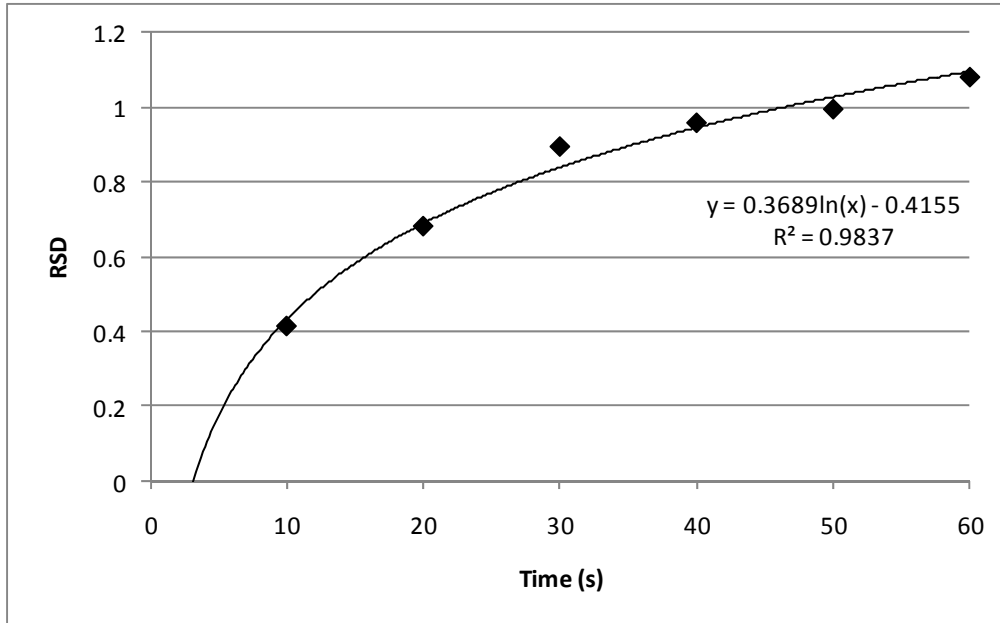
Now, the remainder of the calculation may be performed on the 6 summation values.

	0 s	10 s	20 s	30 s	40 s	50 s	60 s
Σ	0	0.0156	0.0420	0.0722	0.0828	0.0892	0.1052
$N - 1$	9	9	9	9	9	9	9
$\Sigma/(N - 1)$	0	0.0017	0.0047	0.0080	0.0092	0.0099	0.0117
$\sqrt{\Sigma/(N - 1)}$	0	0.0416	0.0683	0.0896	0.0959	0.0996	0.1081
/C (RSD)	0	0.4163	0.6831	0.8957	0.9592	0.9955	1.0812

Now the graph of RSD v. time (Which is what was originally requested) may be plotted:



- (b) When any measure of variance (In this case standard deviation) is exactly 0 the samples values are equal to (or *lie on*) the mean and there is absolute uniformity of measure. This occurs here because batch was perfectly mixed.
- (c) The chart displays initially rapid demixing in the 0 — 30 s period, indicated by the increasing RSD. Following this, demixing slowly increases from 30 s on. This has the appearance of being logarithmic; removing the (0, 0) point to add a logarithmic trendline suggests this is the case (except for the fact that the trendline does not pass through (0,0)):



Practically, any jarring or other operation that may cause demixing should be prevented or countered by remixing since the initial response is severe.

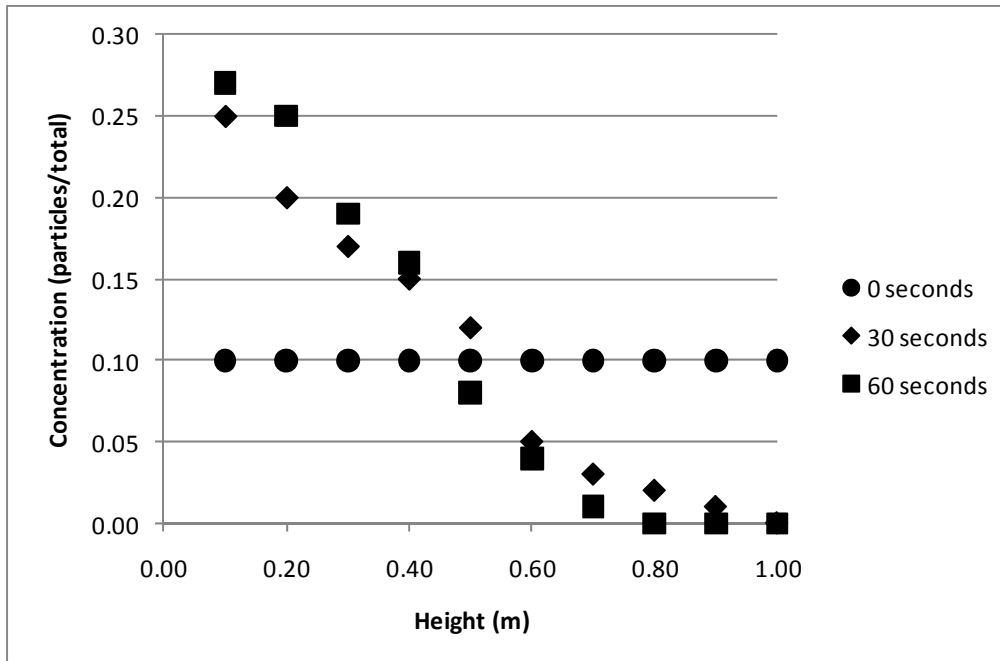
(d) To obtain the height of each tray, the total height is divided by the number of trays

$$h = \frac{1 \text{ m}}{10 \text{ trays}} = \boxed{0.10 \text{ m/tray}}$$

The sample numbers (j) conveniently match up with the height gradations, giving:

<i>j</i>	0 s	10 s	20 s	30 s	40 s	50 s	60 s
1.00	0.10	0.03	0.02	0	0	0	0
0.90	0.10	0.06	0.03	0.01	0	0	0
0.80	0.10	0.08	0.05	0.02	0.01	0	0
0.70	0.10	0.08	0.05	0.03	0.02	0.03	0.01
0.60	0.10	0.09	0.08	0.05	0.07	0.05	0.04
0.50	0.10	0.10	0.10	0.12	0.12	0.11	0.08
0.40	0.10	0.12	0.12	0.15	0.13	0.14	0.16
0.30	0.10	0.15	0.14	0.17	0.16	0.17	0.19
0.20	0.10	0.12	0.18	0.20	0.23	0.24	0.25
0.10	0.10	0.17	0.23	0.25	0.26	0.26	0.27

The problem requests the distribution of concentrations at 0, 30, and 60 seconds

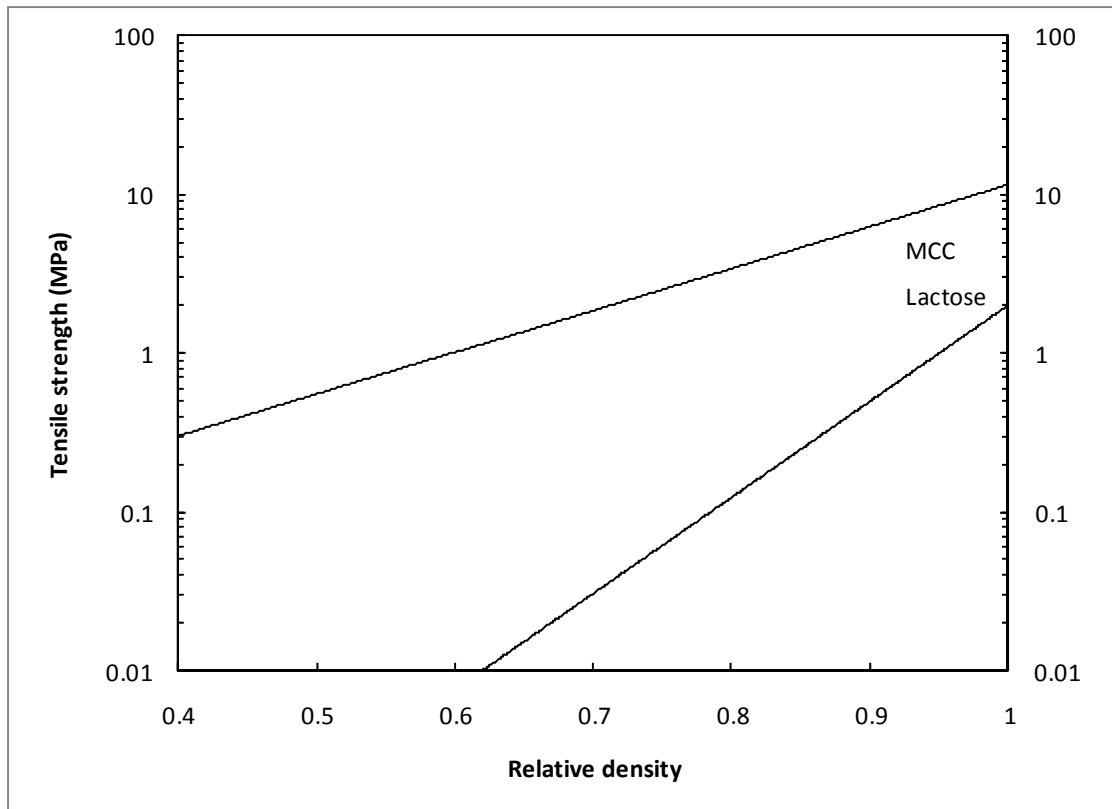


(a) Unsurprisingly, at time 0 the concentration is exactly even. As time increases, the heavier particles fall towards the bottom of the tap tester. Looking at the graph, this is displayed by the concentrations at higher trays (heights) dropping to 0 over time. If there is a significant density difference between the ZOGolift and filler, at $t = \infty$ the concentration would be 0 everywhere except at the bottom.

F&R 2.7d TB1.22 (Tablet strength)

The **tensile strength** of a solid object is its ability to resist strain. In pharmaceutical engineering design, the tensile strength of a tablet determines the strain that it can withstand before crumbling. Striking a balance between sufficient tensile strength and size of the tablet is necessary to obtain a useful product.

You are evaluating two powdered **fillers** to increase tablet volume for dispensing suitability: lactose and microcrystalline cellulose (MCC). Wu and Seville¹ have determined relationships, shown below, between relative density and tensile strength of these compounds.



Give the tensile strengths in MPa and psi for:

- (a) 0.70 relative density lactose
- (b) 0.55 relative density MCC
- (c) 0.90 relative density MCC
- (d) Pure lactose
- (e) 0.60 relative density lactose

¹ Chuan-Yu Wu and Jonathan P.K. Seville. "A comparative study of compaction properties of binary and bilayer tablets". Powder technology, Volume 189 (2008) 285-294.

Solution

This problem tests ability to read graphs (Including semilog graphs) and do unit conversions. The answer to part (a) will be illustrated, and the remaining parts just answered. Note that allowance should be made for the difficulty in uniform interpretation of graphs; allowance should be made for different readings.

- (a) The graph must be read to determine the tensile strength in MPa. The lower line is lactose, and 0.7 relative density corresponds to **0.03 MPa**.

The conversion to psi is:

$$\sigma (\text{tensile strength}) = 0.03 \text{ MPa} \times \frac{14.696 \text{ psi}}{1.01325 \times 10^5 \text{ Pa}} \times 10^6 \frac{\text{Pa}}{\text{MPa}} = \mathbf{4.35 \text{ psi}}$$

- (b) **0.8 MPa, 116 psi**

- (c) **7.5 MPa, 1088 psi**

- (d) **2 MPa, 290 psi**

- (e) The graph does not show the trend line for lactose at this relative density. It is possible to extend the graph and find out the value, but this is dangerous without knowledge that the relationship between relative density and tensile strength is the same as within the field of the graph.

F&R 2.7d TB1.02 (Fractions, decimals and percentages in tablets)

The **tablet** form of a medicine is formed by mixing powdered materials to form the final product. Tablets are composed of **active pharmaceutical ingredients** and inactive ingredients, called **excipients**. Excipients in turn may comprise **binders**, which act as a 'glue' for powders, **fillers**, to add volume to the mixture, and other components. Determine the mass fractions and percentages by mass of tablets formed from the following APIs, binders and fillers.

- (a) Ibuprofen: 100 mg
 - Povidone: 10 mg
 - Lactose: 40 mg
- (b) Phenylephrine: 250 mg
 - Povidone: 45 mg
 - Starch: 155 mg
- (c) Acetaminophen: 50 mg
 - Gelatine: 17 mg
 - Lactose: 123 mg

Solution

This problem is simply a test of ability to do mass fractions when given data. There are no “curveballs” intended in the presentation of the problem or the data.

In all three cases, the masses of the three ingredients are added to determine the total mass. The mass of each ingredient is then divided by the total mass to find the mass fraction. The percent by mass of each is then the mass fraction multiplied by 100.

As an example, the mass fraction of the API in the first tablet is calculated below.

$$m_t = \sum m_i = 100 \text{ mg} + 10 \text{ mg} + 40 \text{ mg} = 150 \text{ mg}$$

$$x_{\text{API}} = \frac{m_{\text{API}}}{m_t}$$

$$x_{\text{API}} = \frac{100 \text{ mg}}{150 \text{ mg}} = 0.667$$

$$\boxed{x_{\text{API}} = 0.667}$$

$$100x_{\text{API}} = 100(0.667) = \boxed{66.7\% \text{ API by mass}}$$

- (a) 0.667, 66.7%
0.067, 6.67%
0.267, 26.7%
- (b) 0.556, 55.6%
0.100, 10.0%
0.344, 34.4%
- (c) 0.263, 26.3%
0.089, 8.9%
0.647, 64.7%

Note that in each case, the mass fractions sum to $1 \pm$ rounding error and the percentages by mass sum to 100%, again with rounding errors in some cases.

Chapter 3

F&R 3.2a *TB1.11 (Determination of flow rate from a hopper)

The weight of a container with nothing in it is called the **tare weight**. To determine the mass of the contents, the tare is subtracted from the **gross weight** of the full container to obtain the **net weight**. In the production of a pharmaceutical, powder is fed into a large storage funnel called a **hopper**¹. The 50 kg hopper is weighed by an electronic scale that connected to the process data recording computer, or **data historian**, which **samples** the scale reading every 30 seconds.

The volumetric flow rate of the powder is related described by the equation

$$\dot{V} = \left| \frac{\Delta m}{\rho \Delta t} \right|$$

where ρ represents the **bulk density** of the powder with the air mixed in, Δm represents the change in mass and Δt the change in time. A typical run, where the bulk density is 633 grains/ft³, is shown below.

Time (s)	0	30	60	90	120	150	180	210
Mass (g)	50,725	50,720	50,715	50,711	50,707	50,702	50,697	50,693

- (a) Create a graph of the flow rate of particles v. time and calculate the range of data scatter. Based on these, is this flow rate consistent? Do you think it is consistent *enough*?
- (b) Determine how long it would take on average, to empty the 0.5 m³ hopper.
- (c) What other methods could be used to determine the particle flow rate from the hopper?

¹ Muzzio, F. "C-SOPS: The Engineering Research Center on Structured Organic Particulate Systems." Annual Meeting, December 1st, 2006.

Solution

This problem introduces a lot of terminology and an unusual unit (grains) that will not be encountered again until the psychrometric charts. The actual mathematics is straightforward, except for a conical volume.

- (a) Before anything else, the net weight (weight of the powder in the hopper) must be found. This is done using the relationship between tare, net and gross:

$$m_{net} = m_{gross} - m_{tare}$$

So, for the first reading:

$$m_{net} = 50725 \text{ g} - 50000 \text{ g} = 725 \text{ g}$$

Applying this to all the entries in the table results in

Time (s)	0	30	60	90	120	150	180	210
Mass (g)	725	720	715	711	707	702	697	693

As an example, calculation of two of Δm and Δt :

$$\Delta m = (720 \text{ g} - 725 \text{ g}) = -5 \text{ g}$$

$$\Delta t = (30 \text{ s} - 0 \text{ s}) = 30 \text{ s}$$

Note the agreement in units being subtracted (grams from grams, seconds from seconds).

Before volumetric flow rate is calculated, the density must be converted to a more reasonable set of units. Noting that $1 \text{ lb}_m = 7000 \text{ grains}$ ¹:

$$\rho = 633 \frac{\text{grain}}{\text{ft}^3} \times \frac{1 \text{ lb}_m}{7000 \text{ grain}} \times \frac{1 \text{ kg}}{2.2 \text{ lb}_m} \times 1000 \frac{\text{g}}{\text{kg}} \times \frac{35.3 \text{ ft}^3}{10^6 \text{ cm}^3} = 0.00145 \frac{\text{g}}{\text{cm}^3}$$

Now the equation may be applied by inserting values, for example:

$$\dot{V} = \left| -5 \text{ g} \times \frac{1 \text{ cm}^3}{0.00145 \text{ g}} \times \frac{1}{30 \text{ s}} \right| = 115 \text{ cm}^3/\text{s}$$

¹ Per de Nevers' Fluid Mechanics book and the "Universal Dictionary of Weights and Measures", 1850, <http://books.google.com/books?id=LnUAAAAAMAAJ>

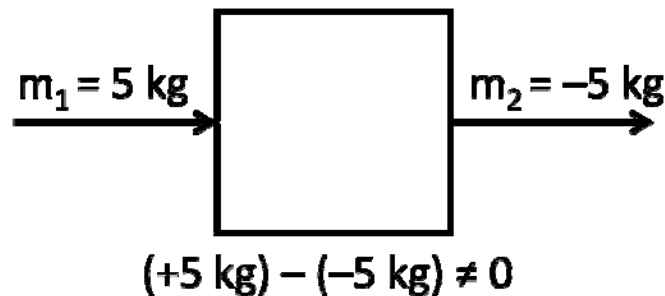
Since mass is leaving the hopper, the Δm term is negative, however this would result in a negative value for \dot{V} . We add absolute value signs to prevent this (Negative volume is impossible).

This (“Why can Δm be negative, but not \dot{V} ?”) is likely to be a significant source of confusion for students, so the explanation will be given in detail here. It may be worthwhile to go over this in class before or after assigning this problem, or copy it and hand it out/post it on the class/professor’s website.

First, Δm (and any other Δx) describes a change in something between two points (Such as time or distance) so negative (Less now than initially) or positive (more here than there) are both possible.

A negative flow or flow rate might seem logical as there is that much leaving the system per second, however flows and flow rates, by convention, are NOT vectors (They do not have direction, only quantity).

This may additionally incite confusion given that we subtract streams leaving systems from those entering the system. The subtraction, it should be remembered, is purely algebraic: We subtract a (positive) flow out from a (positive) flow in. If we decided the flow rates out were going to be negative:



It wouldn’t work!

A student may ask if it would be possible (mathematically) to change the mass equation to be just

$$0 = \sum m$$

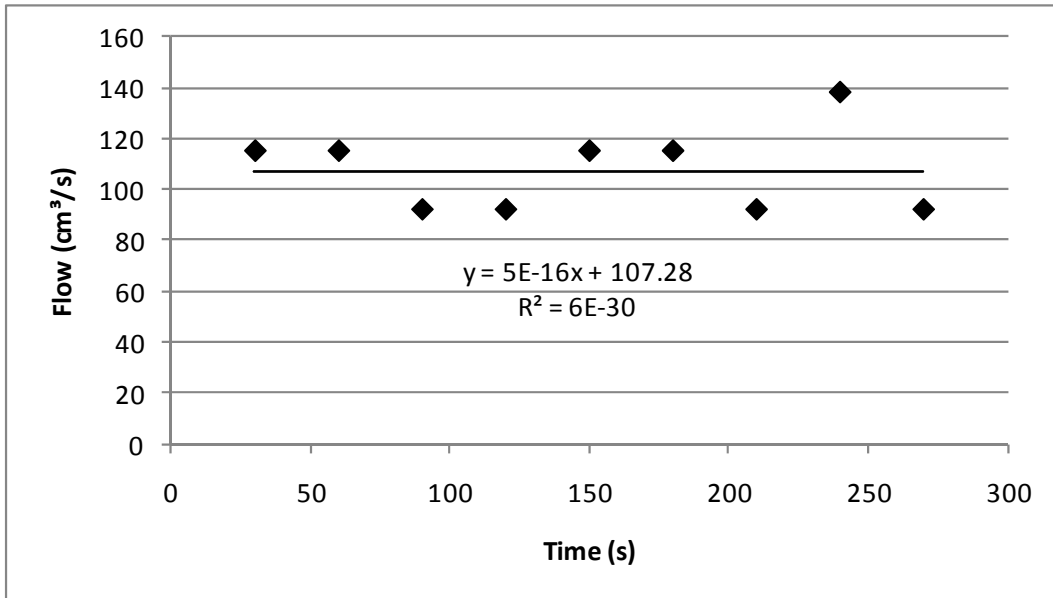
and have the mass flow rates be positive or negative. This is mathematically possible and valid, however there is one benefit to the current system: Outlawing negative flows and flow rates allows engineers and engineering software to “check” themselves

continuously by examining their flows. A negative value anywhere is an immediate sign there's been a bad mistake in the calculations.

A final note: In chapter 7, when the energy equation is introduced, it will be noted that heat and work ARE sign holding (Their sign displays if they enter or exit the system).

We now calculate the remaining flow rates. Note that flow rate at 0 s = 0 because the powder starts flowing at the instant after t = 0. This is common to almost all uses of "Δ" to describe a process over time.

Time (s)	Mass(g)	Flow (cm ³ /s)
0	725	0
30	720	115
60	715	115
90	711	92
120	707	92
150	702	115
180	697	115
210	693	92
240	687	138
270	683	92



Range is calculated by Equation 2.5-2:

$$R = X_{max} - X_{min}$$

$$R = (137.93 - 91.95) \text{ cm}^3/\text{s}$$

$$R = 45.98 \text{ cm}^3/\text{s}$$

As can be seen, the R^2 value is 0, indicating that the flow rate is statistically independent of time and hence “consistent with time”. The range shows a large variability (Nearly half the average flow rate) however. Engineering, especially pharmaceutical engineering, requires a very tight adherence to specified values, so this range of variability the process may not be acceptable if the process is to be approved for drug manufacturing.

- (b)** To find the *average* time to empty the hopper, first the *average* volumetric flow rate is needed. In this case (and most others), average refers to the arithmetic mean, Equation 2.5-1:

$$\bar{X} = \frac{1}{N} \sum_{j=1}^N X_j$$

Substituting our variable of interest for “X”:

$$\bar{\dot{V}} = \frac{1}{N} \sum_{j=1}^N \dot{V}_j$$

We now expand the summation by entering all the values of \dot{V} and the number of numbers added (There are 9 values of \dot{V} , so $N = 9$).

$$\bar{\dot{V}} = \frac{1}{9} (114.94 + 114.94 + 91.95 + 91.95 + 114.94 + 114.94 + 91.95 + 137.93 + 91.95) \text{ cm}^3/\text{s}$$

$$\boxed{\bar{\dot{V}} = 97.06 \text{ cm}^3/\text{s}}$$

To determine the time, volume of the hopper is simply divided by the average volumetric flowrate:

$$\bar{t} = \frac{V}{\bar{\dot{V}}}$$

$$\bar{t} = \frac{0.5 \text{ m}^3}{97.06 \frac{\text{cm}^3}{\text{s}}} \times 10^6 \frac{\text{cm}^3}{\text{m}^3} = 0.5 \text{ m}^3 \times \frac{1}{97.06} \frac{\text{s}}{\text{cm}^3} \times 10^6 \frac{\text{cm}^3}{\text{m}^3}$$

$$\boxed{\bar{t} = 5151 \text{ s} = 85.8 \text{ min} = 1.43 \text{ h}}$$

Note that the formula to find this is not given in the book, and is not one that needs to be gone over in detail. The relationship should be determinable from logic ($\dot{V} = \frac{V}{t} \Rightarrow t = \frac{V}{\dot{V}}$) or by examining the units (There is only one variable with time in the units, and this must be isolated in the numerator).

- (c) Flow can be measured either directly or by field effect. Unless the powder is magnetic or radioactive, it is unlikely this method could be used. Direct measurement can include any method whereby the increase or reduction yields a repeatable and quantifiable response. A likely method is continuous weighing such as described in *Perry's Chemical Engineers Handbook*, 7th edition on page 21-34. More creative options include measuring the static charge generated by the flow, the frictional heating of the pipe or the sound of the flow.

F&R 3.2a TB1.23 (Particle flowability and size reduction)

Currently, most pharmaceutical operations use batch processes, although converting to continuous production presents advantages. One common concern in continuous production of solids is powder flow. Powder flow is a function of the sizes and shapes of the particles, their roughness, and their moisture. A dimensionless number, the *flow function* (FCC), has been defined to describe the quality of a powder flow. An FCC value of less than 1 corresponds to a still or non flowing powder, values between 1 and 4 describe a cohesive powder, between 4 and 10 an easy flowing powder, and values beyond 10 are free flowing.

Your company hopes to make the production of ibuprofen (described in the table below) a continuous process.

Mean particle diameter (μm)	215.2	123.8	39.9
Flow function	10.5 ± 0.7	8.8 ± 0.4	5.3 ± 0.2
Bulk density (kg/m^3)	518 ± 11	509 ± 18	453 ± 23

Process industrialization reports that free flowing powder will be easiest to work with while sales reports a demand that works out to 70 kg/s.

- (a)** What size particles should the incoming powder be reduced to?
- (b)** What will the resulting volumetric powder flow rate be?

Solution

This problem consists primarily of chart interpretation with minor calculations.

- (a) The largest size shown, 215.2 μm , is barely within free flowing, so the particles should not be reduced below this.
- (b) To determine the flow rate, we use Equation 3.2-1:

$$\rho = \frac{\dot{m}}{\dot{V}} \Rightarrow \dot{V} = \frac{\dot{m}}{\rho}$$

Note that bulk density is given as a range (± 11), so we should compute a possible range of flow rates and report it as such.

$$\dot{V}_{\text{high}} = 70 \frac{\text{kg}}{\text{s}} \times \frac{1 \text{ m}^3}{509 \text{ kg}} = 0.1375 \frac{\text{m}^3}{\text{s}}$$

$$\dot{V}_{\text{low}} = 70 \frac{\text{kg}}{\text{s}} \times \frac{1 \text{ m}^3}{529 \text{ kg}} = 0.1323 \frac{\text{m}^3}{\text{s}}$$

So, the flow rate might be reported as:

$$\boxed{0.1323 \text{ m}^3/\text{s} < \dot{V} < 0.1375 \text{ m}^3/\text{s}}$$

F&R 3.3 TB1.01 (Void fractions for forensics)

You are working in a testing lab that has been contacted by the Customs House, which wants to analyze a pharmaceutically active raw material being imported to your country. According to the **shipping manifest**, the 100 L, 25 kg container¹ is filled with completely with powder; they suspect the listing is incorrect. You look up the specific gravity of the compound to be 1.75 and also find that the **void fraction** (volume of air over total volume) should be 0.3875. Because the container is **sealed**, they do not want to open it unless there is good reason to suspect the manifest is incorrect or false. How would you tell the revenueurs to check the package without breaking the seal?

¹ See, EG <http://www.hawman.com/composite-tanks/Product_index.php>, description P1340 MSP for an example. That was used as a “ballpark” estimate of the weight of these things.

Solution

This problem illustrates bulk and particle density and void fraction.

The intended answer is by checking the weight against what you calculate the correct weight to be (if the container contained what it should per the manifest). Note that the weight given is only what is listed on the manifest and is suspect.

We begin with our equations:

$$\varepsilon = \frac{V_v}{V}$$
$$V = V_p + V_v$$

Solving for volume of the powder:

$$V_p = V - V_v$$
$$V_v = \varepsilon V$$
$$V_p = V - \varepsilon V$$
$$V_p = V(1 - \varepsilon)$$

We first begin by taking the volume and using the definition of the void fraction to obtain the volume of powder:

$$V_p = V(1 - \varepsilon)$$
$$V_p = 100 \text{ L} \times (1 - 0.3875)$$
$$V_p = 61.25 \text{ L}$$

Now we may use the specific gravity of the compound to determine the weight of the powder. Equation 3.1-1 is used.

$$SG = \frac{\rho}{\rho_{\text{ref}}} \Rightarrow \rho = SG\rho_{\text{ref}}$$
$$\rho = 1.75 \times 1000 \frac{\text{kg}}{\text{m}^3} = 1750 \frac{\text{kg}}{\text{m}^3}$$

Now the mass of the powder in the container is obtained from the density and Equation 3.2-1:

$$\rho = \frac{m}{V} \Rightarrow m = \rho V$$
$$m = 1750 \frac{\text{kg}}{\text{m}^3} \times 61.25 \text{ L} \times \frac{1 \text{ m}^3}{1000 \text{ L}} = 107.2 \text{ kg}$$

This is the weight of the solid particles, to which we must add the weight of the container. Assume the air contributes a negligible mass to the total container.

$$m = m_{\text{gross}} = m_{\text{net}} + m_{\text{tare}}$$

$$m = (107 + 25) \text{ kg} = 132 \text{ kg}$$

The Customs House weighmaster should put the container on the scale and see if it weighs close to 130 kg. If not, there is reason to doubt the correctness of the manifest and open the container for sampling/inspection.

F&R 3.3 TA3.02 (Concentration in a solution)

To aid absorption into the body, the active ingredients of drugs and supplements are dispersed into microscale particles before further processing. Unfortunately, these small particles attract and stick to each other easily. To prevent small this, liquids called **surfactants** are used to maintain the dispersion. If 8.34×10^{24} ascorbic acid molecules are dispersed into 2750 cm^3 of surfactant, determine the molar concentration of Vitamin C present.

Solution

Students should be able to calculate the molarity from memory or research and work Avogadro's constant into a dimensional equation.

$$\text{Concentration} = \frac{\text{Moles solute}}{\text{Liter solution}} [=] \text{ M}$$

$$C = \frac{N_{\text{particles}}}{N_{\text{A}} \times V}$$

$$C = 8.34 \times 10^{24} \text{ molecules} \times \frac{1 \text{ mole}}{6.02 \times 10^{23} \text{ molecules}} \times \frac{1}{2750 \text{ cm}^3} \times \frac{10^6 \text{ cm}^3}{1000 \text{ L}}$$

$$\boxed{C = 5.04 \text{ M}}$$

Assume that the volume of the solution is the same as the surfactant.

F&R 3.3 TB1.13 (Batch problem for tableting)

In pharmaceutical production, medicine is composed of **active pharmaceutical ingredients** (API) 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?

Solution

This problem is a simple application of mass fractions, with a molar mass conversion required.

- (a) For the first part, the molar amount is converted to mass, and then the mass fractions are obtained.

$$m = \frac{n}{M}$$

$$m = 829 \text{ mol} \times 151 \frac{\text{g}}{\text{mol}}$$

$$m = 125179 \text{ g} = 125.2 \text{ kg}$$

$$x_{\text{API}} = \frac{m_{\text{API}}}{\sum x}$$

$$x_{\text{API}} = \frac{125.2 \text{ kg}}{(125.2 + 62.1) \text{ kg}} = \frac{125.2}{187.3} = 0.668$$

$$\boxed{x_{\text{API}} = 0.668}$$

For a binary system (As we are considering the current system), the second mass fraction is easily found by difference from 1:

$$x_e = 1 - x_{\text{API}} = 1 - 0.668$$

$$\boxed{x_e = 0.332}$$

- (b) The calculation of the mass percentage of the binder is actually much easier than it appears, when mathematic logic is applied: For every 2 units of mass of filler, there is an additional 1 of binder. The sum of these is 3. Therefore, every three mass units will be $\frac{2}{3}$ filler and $\frac{1}{3}$ binder.

This line of logic is applicable to the mass fractions as well, since they are the same as portions of a mass of 1 (kg, lb_m, etc.):

$$x_b = \frac{1}{3} x_e = \frac{0.332}{3}$$

$$\boxed{x_b = 0.111}$$

- (c) To determine the amount made, we assume ideal mixing, and divide the total mass by the mass of a single tablet:

$$N_{\text{tablets}} = \frac{\sum m}{m_t} = (125.2 + 62.1) \text{ kg} \times \frac{\text{tablet}}{750 \text{ mg}} \times 1000 \frac{\text{g}}{\text{kg}} \times 1000 \frac{\text{mg}}{\text{g}}$$

$$\boxed{N_{\text{tablets}} = 250000 \text{ tablets}}$$

(d) Finally, to determine the number of prescriptions, we simply divide the number of tablets by the number of tablets per prescription.

$$N_{\text{prescriptions}} = 250000 \text{ tablets} \times \frac{1 \text{ prescription}}{10 \text{ days}} \times \frac{1 \text{ day}}{2 \text{ tablets}}$$

$$\boxed{N_p = 12500 \text{ prescriptions}}$$

F&R 3.3a TB1.06 (Molar conversions for tableting)

Pharmaceutical tablets are manufactured by combining a powdered **active pharmaceutical ingredient** (API) with **filler** to increase the volume to usable sizes and a **binder** to act as a 'glue'.

An antibiotic tablet consists of 325 mg of amoxicillin ($C_{16}H_{19}N_3O_5S$), 25 mg of sucrose ($C_{12}H_{22}O_{11}$), and 100 mg of calcium sulfate dihydrate ($CaSO_4 \cdot 2H_2O$) as a filler.

- (a)** Determine the molecular weight of each of the ingredients in the tablet.
- (b)** Calculate how many moles of each ingredient must be used to create 1,000 tablets.
- (c)** Which of the ingredients is likely to be the API and which is the binder?

Solution

This problem is a simple mass to molar amount conversion. The only “curveballs” are the MW of the filler (Students must remember to read $(\text{H}_2\text{O})_2$ as $2 \times \text{H}_2\text{O}$ not H_2O_2) and (c), which is conceptual in a way.

- (a) The calculations of molecular weights are simply done by multiplying the atomic masses by the number of times the atom occurs in the compound. This is easily done in a spreadsheet.

For example, the molecular weight of carbon in amoxicillin is:

$$M_{\text{C}} = 16 \text{ carbon atoms} \times 12 \frac{\text{atomic mass}}{\text{carbon atom}} = 192$$

Additionally, diatomic elements (Hydrogen, Nitrogen and Oxygen) must not have their molecular weights (1, 14 and 16) confused with the molecular weight of their natural states (2, 28, 32):

$$M_{\text{N}} = 3 \text{ nitrogen atoms} \times 14 \frac{\text{atomic mass}}{\text{nitrogen atom}} = 42$$

Not

$$M_{\text{N}} = 3 \text{ nitrogen atoms} \times 28 \frac{\text{atomic mass}}{\text{nitrogen atom}} = \boxed{\text{WRONG}}$$

Once all the individual atoms' calculations are performed, the molecular weight is simply their sum. This type of calculation is doable in a spreadsheet. Even when done by hand, though, it is still extremely useful to set up the problem in a tabular format. As shown below, once the occurrences of atoms in a molecule are counted, and the atomic masses found, the molecular weight is easily found by multiplication and addition.

Molecular weight of amoxicillin			
Atom	Occurrences	Atomic mass	Product
Carbon	16	12	192
Hydrogen	19	1	19
Nitrogen	3	14	42
Oxygen	5	16	80
Sulfur	1	32	32
M =			365

Molecular weight of sucrose			
Atom	Occurrences	Atomic mass	Product
Carbon	12	12	144
Hydrogen	22	1	22
Oxygen	11	16	176
M =			342

Molecular weight of calcium sulfate dihydrate			
Atom	Occurrences	Atomic mass	Product
Hydrogen	4	1	4
Calcium	1	40	40
Oxygen	6	16	96
Sulfur	1	32	32
M =			172

(b) To determine the moles needed to furnish an arbitrary amount of tablets, the Ms found in part (a) are used as conversion factors.

$$n_{\text{API}} = \frac{1 \text{ mol}}{365 \text{ g}} \times 325 \frac{\text{mg}}{\text{tablet}} \times 1000 \text{ tablets} \times \frac{1 \text{ g}}{1000 \text{ mg}}$$

$$n_{\text{API}} = \frac{325}{365} \text{ mol} = \boxed{0.89 \text{ mol}}$$

$$n_{\text{binder}} = \frac{1 \text{ mol}}{346 \text{ g}} \times 25 \frac{\text{mg}}{\text{tablet}} \times 1000 \text{ tablets} \times \frac{1 \text{ g}}{1000 \text{ mg}}$$

$$n_{\text{binder}} = \frac{25}{346} \text{ mol} = \boxed{0.072 \text{ mol}}$$

$$n_{\text{filler}} = \frac{1 \text{ mol}}{172 \text{ g}} \times 100 \frac{\text{mg}}{\text{tablet}} \times 1000 \text{ tablets} \times \frac{1 \text{ g}}{1000 \text{ mg}}$$

$$n_{\text{filler}} = \frac{100}{172} \text{ mol} = \boxed{0.58 \text{ mol}}$$

(c) There are at least two ways of reasoning this:

- a. First, that amoxicillin has the same -cillin ending as penicillin and other medicines, so is probably the active ingredient.
- b. Secondly, sucrose is not a medical sounding name. Many students will recognize this as sugar (From either the -ose ending or memory), which is clearly not a pharmaceutically active substance.

F&R 3.3b TB1.09 (Tablet press calculations)

Over 80% of the drugs produced today appear as tablets¹, or mixtures of powdered components compressed into their final form in a **tablet press**. The actual medicine, or **active pharmaceutical ingredient** (API), is mixed with bulk **fillers** and a **binder** to hold the powder together as a solid tablet. In most cases the API makes up a small fraction of the final mass. For example, a Vitamin C tablet may contain 500 mg of ascorbic acid (API), while the whole tablet weighs 1.33 grams.

A batch of 1,500 Vitamin C tablets was ordered for testing of a new formulation process. The final mass of a Vitamin C tablet is 1.33 grams with 37.5 wt% API, 55.25 wt% filler, and 7.25 wt% binder.

- (a) What is the total mass (grams) of each ingredient in the batch?
- (b) The accounts payable department neglected to release payment for the weekly shipment of filler, so the batch was erroneously made up with only API and binder. Calculate the new mass fractions.
- (c) If the correct ingredients were charged in the reactor, but 1.05 wt% of each was spilled, what are the percentages by mass of this batch?

¹ Glasser, B.J. "Lecture 1: Introduction and Course Overview." CBE 546 Pharmaceutical Unit Operations.

Solution

This problem is a simple problem with mass fractions, mass percents, and percents in general. The second two will be hard for anyone with only a cursory understanding of these subjects.

- (a) This may be done by either calculating the total mass required for 1500 pills and then the fractions, or by finding the masses in a single pill and then multiplying by 1500. The former method is easier and is shown below.

$$1500 \text{ tablets} \times 1.33 \frac{\text{g}}{\text{tablet}} = 2000 \text{ g}$$

Now the mass fractions may be applied to discover the mass needed for each component. The calculation for the API is shown below.

$$m_{\text{API}} = 2000 \text{ g} \times 0.375 = \boxed{748. \text{g}}$$

Masses of filler and binder are determined with the same equations and are:

$$\boxed{m_{\text{f}} = 1102 \text{ g}}$$

$$\boxed{m_{\text{b}} = 145 \text{ g}}$$

- (b) To find the new mass fractions, the previous ones may be divided by their sum. Consider that the API and filler are now the only component and their mass fractions must sum to 1. Dividing by them in effect sets their sum to 1 (this is termed “normalization”).

$$x'_1 = \frac{x_1}{\sum x}$$

$$x'_{\text{API}} = \frac{x_{\text{API}}}{x_{\text{API}} + x_{\text{f}}} = \frac{0.375}{0.375 + 0.0725} = \boxed{0.838}$$

Since this new system is binary (API and binder only), the second mass fraction may be easily found by difference from 1:

$$x'_f = 1 - x'_{\text{API}} = 1 - 0.838 = \boxed{0.162}$$

- (c) To determine the mass percents for a certain difference, the actual mass added is determined by multiplying the masses by their “effective percent”:

$$m_i^e = m_i(1 - 0.0105)$$

$$m_i^e = 0.9895m_i$$

For example, for the API:

$$m_{\text{API}}^e = 748 \text{ g} \times (1 - 0.0105)$$

This results in:

$$m_{\text{API}}^e = 740 \text{ g}$$

$$m_f^e = 1090 \text{ g}$$

$$m_b^e = 143.5 \text{ g}$$

The mass fractions are then found using the normal formula and the last one by difference from 100%.

$$x_i = \frac{m_i}{\sum m}$$

$$x_{\text{API}} = \frac{740 \text{ g}}{(740 + 1090 + 143.5) \text{ g}} = 0.375 = \boxed{37.5\%}$$

$$x_f = \frac{1090 \text{ g}}{(740 + 1090 + 143.5) \text{ g}} = 0.552 = \boxed{55.25\%}$$

$$x_b = 1 - \sum x = 1 - (0.375 + .552) = 1 - .927 = 0.073 = \boxed{7.25\%}$$

These should look familiar; they are the original mass fractions! Since an equal fraction is removed from each substance, the overall mass decreases, but the mass fractions are unchanged.

F&R 3.3b TB1.07 (Drying acetaminophen powder)

In pharmaceutical process engineering, almost all **active pharmaceutical ingredients** (APIs) must be made in solution and then recovered by separation. Acetaminophen, a pain killing agent, is being recovered from an aqueous solution prior to processing. 100 moles of acetaminophen ($M = 151 \text{ g/mol}$) is fed to a dryer in a **wet cake** containing 10 wt% of water. The water is completely evaporated, leaving the acetaminophen bone dry.

- (a) Determine how many liters of water are removed from the wet cake.
- (b) If the water is leaving the dryer at a rate of 50 L per hour, how much time must the acetaminophen cake spend in the dryer?

Solution

This problem is simple arraignment of terms to solve for the dimension (volume) in the units wanted (liters).

(a) This step may be done in a single equation or spread out. The latter will be shown here.

$$m_{\text{API}} = 100 \text{ mol} \times 151 \frac{\text{g}}{\text{mol}} = 15100 \text{ g}$$

This is the non-water part of the wet cake. Using the mass fraction, we determine the mass cake:

$$m_{\text{cake}} = \frac{m_{\text{API}}}{x_{\text{API}}} = \left(\frac{15100}{1 - 0.10} \right) \text{ g} = 16778 \text{ g}$$

The mass of the water is then obtained by subtracting the mass of API from the total:

$$m_{\text{H}_2\text{O}} = m_{\text{cake}} - m_{\text{API}} = (16778 - 15100) \text{ g} = 1678 \text{ g}$$

$$V_{\text{H}_2\text{O}} = m_{\text{H}_2\text{O}} \rho = 1678 \text{ g} \times 1 \frac{\text{L}}{\text{kg}} \times 0.001 \frac{\text{kg}}{\text{g}} = \boxed{1.678 \text{ L}}$$

(b) The time calculation is very simple.

$$t = \frac{V}{\dot{V}} = 1.678 \text{ L} \times \frac{1 \text{ h}}{50 \text{ L}} \times 60 \frac{\text{min}}{\text{h}} \times 60 \frac{\text{s}}{\text{min}} = \boxed{121 \text{ s}}$$

F&R 3.3c TB2.01 (Determining concentrations in substrates)

Currently, possible **active pharmaceutical ingredients** (APIs) that do not dissolve well in water are not as viable as more soluble ingredients. Because of this, many potential drugs have been disregarded. One possible solution is to form the API molecules into **nanoparticles**, which have a higher solubility in aqueous solutions. A possible route of delivery for these nanoparticles is on an edible **substrate**. Determine the concentration for the following substrate volumes.

(a) Length: 10 cm

Width: 10 cm

Thickness: 1×10^4 cm

Mass API: 0.01g

(b) Length: 20 cm

Width: 15 cm

Thickness: 3×10^4 cm

Mass API: 0.07g

(c) A strip with an API concentration of 0.5 g/cm^3 has the following dimensions:

Length: 15 cm

Width: 10 cm

Thickness: 25×10^5 cm

Determine how many grams of API are in the strip.

Solution

These problems are basic process problems relating mass to volume and volume to dimensions of a system.

- (a) First, the volume of the strip must be determined. This is quite simple since the strip is assumed to be a square.

$$V = l \times w \times h$$

$$V = 10 \text{ cm} \times 10 \text{ cm} \times 0.0001 \text{ cm}$$

$$V = [10 \times 10 \times 0.0001] \text{ cm}^3$$

$$V = 0.01 \text{ cm}^3$$

Following this, we simply divide the mass by the volume to determine concentration.

$$C = \frac{m}{V} = \frac{0.01 \text{ g}}{0.01 \text{ cm}^3}$$

$$C = 1 \text{ g/cm}^3$$

- (b) The same calculation is used to obtain the concentration for this substrate

$$C = 0.78 \text{ g/cm}^3$$

- (c) In this case, we are given the concentration and asked to find the total mass. This is accomplished with a minor change to the equation.

$$C = \frac{m}{V} \Rightarrow m = CV$$

Volume is found in the same manner as it was before.

$$V = 0.0375 \text{ cm}^3$$

$$m = 0.5 \frac{\text{g}}{\text{cm}^3} \times 0.0375 \text{ cm}^3$$

$$m = 0.019 \text{ g}$$

F&R 3.3c TB2.02 (Strip film dosages)

Drugs which are transported in the body by the bloodstream must be hydrophilic enough to be carried in solution. Unfortunately, many pharmaceutically active substances are highly hydrophobic, making them medically useless. One way to increase water solubility is by breaking them down¹ to **nanoparticle** size: 900-150 nm. However, when reduced to this size, the particles exhibit an attraction to each other which must be overcome to prevent **agglomeration**. To do this they are dissolved along with a **surfactant**. These surfactant coated nanoparticles may be formed into small, edible strips², similar in size to chewing gum, for administration.

You are working with a nanoparticle suspension of the drug *Ciprofloxacin*. The concentration of the suspension needs to be calculated so that the proper size strips may be used to give 20 mg (drug)/kg (patient weight) doses³. A mixture of 1157 grams of Ciprofloxacin in 5.5 liters of surfactant has been prepared.

- (a) What is the concentration of Ciprofloxacin in the mixture (Assume the volume is constant)?
- (b) Determine the amount of solution needed for: 198 lb_m male, 150 lb_m female, twin 100 lb_m females.

¹ Muller, R H; Jacobs, C; Kayser, O. Nanosuspensions as particulate drug formulations in therapy rationale for development and what we can expect for the future. *Advanced Drug Delivery Reviews*, 2001, 47, 3-19

² "Thrust Area 3." Research. Rutgers C-SOPS. 27 Feb 2008 <<http://ercforsops.rutgers.edu/research.html#>>.

³

<<http://www.fda.gov/downloads/Drugs/EmergencyPreparedness/BioterrorismandDrugPreparedness/UCM130802.pdf>> suggests this is not an unrealistic dosage.

Solution

This problem is a simple unit conversion problem

- (a) Our first step is to determine the concentration of the solution, which is easily done by noting the definition of concentration.

$$C = \frac{m}{V}$$

$$C = \frac{1157 \text{ g}}{5.5 \text{ L}}$$

$$\boxed{C = 210 \text{ g/L}}$$

- (b) To find the volumes required, the concentration and dosage given are applied:

$$V = 198 \text{ lb}_m(\text{patient}) \times \frac{1 \text{ kg}(\text{patient})}{2.2 \text{ lb}_m(\text{patient})} \times 20 \frac{\text{mg}(\text{dose})}{\text{kg}(\text{patient})} \times \frac{1 \text{ L}}{210 \text{ g}(\text{dose})}$$

Note the use of parenthesis to prevent confusion with the two different masses.

$$V = 0.00857 \text{ L}$$

While correct, a more reasonable unit for this small a volume is milliliters:

$$\boxed{V = 8.57 \text{ mL}}$$

The two remaining dosages are calculated in the same way and result in:

$$\boxed{V = 6.50 \text{ mL}}$$

$$\boxed{V = 4.32 \text{ mL each}}$$

F&R 3.3c TB3.01 (Drop on Demand)

Drop on demand (DoD) technology is an emerging form of drug delivery. In it, a device sprays nanometer scale drops onto an edible substrate, much like an inkjet printer works to produce color on a paper¹. The reservoir or cartridge used will contain an **active pharmaceutical ingredient** (API) dissolved in a liquid with a high tendency to evaporate. When the drop makes contact with the edible substrate, the liquid will evaporate, causing the API to crystallize on the substrate. By knowing the concentration of the API in the device reservoir, the operator will be able to administer the exact dose necessary, rather than a fraction or multiple of a tablet.

A DoD machine is charged with $\frac{1}{2}$ liters of 1 molar ibuprofen in hexane.² The molecular weight of ibuprofen is 206.28 g/mol.

- (a) If a drop is 1 nL, how many drops would administer a 350 mg dose?
- (b) If dosage is 2.8 mg (drug)/kg (patient weight)³ determine how many drops of the solution are needed for a 245 pound legislator and her 100 pound son.
- (c) The specific gravity of ibuprofen is 0.7. Determine the volume of API required to treat a 300 pound soldier. How many drops of solution is this?
- (d) Determine the number of tablets that would have to have been supplied for each patient if a tablet is 100 mg API

¹ "Thrust Area 3." Rutgers C-SOPS. 29 Feb 2008 <<http://ercforsops.rutgers.edu/research.html#>>.

² <http://www.ibuprofen-foundation.com/what-ibuprofen/documents/TIbuprofen.pdf>

³ <<http://dailymed.nlm.nih.gov/dailymed/archives/fdaDrugInfo.cfm?archiveid=4372>> suggests this.

Solution

The solution of this problem is based solely on dimensional analysis and the use of given data. The most likely “curveball” is the use of molarity, which should be recalled as mol/L.

(a) The equation may be set up based on the units alone:

$$N_d = 350 \text{ mg} \times \frac{1 \text{ mol}}{206.3 \text{ g}} \times \frac{1 \text{ g}}{1000 \text{ mg}} \times 1 \frac{\text{L}}{\text{mol}} \times 1 \frac{\text{drop}}{\text{nL}} \times 10^9 \frac{\text{nL}}{\text{L}}$$

$$\boxed{N_d = 1.7 \times 10^9 \text{ drops}}$$

It should be noted that the two 1000s are exact and cancelable.

(b) The two problems following are simple variations on the above. Instead of giving a required number of drops, a mass and dosage are given. The equations may be adapted:

$$N_d = 245 \text{ lb}_m \times 2.8 \frac{\text{mg}}{\text{kg}} \times \frac{1 \text{ kg}}{2.2 \text{ lb}_m} \times \frac{1 \text{ mol}}{206.3 \text{ g}} \times \frac{1 \text{ g}}{1000 \text{ mg}} \times 1 \frac{\text{L}}{\text{mol}} \times 1 \frac{\text{drop}}{\text{mL}} \times 10^9 \frac{\text{nL}}{\text{L}}$$

$$\boxed{N_d = 1.52 \times 10^9 \text{ drops}}$$

Having done one problem, the next one is easily solved by noting that the only thing changing is the mass. This allows us to use a ratio to compute the new value:

$$N_d = \frac{1.52 \times 10^9 \text{ drops}}{245 \text{ lb}_m} \times 100 \text{ lb}_m = 6.2 \times 10^8 \text{ drops}$$

(c) The specific gravity given is assumed to be relative to that of water. Equation 3.1-1 may be used to determine the density of ibuprofen.

$$SG = \frac{\rho}{\rho_{\text{ref}}} \Rightarrow \rho = SG\rho_{\text{ref}}$$

$$\rho = 0.7 \times 1.000 \frac{\text{g}}{\text{cm}^3} = 0.700 \frac{\text{g}}{\text{cm}^3}$$

The volume may now be determined from the density and the dosage.

$$V = 300 \text{ lb}_m \times 2.8 \frac{\text{mg}}{\text{kg}} \times \frac{1 \text{ kg}}{2.2 \text{ lb}_m} \times \frac{1 \text{ cm}^3}{0.7 \text{ g}} \times 0.001 \frac{\text{g}}{\text{mg}}$$

$$\boxed{V = 0.54 \text{ cm}^3}$$

The number of drops may be calculated by using the 1 nanoliter per drop conversion factor.

$$N_d = 0.54 \text{ cm}^3 \times 1 \frac{\text{mL}}{\text{cm}^3} \times \frac{10^9 \text{ nL}}{100 \text{ mL}} \times 1 \frac{\text{drop}}{\text{nL}}$$

$$\boxed{N_d = 540000 \text{ drops}}$$

(d) To determine the tableting, the API quantity of each tablet is divided by the amount needed.

$$N_t = \frac{100 \text{ mg}}{245 \text{ lb}_m \times 2.8 \frac{\text{mg}}{\text{kg}} \times \frac{1 \text{ kg}}{2.2 \text{ lb}_m}}$$

$$\boxed{N_t = 1.27 \text{ tablets} \approx 1\frac{1}{4} \text{ tablets}}$$

$$N_t = \frac{100 \text{ mg}}{100 \text{ lb}_m \times 2.8 \frac{\text{mg}}{\text{kg}} \times \frac{1 \text{ kg}}{2.2 \text{ lb}_m}}$$

$$\boxed{N_t = 0.78 \text{ tablets} \approx \frac{3}{4} \text{ tablets}}$$

As can be seen, the tablets are at best close approximations of the correct dose. For doses such as 0.64 tablets, the pharmacist must decide if the correct dose should be $\frac{1}{2}$ or $\frac{3}{4}$ of a tablet (It is not likely that a tablet could be easily divided into $\frac{1}{3}$ s).

F&R 3.3c TB1.14 (Material calculations for tablet press preparations)

Wet acetaminophen paste, the **active pharmaceutical ingredient** (API) in many over-the-counter pain medications, is dried to a powder and mixed with a cellulose **binder** and a starch **filler**. The mixed powder is pressed in a tablet press and coated before being packaged.

Although acetaminophen is the API, the tablet is only 65 wt% acetaminophen. The remainder is binder (5 wt%) and filler. During screening, 2.0% of the powder is filtered out. Prior to coating, a tablet has a mass of 500 mg.

- (a)** Determine how many grams binder and filler are required per kilogram of dry API.
- (b)** Each tablet is coated with 0.25 grams of an aqueous coating solution. If the properties of the coating solution are those of water, how many liters of solution are needed?

Solution

This problem is a simple mass fraction and conversions problem. Recognition of the fact that it is proposed on a 1 kg feed basis is necessary, but the only real “curveball”.

(a) To determine the masses, a simple use of mass fractions is needed:

$$m_i = x_i \left(\frac{m_{\text{API}}}{x_{\text{API}}} \right)$$

$$m_b = 0.05 \times \left(\frac{1 \text{ kg}}{0.65} \right)$$

$$\boxed{m_b = 77 \text{ g}}$$

$$\boxed{m_f = 462 \text{ g}}$$

(b) Solving for the amount of liquid needed is a two step process. First we find the number of tablets produced:

$$N_t = 1 \text{ kg} \times \frac{1}{0.65} \frac{\text{g powder mix}}{\text{g Acetaminophen}} \times \frac{1}{500} \frac{\text{tablet}}{\text{mg}} \times 1000 \frac{\text{mg}}{\text{g}} \times 1000 \frac{\text{g}}{\text{kg}}$$

$$N_t = 3077 \text{ tablets}$$

Now we may calculate the total volume needed for this batch:

$$V = 3077 \text{ tablets} \times 0.25 \frac{\text{g}}{\text{tablet}} \times \frac{1}{0.977} \frac{\text{cm}^3}{\text{g}} \times 0.001 \frac{\text{L}}{\text{cm}^3}$$

$$\boxed{V = 0.787 \text{ L}}$$

Chapter 4

F&R 4.1 TA1.01 (Powder flow)

Currently, many pharmaceutical processes are batch processes. One important consideration in converting to continuous processes is powder flow. Powders, though composed of solids, can flow like fluids under certain conditions (such as in well engineered processes).

You are a consulting for a pharmaceutical manufacturing company looking to convert their process into a continuous system. The senior process engineer wants to reuse a old **hopper** (large funnel) they have in storage. The hopper, which may be considered a cone with radius of 5 ft and height 6.5 ft, has been tested to determine the time required to completely empty it. To regulate the feed rate, the hopper is welded to **screw feeder**, which is a large metal spiral or augur which is rotated by a motor at a constant rate. In some applications (particularly water resources engineering) this is known as an **Archimedes screw**.

Data on time from full to totally empty is shown below.

Trial	1	2	3	4	5	6
Time (min)	5.86	7.55	4.89	6.35	5.50	4.99

- (a) Determine the average flow rate of the powder out of the hopper.
- (b) If the motor is operating at 77 **RPM**, determine the volume removed per revolution.
- (c) Determine how long the hopper will feed the process if it is filled to 5 feet.

Solution

This problem is easily solved with geometry and unit conversions. The only real “curveball” is the fact that the volume concerned here is conical.

- (a) First the average time to drain the hopper is found by the (arithmetic) average or mean is easily found using Equation 2.5-1:

$$\bar{X} = \frac{1}{N} \sum_{i=1}^N X_i$$

$$\bar{t} = \frac{1}{N} \sum_{i=1}^N t_i$$

$$\bar{t} = \frac{1}{6} (5.86 + 7.55 + 4.89 + 6.35 + 5.50 + 4.99)$$

$$\bar{t} = 5.86 \text{ min}$$

Now the volume is found using solid geometry (assuming that the cone is a right cone):

$$V_{\text{cone}} = \frac{1}{3} \pi r^2 h$$

$$V_{\text{cone}} = \frac{1}{3} \pi (5 \text{ ft})^2 (6.5 \text{ ft})$$

$$V_{\text{cone}} = 168 \text{ ft}^3$$

Now the flow rate is easily found by dividing volume by time:

$$\bar{V} = \frac{V}{\bar{t}} = \frac{168 \text{ ft}^3}{5.86 \text{ min}}$$

$$\boxed{\bar{V} = 28.7 \frac{\text{ft}^3}{\text{min}}}$$

- (b) Determining amount per turn is done in a single dimensional equation. Care should be taken to note that “N” here means the number of revolutions per minute, not the sample N from statistics.

$$m_{\text{rev}} = \frac{\bar{V}}{N} = 28.7 \frac{\text{ft}^3}{\text{min}} \times \frac{1 \text{ min}}{77 \text{ rev}}$$

$$m_{\text{rev}} = 0.37 \text{ ft}^3/\text{rev}$$

- (c) To determine the time to feed the process for partial filling we first calculate the volume of the cone formed when the hopper is only 5 feet full:

$$V_{\text{cone}} = \frac{1}{3} \pi r^2 h$$

$$V_{\text{cone}} = \frac{1}{3} \pi (5 \text{ ft})^2 (5 \text{ ft})$$

$$V_{\text{cone}} = 131 \text{ ft}^3$$

Now we divide this by the volumetric flow rate obtained previously.

$$t' = \frac{V}{\dot{V}} = \frac{131 \text{ ft}^3}{5.86 \text{ min}}$$

$$t' = 22.4 \text{ min}$$

This assumes that the flow rate is not a function the volume/mass in the hopper. Since there is a screw drive removing a regular amount of powder per revolution at a steady RPM, this is a reasonable assumption.

F&R 4.1 TB1.10 (Continuous v. batch comparison)

Characterize the following as batch, semibatch or continuous processes.

- (a)** Salt dissolving in a flask of water
- (b)** A Büchner funnel filter cake being heated to dry it
- (c)** A reactor being drained of a drug product
- (d)** A window AC cooling a lab
- (e)** Students attending a class
- (f)** A printer printing homework

Solution

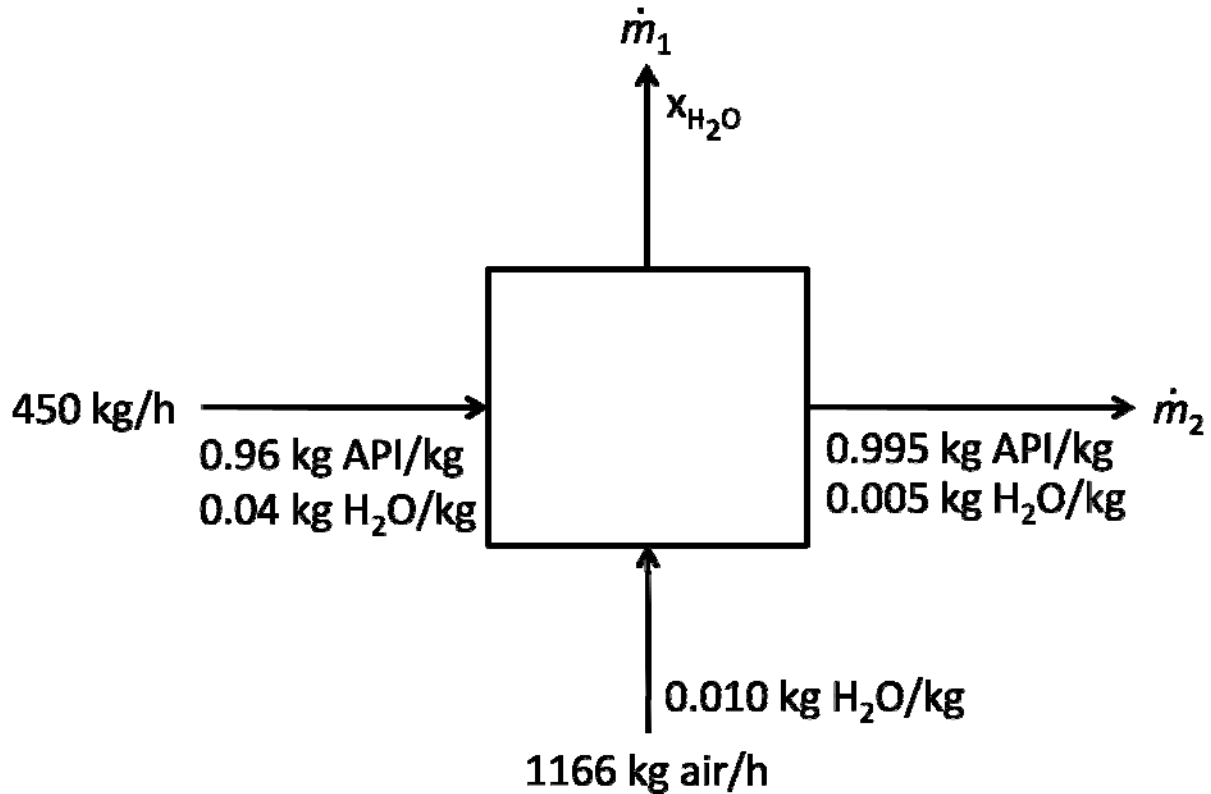
- (a)** Batch. All ingredients are present in the flask (system) and no mass crosses the system boundaries.
- (b)** Batch or semibatch. If the water vapor leaving the cake is counted, this is semibatch, if it has not been heated enough to start driving off water, batch.
- (c)** Semibatch. The products of the reaction are being added to the reactor, but no mass is removed from it.
- (d)** Continuous. Air is drawn into the system and condensed water and cool are expelled from the unit at the same time. There is (ideally) no accumulation of mass within the unit.
- (e)** Batch. If the classroom is considered the system, the students enter at time = 0, stay in the room until dismissal, and then leave, changed for the time spent in the room (system).
- (f)** Semibatch. Assume the printer is the system. Mass is being removed from the printer as product, but none is added until the printer is refilled (the system is charged with additional reactant) or the ink cartridge is changed.

F&R 4.3 TB1.15 (Drying an API)

In production of a certain **active pharmaceutical ingredient** (API), the pure crystals are crystallized out of an aqueous solution. After a **wet cake** of 96 wt% API has formed, the mass is sent to the dryer. The cake is dried by blowing plant air at 0.010 **absolute humidity** (mass fraction water) over it until it is 0.995 mass fraction API. In one hour, 1166 kg air is used to dry 450 kg of cake. How much water (kg) was removed from the API and what is the absolute humidity in the exiting air?

Solution

First, the flowchart:



We first examine the system to see where we can write an equation with only one unknown. The API suggests itself as it is present in only 2 streams, one of which is fully specified and the other specified in composition.

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

$$450 \frac{\text{kg}}{\text{h}} \times 0.96 \frac{\text{kg API}}{\text{kg}} = \dot{m}_2 \times 0.995 \frac{\text{kg API}}{\text{kg}}$$

$$\dot{m}_2 = 434 \text{ kg}$$

We can then take the difference between this and the feed stream to find the water loss:

$$\dot{m}_{\text{H}_2\text{O}} = (450 - 434) \frac{\text{kg}}{\text{h}}$$

$$\boxed{\dot{m}_{\text{H}_2\text{O}} = 16 \text{ kg H}_2\text{O/h}}$$

To find the absolute humidity of the air out, we first need to find the mass flow of the stream.

$$\sum_{\text{in}} \dot{m} = \sum_{\text{out}} \dot{m}$$

$$(450 + 1166 - 434) \frac{\text{kg}}{\text{h}} = \dot{m}_{\text{out}}$$

$$\dot{m}_{\text{out}} = 1182 \frac{\text{kg}}{\text{h}}$$

Now we set up our equation describing water in the flow rates:

$$450 \frac{\text{kg}}{\text{h}} \times 0.04 + 1166 \frac{\text{kg}}{\text{h}} \times 0.04 = 1166 \frac{\text{kg}}{\text{h}} \times 0.01 + 1182 \frac{\text{kg}}{\text{h}} \times x_{\text{H}_2\text{O}}$$

$$\boxed{x_{\text{H}_2\text{O}} = 0.023}$$

F&R 4.3 TB1.05 (Wet granulation processing)

In pharmaceutical engineering, **wet granulation** is often used in the production of compressed tablets. This process entails the breaking down of particles for pills into granules which become compressed into tablets and may be described in the following steps:

1. The wet **active pharmaceutical ingredient (API)** powder is mixed with an inactive **filler** to form the bulk of the pill.
2. A **binder** is added to allow the powder to be molded into a shape.
3. The powder is dried of excess water in a dryer.
4. The powder is pressed in a **pill press**, which gives the pill its distinctive shape and name.
5. Dry lubricant is applied to give a smooth surface to the final tablet.

A new drug called *Costelol* is being produced using wet granulation. The final pill will contain 30% API, 65% sucrose filler and 5% aqueous cornstarch binder. The dosage of each tablet is 81 mg and API is fed into the mixer at 17 g/s.

- (a) What is the total output powder flow (g/s)?
- (b) What is the output of the process (tablets/minute)?
- (c) What is the concentration (mg/tablet) of each **excipient** (inactive ingredient) the tablet?

Solution

This problem is a mostly simple mass equation manipulation.

- (a) The total flow is determined by dividing the only flow rate we know (The API flow rate) by its mass fraction.

$$\dot{m}_T = \frac{\dot{m}_{API}}{x_{API}}$$
$$\dot{m}_T = \frac{17 \frac{\text{g}}{\text{s}}}{0.30} = \boxed{56.67 \frac{\text{g}}{\text{s}}}$$

- (b) To determine the number of pills made, the amount of API fed is divided by the amount needed per pill.

$$N_{\text{tablets}} = \frac{\dot{m}_{API}}{m_{API_{\text{tablet}}}}$$
$$N_{\text{tablets}} = 56.67 \frac{\text{g}}{\text{s}} \times \frac{1 \text{ tablet}}{81 \text{ mg}} \times 1000 \frac{\text{mg}}{\text{g}} \times 60 \frac{\text{s}}{\text{min}} = \boxed{41975 \approx 42000 \text{ tablets/min}}$$

- (c) The amount of each excipient may be calculated by taking the mass fraction of the excipient and multiplying it by the ratio of the mass fraction of API to the mass fraction of the API:

$$m_i = x_i \left(\frac{m_{API}}{x_{API}} \right)$$
$$m_f = x_f \frac{m_{API}}{x_{API}} = 0.65 \times \frac{81 \text{ mg/tablet}}{0.30} = \boxed{175.5 \text{ mg/tablet}}$$
$$m_b = x_b \frac{m_{API}}{x_{API}} = 0.05 \times \frac{81 \text{ mg/tablet}}{0.30} = \boxed{13.5 \text{ mg/tablet}}$$

F&R 4.3a KM-1 (Lab scale drug production calculations)

You are given the following¹ **Bill of Materials (BoM)** of a drug preparation your company is interested in producing.

<u>Name</u>	<u>Item</u>	<u>Quantity (g) per 1000 tablets</u>
Hyoscine butyl bromide	1	10.000
Lactose monohydrate	2	16.500
Lactose monohydrate, dense	3	28.000
Cornstarch	4	19.720
Povidone	5	2.240
Purified water	6	5.080
Magnesium stearate	7	0.400
Starch 1500	8	2.740

- (a) You have an empty laboratory **staging area** that can accommodate raw materials for only 540 pills at a time. Derive an equation for the total amount of material required (Y) in terms of the number of 540 pill batches (X).
- (b) Before ordering materials for the first test run you have to submit a review of the hazards and precautions to the company's Safety Office. They deem a review of the MSDS's sufficient for this. What safety precautions do you recommend be taken, and on account of what materials? *Reference the MSDS(s) you have used.*
- (c) Research the ingredients and determine the category (binder, filler, active ingredient, solvent) of each. *Hint: One of the ingredients does not fit in these categories.*
- (d) It is desired to make the product in a continuous process. The foreseen **production line** is as follows: Dissolve 5 in 6. Mix 1, 2, 3 and 4 together in a mixing vessel while adding the previous dissolution to the mix. Pass the resulting mix through drying and milling processes. Mix 7 and 8 and add in the milling process. Send to tablet press.
- Draw a labeled flowchart of this process (You can use the numbers in the BoM)
 - Determine as many flowrates as possible in terms of X and label them on a new copy of the flowchart
- (e) Look up the active ingredient (hyoscine butyl bromide) in a copy of the Merck Index. What is this medication generally intended to treat?

¹ Handbook of Pharmaceutical Manufacturing Formulations, page 313. Note part (c), the production step, is very simplified from the instructions given. In particular, this assumes that all feeds and products are satisfactory and do not require screening, addition of makeup streams, etc. Several steps (EG. Drying) are completely left out.

Solution

This is intended to provide some facility in researching commonly needed/used information from external sources.

- (a) The equation may be developed by first noting that the amounts in the Bill of Materials are in terms of 1000 pills. The conversion between 1000 and 540 is done in the same manner as a unit conversion:

$$\left(\frac{\text{amt}}{1000 \text{ pills}}\right) \times 540 \frac{\text{pills}}{\text{batch}} = \left(\frac{\text{amt}}{\text{batch}}\right)$$

Defining $Q_{u_{1000}}$ as the quantity of each per 1000 tablets, we write:

$$\left\{ \left[\sum Q_{u_{1000}} \left(\frac{\text{g}}{1000 \text{ pills}}\right) \right] \times 540 \frac{\text{pills}}{\text{batch}} \right\} \times X(\text{batches}) = Y(\text{g})$$

Note that students may write out the summation. It is presented as shown to save space. Performing the summation results in

$$\left(84.68 \frac{\text{g}}{1000 \text{ pills}} \times 540 \frac{\text{pills}}{\text{batch}}\right) \times X(\text{batches}) = Y(\text{g})$$

$$\boxed{\left(45.73 \frac{\text{g}}{\text{batch}}\right) \times X(\text{batches}) = Y(\text{g})}$$

- (b) Any legitimate MSDS may be cited here. Because knowledge of the hazardousness of substances is not fully developed yet, answers given now may change after publication (Think of benzene and carbon tetrachloride as common solvents). If this occurs, you should alter the problem on your own to make use of that fact (IE. Have the students research the no longer considered safe compound). As an example of what is desired, an MSDS for the active ingredient is shown below.

According to the EDQM MSDS¹ hyoscine butylbromide is a “powerful sedative” that affects the central nervous system. Section 8 contains a short description of the appropriate safety precautions:

8. EXPOSURE CONTROLS/PERSONAL PROTECTION

[...]

Mechanical exhaust required. Safety shower and eye bath.

Respiratory protection: Protecting mask (filter P2).

Hand protection: Compatible chemical-resistant gloves category III (EN 374). Camatril, green (nitrile), resistance (permeability) level 6.

Eye protection: Wear protective chemical safety goggles.

¹ Available at <http://crs.edqm.eu/db/4DCGI/db/4DCGI/MSDS?MSDS=H1450000>

(c) For this, any reasonable source may be used to determine this. The following were obtained from the sources given:

Hyoscine butyl bromide — Active ingredient¹

Lactose monohydrate — Filler²

Lactose monohydrate, dense — Assumed same as lactose monohydrate

Cornstarch — Binder³

Povidone — (Dry) binder⁴

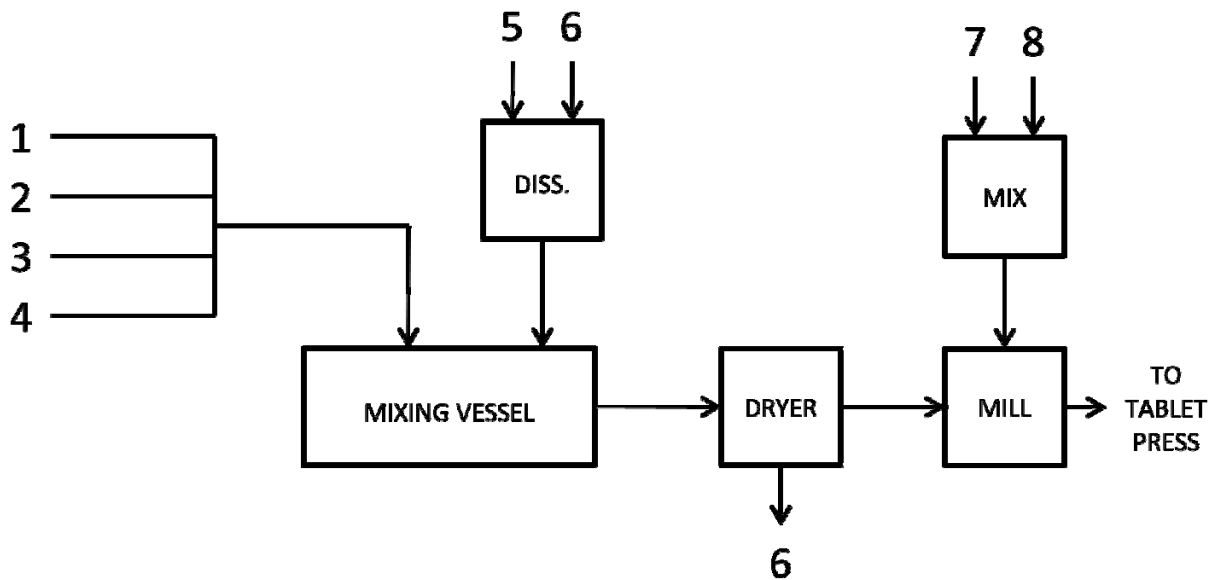
Purified water — Solvent (This should be obvious)

Magnesium stearate — Lubricant⁵

Starch 1500 — Binder⁶

(d) We obtain:

(i) For the flowchart, something like this should be presented:



(ii) To determine the flowrates in terms of X , we apply the formula from part (a) to each individual component

$$\left[Qu_{1000} \left(\frac{\text{g}}{1000 \text{ pills}} \right) \times 540 \frac{\text{pills}}{\text{batch}} \right] \times X(\text{batches}) = Y(\text{g})$$

¹ <<http://www.umm.edu/altmed/drugs/scopolamine-derivatives-113900.htm>>

² <<http://www.ca9.uscourts.gov/opinions/04-1506.pdf>>, pg 18.

³ <<http://www.epa.gov/guide/pharm/econanal/econ-ch3.pdf>>, pg 3-19

⁴ <http://grande.nal.usda.gov/ibids/index.php?mode2=detail&origin=ibids_references&therow=150019>

⁵ <<http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm142591.htm>>, search on page for “Mazen Hamad”

⁶ <<http://www.ncbi.nlm.nih.gov/pubmed/18930870>>

As an example, for item 1:

$$\left[10.000 \frac{\text{g}}{1000 \text{ pills}} \times 540 \frac{\text{pills}}{\text{batch}} \right] \times X(\text{batches}) = 1 \text{ (g)}$$

$$1 \text{ (g)} = 5.40X$$

We repeat this for the remaining seven items to obtain:

$$2 \text{ (g)} = 8.91X$$

$$3 \text{ (g)} = 15.12X$$

$$4 \text{ (g)} = 10.65X$$

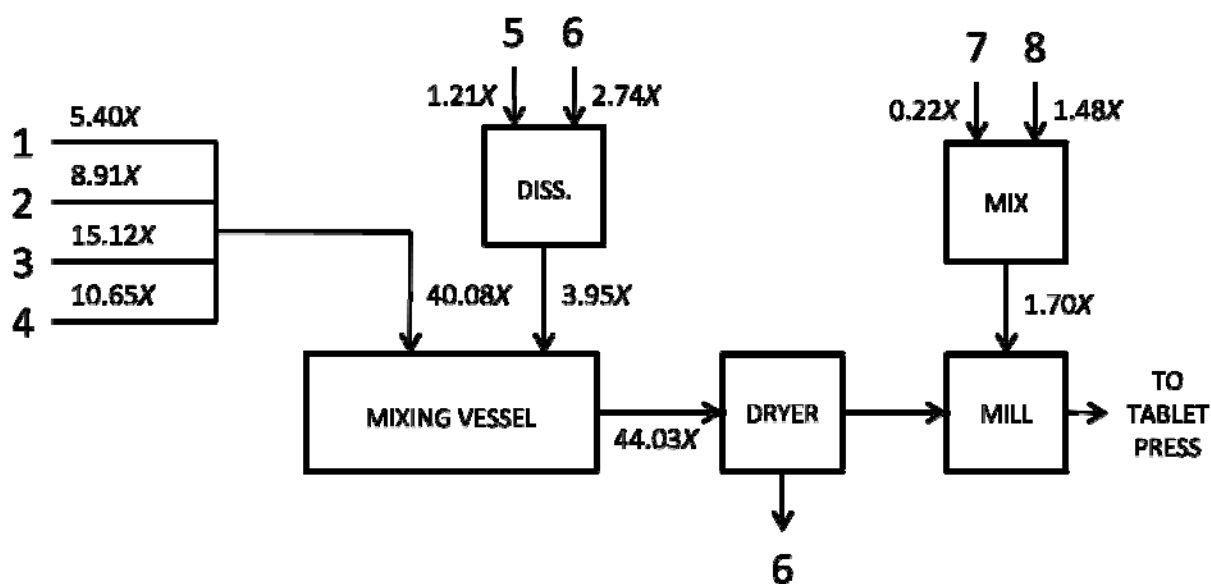
$$5 \text{ (g)} = 1.21X$$

$$6 \text{ (g)} = 2.74X$$

$$7 \text{ (g)} = 0.22X$$

$$8 \text{ (g)} = 1.48X$$

Putting these on the previously obtained flowchart, we obtain:



Note the trap at the dryer. We are not given information on the amount of water removed, so all flows after it are unspecified. We could obtain a range of possible flowrates (No water removed to all water removed), however that is not asked for here.

(e) In the 14th (2006) edition of the Merck Index, the therapeutic categorization of hyoscine butylbromide (called "*N*-Butylscopolammonium Bromide" there) is "antispasmodic".

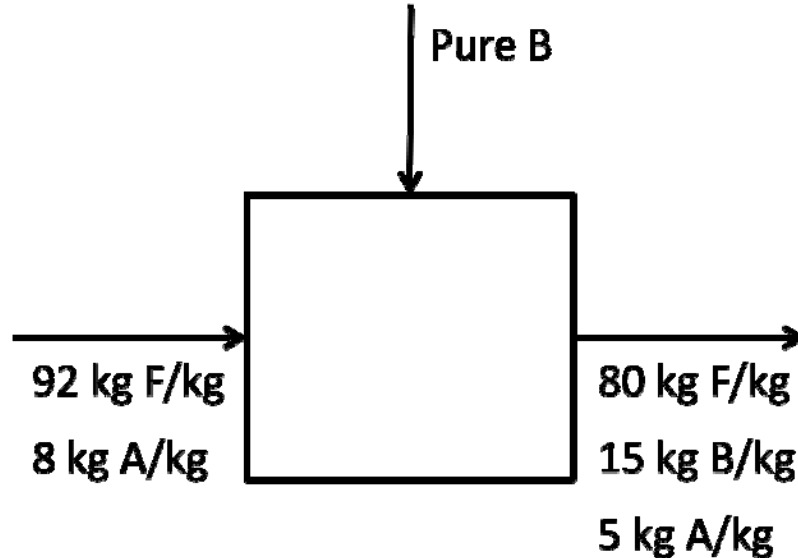
F&R 4.3c TB1.20 (Pharmaceutical granulation)

Granulation is a process that increases the average size of powder particles by combining smaller ones, enhancing the flow of the powder. Granulation is widely used in pharmaceutical engineering to combine all the ingredients of a medicine into a single powder for further processing. Wet granulation blends powdered **filler** (to dilute the active ingredient to a useful concentration) and **active pharmaceutical ingredient (API)** before mixture with a paste forming liquid **binder**.

In the production of pain killing medication, a stream of powder containing 92 wt% lactose filler and the balance salicylic acid (API) are sent to a granulator. A common liquid binder, povidone, is added as an additional stream to the mixture. The composition of the stream exiting the system is 5 wt% API, 80 wt% filler, and 15 wt% liquid binder. If 6000 pills/h are to be produced, each containing 180 mg of API, what flow rates (steady state) are to be set by the operator?

Solution

As with any process problem, we draw a flowchart with the information on the process itself. Here F, B, and A are used to represent the filler, binder and API, respectively.



Additionally we know that 6000 pills with 180 mg of API are to be produced in an hour.

To begin, we must incorporate the only data we have on actual rates:

$$\dot{m}_{\text{API out}} = 6000 \frac{\text{pills}}{\text{h}} \times 180 \frac{\text{mg A}}{\text{pill}} = 1080000 \frac{\text{mg A}}{\text{h}} = 1.08 \frac{\text{kg A}}{\text{h}}$$

This is our flow of A out of the process. With this we can determine the total flow out:

$$\dot{m}_{\text{out}} = 1.08 \frac{\text{kg A}}{\text{h}} \times \frac{1 \text{ kg}}{0.05 \text{ kg A}} = 21.6 \text{ kg}$$

Noting the mass fraction of binder entering the system (1.00), we determine that flow rate.

$$\dot{m}_{\text{b}} = 21.6 \text{ kg} \times 0.15 \frac{\text{kg B}}{\text{kg}}$$

$$\boxed{\dot{m}_{\text{b}} = 3.24 \text{ kg}}$$

The other input flow rate is easily determined by the difference of the two:

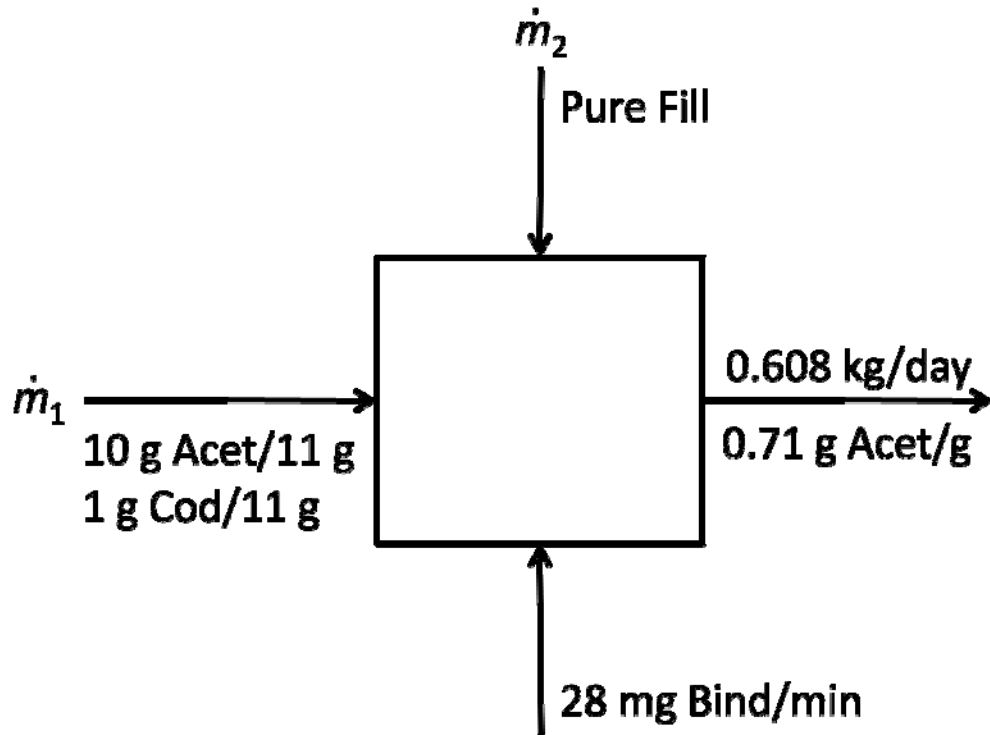
$$\begin{aligned} \dot{m}_{\text{in}} &= \dot{m}_{\text{out}} \\ \dot{m}_{\text{feed}} + \dot{m}_{\text{b}} &= \dot{m}_{\text{out}} \\ \dot{m}_{\text{feed}} + 3.24 \text{ kg} &= 21.6 \text{ kg} \\ \dot{m}_{\text{feed}} &= 18.36 \text{ kg} \end{aligned}$$

F&R 4.3c TB1.16e (Powder blending calculations)

One of the unit operations in the pharmaceutical engineering is **powder blending** in which multiple powders are mixed together to give a uniform product. In the production of a tablet, **binders** (effectively glue for powders), **fillers** (for dilution) and the **active pharmaceutical ingredients** (APIs) are blended. In a lab blender being tested, 10 parts acetaminophen to one part codeine are being fed as API. Pure starch enters at 28 mg/min along with a pure stream of microcrystalline cellulose (MCC) filler. The mixer is run continuously in order to produce 3.04 kg in 5 days at 71 wt% acetaminophen. Draw and label a flowchart and determine all mass flow rates and compositions.

Solution

We begin with our flowchart:



Note the conversion of the awkward kg/5 days to kg/day.

At this point, we may examine the diagram to see where best to start. We are given enough data to solve an equation on acetaminophen ("Acet" in the figure).

$$\sum_{\text{in}} \dot{m} = \sum_{\text{out}} \dot{m}$$

$$\dot{m}_1 \times \frac{10 \text{ g Acet}}{11 \text{ g}} = 0.71 \frac{\text{g Acet}}{\text{g}} \times 0.608 \frac{\text{kg}}{\text{day}}$$

$$\dot{m}_1 = 0.475 \frac{\text{kg}}{\text{day}} \times 1000 \frac{\text{g}}{\text{kg}} \times \frac{1 \text{ day}}{24 \text{ h}} \times \frac{1 \text{ h}}{60 \text{ min}} = 0.330 \frac{\text{g}}{\text{min}}$$

From this the total flow may be determined

$$\sum_{\text{in}} \dot{m} = \sum_{\text{out}} \dot{m}$$

$$0.330 \frac{\text{g}}{\text{min}} + \dot{m}_2 + 28 \frac{\text{mg}}{\text{min}} \times \frac{1 \text{ g}}{1000 \text{ mg}} = 0.608 \frac{\text{kg}}{\text{day}} \times 1000 \frac{\text{g}}{\text{kg}} \times \frac{1 \text{ day}}{24 \text{ h}} \times \frac{1 \text{ h}}{60 \text{ min}}$$

$$\dot{m}_2 = [0.422 - (0.330 + 0.028)] \frac{\text{g}}{\text{min}}$$

$$\dot{m}_2 = 0.064 \frac{\text{g}}{\text{min}}$$

Now, since the problem asked for everything specified, this is best answered as a table:

		Mass flows (g/min)			
		m1	m2	Bind	Out
		0.330	0.064	0.028	0.422
Mass fractions	xA	0.909	0	0	0.7109
	xC	0.091	0	0	0.071
	xB	0	0	1	0.066
	xF	0	1	0	0.152

F&R 4.4 MI-2 (Tamoxifen Formulation)

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. For women who have undergone a hysterectomy Estrogen Replacement therapy¹ is provided. Prolonged usage of estrogen could result in certain types of breast cancers². 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% water³ 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 that evaporates 94.23% of water?

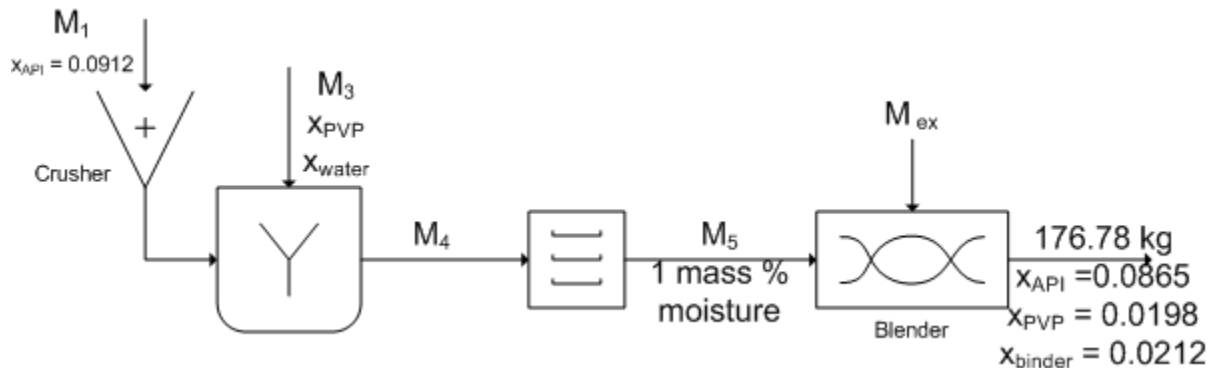
¹ "Estrogen Replacement therapy (ERT)" Web.Sept.2009 <www.cancer.org>

² "Tamoxifen." *Drugs.com*. Web. 1 Dec. 2009. <<http://www.drugs.com/tamoxifen.html>>.

³ Handbook of Pharmaceutical Manufacturing Formulations, page 476.

Solution

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.



From here it can be assumed that the system is at steady state (no accumulations and no generation terms). From the outlet stream, the mass of the API, binder, and the final set of excipients are calculated.

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

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.

$$\begin{aligned}
 m_5 &= 176.78 \text{ kg} - 3.75 \text{ kg} = 173.03 \text{ kg} \\
 \frac{5.77}{100} &= \frac{(0.01)173.03 \text{ kg}}{m_{\text{water}}} \rightarrow m_{\text{water}} = 30.0 \text{ kg water entering the dryer}
 \end{aligned}$$

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

$$\begin{aligned}
 m_1 &= \frac{m_{\text{API}}}{x_{\text{API}}} = \frac{15.3 \text{ kg}}{0.0912} = 167.8 \text{ kg} \\
 m_{\text{ex}} &= m_1 x_{\text{ex}} = 167.8 \text{ kg}(1 - 0.0912) = 152.5 \text{ kg}
 \end{aligned}$$

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

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

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

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

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

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

F&R 4.4 MI-3 (Vytorin Formulation [10 mg/10 mg])

About one in five americans have a cholesterol level of above 200 mg/dL, this is considered to be very unhealthy¹. A pharmaceutical company sets up a batch process in order to manufacture 1000 Vytorin tablets. Vytorin works by decreasing lowering LDL and increases HDL². The process³ of creating these tablets is initiated by adding equal amounts of two active ingredients and 50.16g of an excipient to a kneader. Once this is done another stream of excipients consisting of 90.7% liquid by mass is added to the kneader. The resulting liquid mixture consists of two parts of water and one part ethanol. The kneader produces a wet mass called a **cake**, which is spread over trays and kept in an oven at 45°C for eight hours. During the course of this time 17.3 wt% of the mass of the cake is evaporated. This dry substance is blended with a lubricant and a binder, it is then finally sent to be compressed into 100mg tablets. The end product (tablets) has the following composition (% wt): 20% API, 51.7% excipients, 27.5% binder and the remaining lubricant. How much of each liquid is added to the kneader?

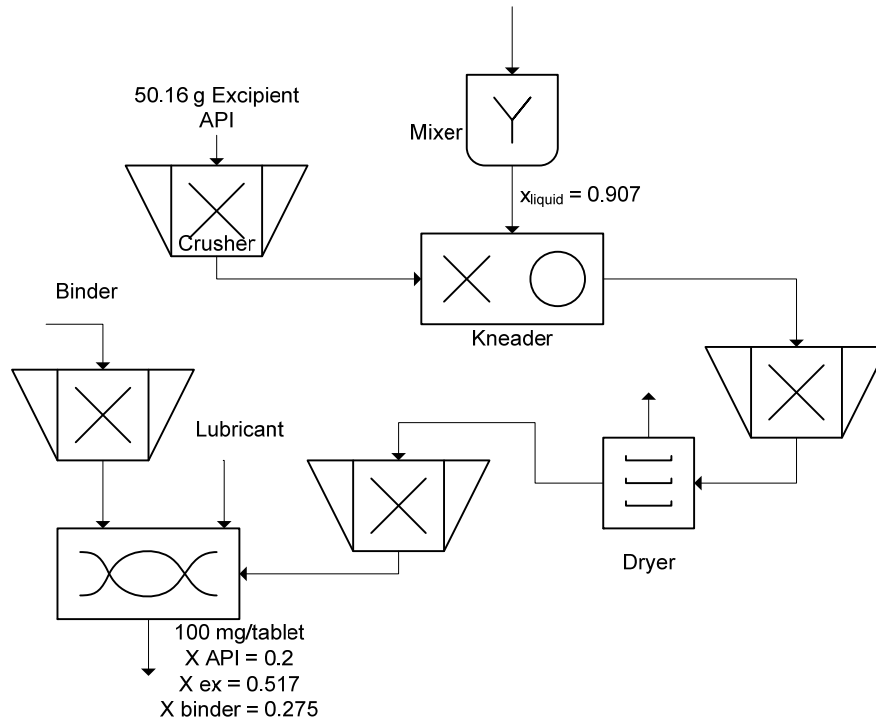
¹ American Heart Association. *Cholesterol Statistics*. [Online] 2009. [Cited: Dec. 8, 2009.] <http://www.americanheart.org/presenter.jhtml?identifier=4506>.

² Drugs.com. *Vytorin*. [Online] 2000-2009. [Cited: Dec. 8, 2009.] <http://www.drugs.com/vytorin.html>.

³ Handbook of Pharmaceutical Manufacturing Formulations, page 527.

Solution

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



We know that each tablet weighs 100 mg and the process produces 1000 tablets. Based on the finished tablet formulation we can calculate the weight of 1000 tablets and its contents.

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

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

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

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

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

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

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

Mass balance on the dryer:

$$m_{\text{in}} = m_{\text{evap}} + m_{\text{out}}$$

$$m_{\text{evap}} = 0.173m_{\text{in}}$$

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

$$m_{\text{evap}} = m_{\text{in}} - m_{\text{out}} = 86.7\text{ g} - 71.7\text{ g} = 15.0\text{ g}$$

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

We found the mass of the API to be 20.0 g in the initial steps and the problem statement give the weight of the excipient in the stream with the API. We can now do a mass balance around the kneader and find the contents of each stream.

Mass balance around the kneader:

$$\overset{m_1}{\text{(stream with API)}} + \overset{m_2}{\text{(stream with liquid)}} = m_3 = 86.7\text{ g}$$

$$m_1 = m_{\text{API}} + m_{\text{ex}} = 20.0\text{ g} + 50.16\text{ g} = 70.16\text{ g}$$

$$m_2 = m_3 - m_1 = 86.7\text{ g} - 70.16\text{ g} = 16.54\text{ g}$$

$$m_{\text{liquid}} = 0.907m_2 = 0.907(16.54\text{g}) = 15.0\text{ g}$$

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

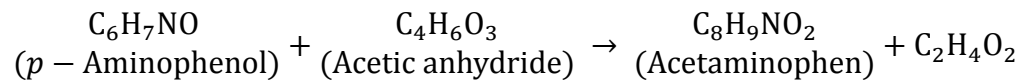
$$15\text{g} = 3x$$

$$x = \boxed{5.0\text{ g ethanol}}$$

$$2x = \boxed{10.0\text{ g water}}$$

F&R 4.6 MI-1 (Reaction Stoichiometry of Acetaminophen)

Acetaminophen is used to treat many conditions such as headaches, arthritis, backache, toothaches, colds, and fever¹. To produce Acetaminophen, *p*-Aminophenol and acetic anhydride in dichloromethane are fed to the reactor in the presence of NaHSO₄·SiO₂ as a **heterogeneous** catalyst². The reaction stoichiometry is given below:



The feed to the reactor contains 45.5 mole % *p*-Aminophenol and the remaining is acetic anhydride. For a 48.18 kg-mole feed of reactants and a fractional conversion of 95% of the limiting reactant is achieved, find the following:

- (a) Limiting reactant
- (b) The percentage by which it is in excess
- (c) How many kg of Acetaminophen is produced?

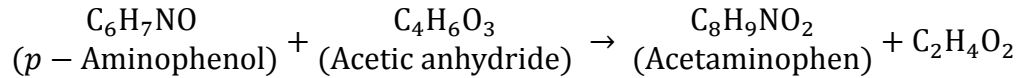
¹ Acetaminophen. *Drugs.com*. [Online] 2009. [Cited: November 12, 2009.] <http://www.drugs.com/acetaminophen.html>.

²Biswanath Das, P. T. (2007). A highly selective and efficient acetylation of alcohols and amines with acetic anhydride using NaHSO₄·SiO₂ as a heterogeneous catalyst. *Journal of Molecular Catalysis A: Chemical*, 269 (1-2), 12-16.

Solution

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 form¹.

Dichloromethane (*l*) serves as the medium in which the reaction takes place. After the completion of reaction the mixture is filtered to obtain Acetaminophen.

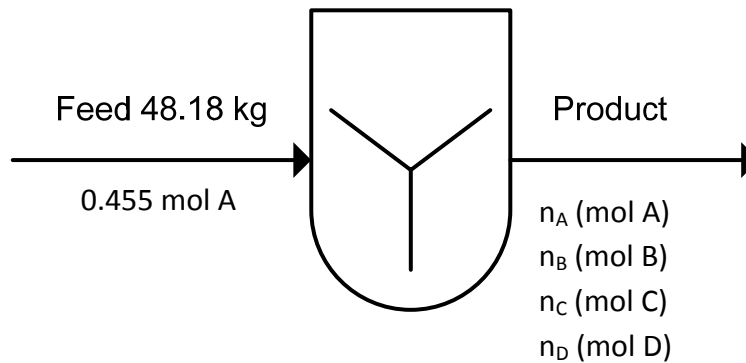


A = *p*-Aminophenol (M = 109.13)

B = Acetic anhydride (M = 102.09)

C = Acetaminophen

D = Acetic acid



- (a) First the average molecular weight of the feed needs to be determined and the feed needs to be calculated in terms of molar flow. Then the moles of each reactant need to be determined so the limiting reactant can be calculated from the stoichiometric coefficients.

$$MW_{reactants} = 0.455 \frac{\text{mol A}}{\text{mol}} \frac{109.13 \text{ kg}}{\text{mol A}} + 0.545 \frac{\text{mol B}}{\text{mol}} \frac{102.09 \text{ kg}}{\text{mol B}} = 105.29 \frac{\text{kg}}{\text{kmol}}$$

$$\text{kmol}_{reactant} = 48.18 \text{ kg} \frac{\text{kmol}}{105.29 \text{ kg}} = 0.4576 \text{ kmol}$$

$$(n_A)_0 = 0.455(457.6 \text{ mol}) = 208.2 \text{ mol}$$

$$(n_B)_0 = 0.545(457.6 \text{ mol}) = 249.4 \text{ mol}$$

↓

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

¹ Fogler, H. Scott. *Elements of Chemical Reaction Engineering*. Fourth Edition. s.l. : Prentice Hall, 2006. p. Page 647. ISBN: 9780130473943.

p – Aminophenol is the limiting reactant

(b) Percentage excess

$$(\% \text{ excess})_B = \frac{n_{B0} - n_{B \text{ stoich}}}{n_{B \text{ stoich}}} \times 100 = \frac{249.4 - 208.2}{208.2} \times 100 = \boxed{20 \%}$$

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

Fractional conversion of *p*-Aminophenol is 95%, than

$$n_{A_{out}} = 0.05(n_A)_o = 0.05(208.2 \text{ mol}) = 10.41 \text{ mol A (} p \text{ – Aminophenol)}$$
$$\xi = n_{A0} - n_{A_{out}} = 208.2 \text{ mol} - 10.41 \text{ mol} = 197.79 \text{ mol}$$

$$n_B = 249.4 \text{ mol} - \xi = 50.61 \text{ mol}$$

$$n_C = \xi = \boxed{197.79 \text{ mol}}$$

$$n_D = \xi = 197.79 \text{ mol}$$

Convert mole to kg of Acetaminophen.

$$m_{Ace} = nM_{Ace} = 197.79 \text{ mol} \left(\frac{151.17 \text{ g}}{\text{gmol}} \right) \left(\frac{1 \text{ kg}}{1000\text{g}} \right) = \boxed{29.9 \text{ kg}}$$

F&R 4.9 TB1.04 (Acetylsalicylic acid milling)

Milling is the breakdown of solids into smaller particles. In pharmaceutical engineering a **mill** is used to convert coarse material into a uniform powder, necessary for accurate **dosage**.

In the production of aspirin, crystalline acetylsalicylic acid is fed to a granulation process to grind the ASA powder into smaller particles. To produce the powder, the operator of the mill sets powder flow in to 26 g/s, the pill press down the line reports 321 aspirin tablets are being produced per second from this. Assume no loss of powder.

- (a) Draw and label a flowchart of this process. You are likely to find this exercise a waste of time for such a simple process; give a reasonable justification of why this should be done anyway.
- (b) What is the dosage (mg) of acetylsalicylic acid in each tablet, assuming each has identical composition?

Solution

This problem is a very simple mass flow problem with one process and no real “curveballs”.

(a) The following is approximately what should be drawn¹:



Possible justifications: Good practice, learning system, book keeping, this unit operation may be part of a larger system that this diagram will fit into.

(b) This is pure algebra:

$$\begin{aligned} \text{Dosage} &= \frac{\text{mass}}{\text{tablet}} \\ \text{Dosage} &= \frac{26 \frac{\text{g ASA}}{\text{s}}}{321 \frac{\text{tablet}}{\text{s}}} \\ \text{Dosage} &= 26 \frac{\text{g ASA}}{\text{s}} \times \frac{1}{321} \frac{\text{s}}{\text{tablet}} \\ \text{Dosage} &= \frac{26 \text{ g ASA}}{321 \text{ tablet}} \\ \text{Dosage} &= 0.081 \frac{\text{g ASA}}{\text{tablet}} \times 1000 \frac{\text{mg}}{\text{g}} \\ \text{Dosage} &= 81. \frac{\text{mg ASA}}{\text{tablet}} \end{aligned}$$

¹ According to the CAS <<http://www.commonchemistry.org/ChemicalDetail.aspx?ref=50-78-2>>, “ASA” is an accepted abbreviation for acetylsalicylic acid.

Chapter 5

F&R 5.3b KM-2 (Inhaler modeling with Virial EOS)

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 12¹, has been replaced by HFC 227ea². Both inhalers contain 100 mL of propellant under³ 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.

¹ See doi:10.1016/j.physletb.2003.10.071

² See <<http://www.ncbi.nlm.nih.gov/pubmed/10469920>>. Note that "HFC" is almost universally preferred to "HFA". Both are valid: <http://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?cid=67940>

³ See <<http://patft.uspto.gov/netacgi/nph-Parser?Sect1=PTO2&p=1&u=%2Fnethtml%2FPTO%2Fsearch-bool.html&r=1&f=G&l=50&co1=AND&d=PALL&s1=3897779.PN.>> Patent # 3 897 779, which concerns CFC 12.

Solution

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 (from AiChE Elibrary) for the critical constants and two¹² 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:

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

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

$$T_r = \frac{T}{T_c}$$

$$T_r = \frac{298 \text{ K}}{384.95 \text{ K}} = 0.774$$

Substituting this into the equations for B_0 and B_1 :

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

¹ doi:10.1016/S0009-2509(02)00017-9

² doi:10.1016/j.fluid.2009.08.023

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

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

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

We now substitute these values into the formula for B:

$$B = \frac{RT_c}{P_c} (B_0 + \omega B_1)$$

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

$$B = -0.480 \text{ L/mol}$$

Inserting this and other values into the virial equation:

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

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

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

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:

$$\hat{V} = (3.944, 0.546) \text{ L/mol}$$

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:

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

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:

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

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

Doing the same thing for HFC 227ea gives us:

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

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:

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

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

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

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.

Chapter 6

F&R 6.5 TB1.21a (Crystallization process calculations)

One of the processes used in producing (specifically purifying) an **active pharmaceutical ingredient** (API) is a crystallizer. In this process solid API particles precipitate out of a liquid solution, usually incited by a temperature change.

The table¹ below contains saturation data for acetaminophen (a common painkilling API) in a **co-solvent** (One phase, two liquid) solution of ethanol and water. To use the table, specify the mass fraction of ethanol in the solution on the ordinate and the temperature of the solution on the abscissa. The body of the table contains mole fractions multiplied by 10² of acetaminophen in solution at saturation.

kg EtOH/kg	20.0°C	25.0°C	30.0°C	35.0°C	40.0°C
0	0.15	0.19	0.21	0.26	0.32
0.10	0.24	0.33	0.38	0.44	0.57
0.20	0.47	0.69	0.75	0.87	1.07
0.30	1.05	1.32	1.54	1.81	2.18
0.40	1.87	2.22	2.54	2.91	3.42
0.50	3.02	3.47	3.94	4.45	5.21
0.60	4.19	4.55	5.20	5.75	6.74
0.70	5.24	5.72	6.25	6.88	7.91
0.80	6.00	6.58	7.10	7.81	8.88
0.90	6.25	6.61	7.41	8.09	9.13
1	5.04	5.46	6.20	6.68	7.05

To manufacture acetaminophen a crystallizer must be used in order to extract acetaminophen powder. The crystallizer contains 1000 g of a saturated solution of acetaminophen (M = 151.7) in a 60/40 ethanol solution at 40 °C. It is required to crystallize 50 g of acetaminophen from this solution. To what temperature must the solution be cooled?

¹ Jackson A. Jimenez and Fleming Martinez. "Thermodynamic Magnitudes of mixing and solvation of acetaminophen in ethanol + water mixtures". Quimica, Volume 114 (2006) 87-99.

Solution

To solve this problem, the amount of acetaminophen present in solution is calculated, the amount to be crystallized out is subtracted and the new mass fractions are calculated. These are compared to the table to find out at what temperature they occur.

Entering the data table with 60/40 ethanol (0.60 kg EtOH/kg) and 40 °C the mole fraction is found to be $6.74 \times 10^{-2} = 0.0674$. Using these two pieces of data, we calculate the mole fractions, average molecular weight and the total amount of substance of the system:

$$x_{\text{EtOH}} + x_{\text{H}_2\text{O}} + x_{\text{acet}} = 1$$

$$x_{\text{EtOH}} + x_{\text{H}_2\text{O}} = 1 - x_{\text{Acet}} = 1 - 0.0674 = 0.9326$$

$$x_{\text{EtOH}} = 0.60 \times (x_{\text{EtOH}} + x_{\text{H}_2\text{O}}) = 0.60 \times 0.9326$$

$$x_{\text{EtOH}} = 0.5596$$

$$x_{\text{H}_2\text{O}} = 1 - x_{\text{acet}} + x_{\text{EtOH}}$$

$$x_{\text{H}_2\text{O}} = 0.3730$$

Now we use Equation 3.3-7 to determine the average molecular weight and moles present:

$$\bar{M} = 0.0674 \frac{\text{mol Acet}}{\text{mol}} \times 151.7 \frac{\text{g}}{\text{mol}} + 0.5596 \frac{\text{mol EtOH}}{\text{mol}} \times 46 \frac{\text{g}}{\text{mol}} + 0.3730 \frac{\text{mol H}_2\text{O}}{\text{mol}} \times 18 \frac{\text{g}}{\text{mol}}$$

$$\bar{M} = 42.7 \frac{\text{g}}{\text{mol}}$$

$$n = 1000 \text{ g} \times \frac{1 \text{ mol}}{42.7 \text{ g}} = 23.43 \text{ mol}$$

Using this we then determine the mass of acetaminophen present in the system:

$$n_{\text{acet}} = 23.43 \text{ mol} \times 0.0674 \frac{\text{mol Acet}}{\text{mol}} = 1.58 \text{ mol Acet}$$

$$m_{\text{acet}} = 1.58 \text{ mol Acet} \times 151.7 \frac{\text{g}}{\text{mol Acet}} = 240 \text{ g Acet}$$

Now we determine the amount of acetaminophen that is to be left in the system

$$n_{\text{remainder}} = (240 - 50) \text{ g Acet} = 190 \text{ g Acet}$$

We now convert this back into a mole fraction so we can use the table again to find the temperature at we need to resort to obtain this.

$$190 \text{ g Acet} \times \frac{1 \text{ mol}}{151.7 \text{ g}} = 1.25 \text{ mol Acet}$$

$$23.43 \text{ mol} - 1.25 \text{ mol Acet} = 22.18 \text{ mol}$$

$$x_{\text{Acet}} = \frac{n_{\text{acet}}}{\sum n} = \frac{1.25 \text{ mol}}{22.18 \text{ mol}} = 0.0563 = 5.63 \times 10^{-2}$$

When we examine the table to determine at what temperature 5.63×10^{-2} mol acetaminophen/mol occurs in our 60/40 solution, we find it is between 30 and 35 °C, requiring us to do linear interpolation (Equation 2.7-1):

$$y = y_1 + \frac{x - x_1}{x_2 - x_1} (y_2 - y_1)$$

Where:

$$y_1 = 30.0 \text{ }^\circ\text{C}$$

$$y_2 = 35.0 \text{ }^\circ\text{C}$$

$$x = 5.63$$

$$x_1 = 5.20$$

$$x_2 = 5.75$$

$$y = 30.0 \text{ }^\circ\text{C} + \frac{5.63 - 5.20}{5.75 - 5.20} (35.0 \text{ }^\circ\text{C} - 30.0 \text{ }^\circ\text{C})$$

$$y = \boxed{T = 33.9 \text{ }^\circ\text{C}}$$

Chapter 7

F&R 7.3 KM-5 (Sneaky 1st Law of Thermodynamics problem)

You have a medical radionucleotide tracer in an aqueous solution flowing through a leak proof horizontal pipe. A pump uses $\frac{1}{2}$ W of frictionless shaft work to force 0.166 kg/s of liquid up a 0.2 m incline to the top of a bottling machine. The liquid has a constant heat capacity of 1.05 kJ/kg·K. As the liquid leaves the top of the pipe it has lost one one-thousandth of a centigrade degree. Apply the first law of thermodynamics to this system and present your conclusions. Because this is a very dilute and highly sensitive substance, use high precision in your calculations. (*Hint: You should find something missing the first time*)

Solution

This problem is an excuse to make use of an almost universally ignored part of the 1st law of thermodynamics.

Our system is a very simple one on the surface but has one hidden catch that is likely to be missed the first time through by students (This is the intent).

We begin with our first law of thermodynamics for open systems (Equation 7.4-15):

$$\Delta\dot{H} + \Delta\dot{E}_k + \Delta\dot{E}_p = \dot{Q} - \dot{W}_s$$

We assume a constant velocity ($\Delta\dot{E}_k = 0$) and no heating ($\dot{Q} = 0$):

$$\Delta\dot{H} + \Delta\dot{E}_p = -\dot{W}_s$$

For enthalpy flow we substitute our already integrated heat capacity equation:

$$\Delta\dot{H} = \dot{m}C_p\Delta T$$

For potential energy flow, Equation 7.2-2a:

$$\Delta\dot{E}_p = \dot{m}gz$$

Therefore:

$$\dot{m}C_p\Delta T + \dot{m}gz = -\dot{W}_s$$

We substitute in values where know:

$$0.166 \frac{\text{kg}}{\text{s}} \times 1.05 \frac{\text{kJ}}{\text{kg} \cdot \text{K}} \times 0.001 \text{ C}^\circ + 0.166 \frac{\text{kg}}{\text{s}} \times 9.81 \frac{\text{m}}{\text{s}^2} \times 0.2 \text{ m} = -(-0.5 \text{ W})$$

Immediately it should appear that the problem is overspecified since there is nothing to solve for. Further calculations show that this is not exactly the case:

$$0.1743 \text{ W} + 0.325692 \text{ W} = 0.5 \text{ W}$$

Collecting like terms does not result in complete cancellation as normal though:

$$0 = 0.000008 \text{ W} = 8 \mu\text{W}$$

This is the true problem: Where did this go? The answer is given in the original definition of shaft work, which includes *radiation crossing the system boundary*. This 8 μW is then the amount of energy that leaves the system as radiation.

F&R 7.7 TB2.04 (High-pressure homogenization through an orifice)

Many potential drugs have low water solubility, hindering their transport in the body's aqueous material distribution medium (blood). One way to improve solubility is to decrease particle size below 1 μm diameter. One method to do this is by high pressure **homogenization**. In this process, the drug is dispersed in a solvent and forced through a narrow orifice at high pressure. As the liquid enters the orifice, it experiences a pressure drop so great it partially vaporizes. As it exits the constriction, the vapor bubbles collapse violently and produce local disturbances, breaking up the surrounding solid particles.

A high pressure homogenizer is being used to decrease the size of some drug particles. The particles are suspended in water at 25 °C and sent through the homogenizer at 250 mL per minute.¹ The pressure before the orifice is 5,000 psi and the diameter of the pipe is 0.1 m. Determine the maximum diameter orifice that send the pressure below the vapor pressure of water.

¹ "Products - Laboratory." Laboratory Equipment High Pressure Homogenizers Pharmaceutical Supplier. 2005. Bee International. 15 Feb 2009 <http://www.beei.com/products_lab.html>.

Solution

Since this is a mechanical problem we start with the mechanical energy equation (7.7-2):

$$\frac{\Delta P}{\rho} + \frac{\Delta u}{2} + g \Delta z + \hat{F} = \frac{-\dot{W}_s}{\dot{m}}$$

Now we start evaluating our data to determine what terms we may cancel. We are not given information on the friction of the system, the pump's shaft work, or change in height of streams. This reduces our equation to:

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

At this point we cannot make any further simplifications. We know there is a pressure change, so the first term is nonzero. Because of this, we need at least one other term in the equation.

Now, we begin to look up data. The vapor pressure of water at this temperature is found in Table B.3, the density of water is given in Equation 3.1-2:

$$\rho_{\text{H}_2\text{O}} = 1000 \text{ kg/m}^3$$

$$p^* = 23.786 \text{ mmHg}$$

To aid in the calculation, we convert all units to basic metric units:

$$p^* = P_2 = 3167.2 \text{ Pa} [=] \frac{\text{kg m}^2}{\text{s}^2}$$

$$P_1 = 5000 \text{ psi} = 34.5 \text{ MPa} = 34500000 \frac{\text{kg m}^2}{\text{s}^2}$$

$$\dot{V} = 250 \text{ mL/min} = 4.17 \times 10^{-6} \text{ m}^3/\text{s}$$

We now possess enough information to calculate the linear velocity at point 1:

$$u_1 = \frac{\dot{V}}{\pi \left(\frac{D}{2}\right)^2} = \frac{4.17 \times 10^{-6} \frac{\text{m}^3}{\text{s}}}{\frac{\pi}{4} (0.1 \text{ m})^2}$$

$$u_1 = 5.31 \times 10^{-4} \text{ m/s}$$

Entering this into our Bernoulli equation allows us to solve for the velocity at point 2.

$$\frac{(3167.2 - 34500000) \frac{\text{kg m}^2}{\text{s}^2}}{1000 \frac{\text{kg}}{\text{m}^3}} + \frac{u_2^2 - 2.82 \times 10^{-7} \frac{\text{m}}{\text{s}}}{2} = 0$$

$$u_2 = 263 \text{ m/s}$$

We now calculate diameter of the orifice

$$u_1 = \frac{\dot{V}}{\pi \left(\frac{D}{2}\right)^2} \Rightarrow D = 2 \sqrt{\frac{\dot{V}}{\pi u_1}}$$

$$D = 2 \sqrt{\frac{4.17 \times 10^{-6} \text{ m}^3/\text{s}}{\pi \times 263 \text{ m/s}}}$$

$$\boxed{D = 0.000142 \text{ m} = 142 \text{ } \mu\text{m}}$$

While small, this is much larger than the 1 μm particle diameter being sought.

Chapter 8

F&R 8.3a KM-4 (Friability tester analysis)

In pharmaceutical production, pills are subjected to significant forces. To ensure the pills will be able to withstand these forces without cracking or shattering, a **friability tester**¹ is used. A batch of proposed pills is made and put in a cylindrical drum which spins around at a fixed rate, lifting the pills up and then letting them fall.



If the pills survive without cracking, chipping or weight loss beyond the desired specification they are considered to have passed the test.

- (a) Apply the first law of thermodynamics to the three states (At rest, top of drum, bottom of drum) of a 300 mg pill in a 30 cm diameter drum. Neglect the rotational kinetic energy caused by the **vane** moving the pill.
- (b) Determine how much work has been done on the pill by the equipment
- (c) If the work done on the pill is converted to heat, what is the temperature increase if the pill is assumed to be made of pure cellulose ($C_p = 1.2$ kJ/kg K)

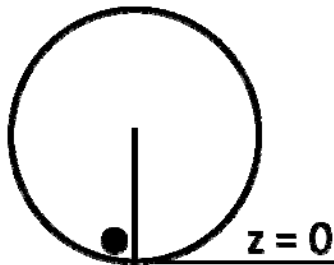
¹ See Varian, Inc.'s tester: <http://www.varianinc.com/cgi-bin/nav?products/dissolution/testing/friab>

² doi:10.1016/j.compositesa.2009.07.006

Solution

This problem is an excuse to use the ever ignored kinetic and potential energy terms in an equation and maybe review some physics, or show its application to nontraditional problems. It also may (just) explain why physics is a prerequisite for this course...

- (a) This part is almost entirely algebraic with no actual calculations. We begin by defining the bottom of the drum as $z = 0$ (cm). This allows us to set up our flowchart (Which will start to look a lot like a kinematics sheet from physics).



We now break out our equation (7.3-4):

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

And start cancelling terms. At rest there is no change in kinetic or potential energy, the system is not being heated and no work has been added to the system yet. All of the terms therefore are cancelled.

$$\Delta E_k = 0$$

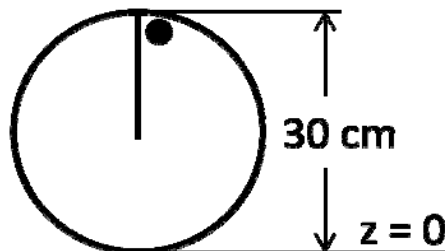
$$\Delta E_p = 0$$

$$Q = 0$$

$$W = 0$$

$$\therefore \Delta U = 0$$

Now we examine it at the extreme point in elevation (30 cm):



At this point the vane has ceased moving the pill and it begins to free fall. The potential energy is at its maximum but kinetic energy has not developed yet. Heat is still 0 and the internal energy of the system (pill) has not been changed.

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

$$\Delta E_k = 0$$

$$Q = 0$$

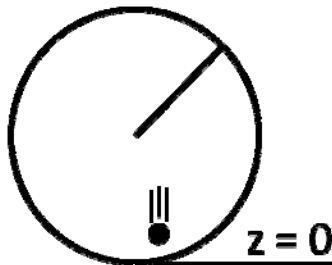
$$\Delta U = 0$$

Now, we actually have something to show, namely

$$\boxed{\Delta E_p = -W}$$

The testing equipment motor has put enough work in to the system to raise the pill by 30 cm (neglecting the energy required to get the cylinder rotating from a standstill).

Finally we analyze it in the final position, when the pill is at the end of its fall.



At this instant potential energy has returned to zero, but the pill possesses a maximum of kinetic energy.

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

$$\Delta E_p = 0$$

We cannot here decide what else to cancel based on the information given. The kinetic energy will be changed into some other form of energy, but it could be work (pill strikes drum and moves it slightly), heat (pill hits drum and friction heats up the pill) or internal energy (pill heats up). It should be reasonable to state that all of these will occur.

$$\boxed{\Delta U + \Delta E_k = Q - W}$$

(b) To find the work we must determine what relations we know of that include work. A review of the previous part of the problem immediately discovers the result of the second state:

$$\Delta E_p = -W$$

Now we refer back to the equation defining the potential energy, Equation 7.2-2a:

$$E_p = mgz$$

The Δ , signifying difference, results in:

$$\Delta E_p = mgz_f - mgz_i$$

This may also be expressed in a more compact way (Also a more useful way, given the way the data in the problem is specified):

$$\Delta E_p = mg(z_f - z_i) = mg\Delta z$$

Substituting values for variables and adding some conversion factors:

$$\begin{aligned} \Delta E_p = mg\Delta z &= 300 \text{ mg} \times 9.81 \frac{\text{m}}{\text{s}^2} \times 30 \text{ cm} \times \frac{1 \text{ m}}{100 \text{ cm}} \times \frac{1 \text{ g}}{1000 \text{ mg}} \times \frac{1 \text{ kg}}{1000 \text{ g}} \\ \Delta E_p &= 8.829 \times 10^{-4} \frac{\text{kg} \cdot \text{m}^2}{\text{s}^2} \end{aligned}$$

Using more conversion factors:

$$\Delta E_p = 8.829 \times 10^{-4} \frac{\text{kg} \cdot \text{m}^2}{\text{s}^2} \times \frac{\text{N} \cdot \text{s}^2}{\text{kg} \cdot \text{m}} \times \frac{\text{J}}{\text{N} \cdot \text{m}}$$

$$\Delta E_p = -W = 8.829 \times 10^{-4} \text{ J}$$

$$\boxed{W = -8.829 \times 10^{-4} \text{ J}}$$

- (c) Here we are given essentially the scenario from the end of part (a) and told that the work is converted into internal energy.

$$\Delta U = -W$$

We know from Equation 8.3-8 that we can integrate a heat capacity (C_v) to obtain the specific internal energy. Similarly, Equation 8.3-11 shows us that we can assume that our C_p is essentially equal to C_v for solids.

$$\Delta \hat{U} \approx \int_{T_1}^{T_2} C_v(T) dT$$

$$C_p \approx C_v$$

$$\Delta \hat{U} \approx \int_{T_1}^{T_2} C_p(T) dT$$

Now since C_p is a constant (It is given as such), we may factor it out of the integral:

$$\Delta \hat{U} \approx C_p \int_{T_1}^{T_2} dT$$

This is easily integrated:

$$\Delta \hat{U} \approx C_p \Delta T$$

Here we should make a decision on how we will convert between specific and actual internal energies. We can either multiply the former by the mass of the pill or divide the latter by it.

$$\Delta \hat{U} \approx C_p \Delta T$$

$$m \Delta \hat{U} \approx m C_p \Delta T$$

$$\Delta U \approx m C_p \Delta T$$

Rearranging:

$$\Delta T \approx \frac{-W}{m C_p}$$

$$\Delta T \approx 8.829 \times 10^{-4} \text{ J} \times \frac{1}{300 \text{ mg}} \times \frac{\text{kg} \cdot \text{K}}{1.2 \text{ kJ}} \times \frac{1 \text{ kJ}}{1000 \text{ J}} \times 1000 \frac{\text{mg}}{\text{g}} \times 1000 \frac{\text{g}}{\text{kg}}$$

Note that two of the 1000s cancel. Performing the math results in:

$$\boxed{\Delta T \approx 0.00245 \text{ K} = 0.00245 \text{ }^\circ\text{C}}$$

F&R 8.4d TB1.19 (Product storage)

Note: This problem was a rehash of problem 8.74 in the current (3rd) edition of F&R. To save space and time, the entire problem will not be recapitulated. The description of the problem would be changed to the following:

Powders used in pharmaceutical manufacturing must be kept dry to prevent **clumping**. In hot and humid climates, this is accomplished by an air conditioner. In air conditioners, outside air is drawn into a cooler, which causes water to condense and then reheated to a desired temperature, at which point it has the same absolute humidity as the inside (room) air. Sucrose powder, commonly used in the manufacture of drug tablets, is to be stored at 75 °F and 40% relative humidity.

Solution

The solution to this problem is the same as for Problem 8.74 in F&R, only the problem statement has been changed.

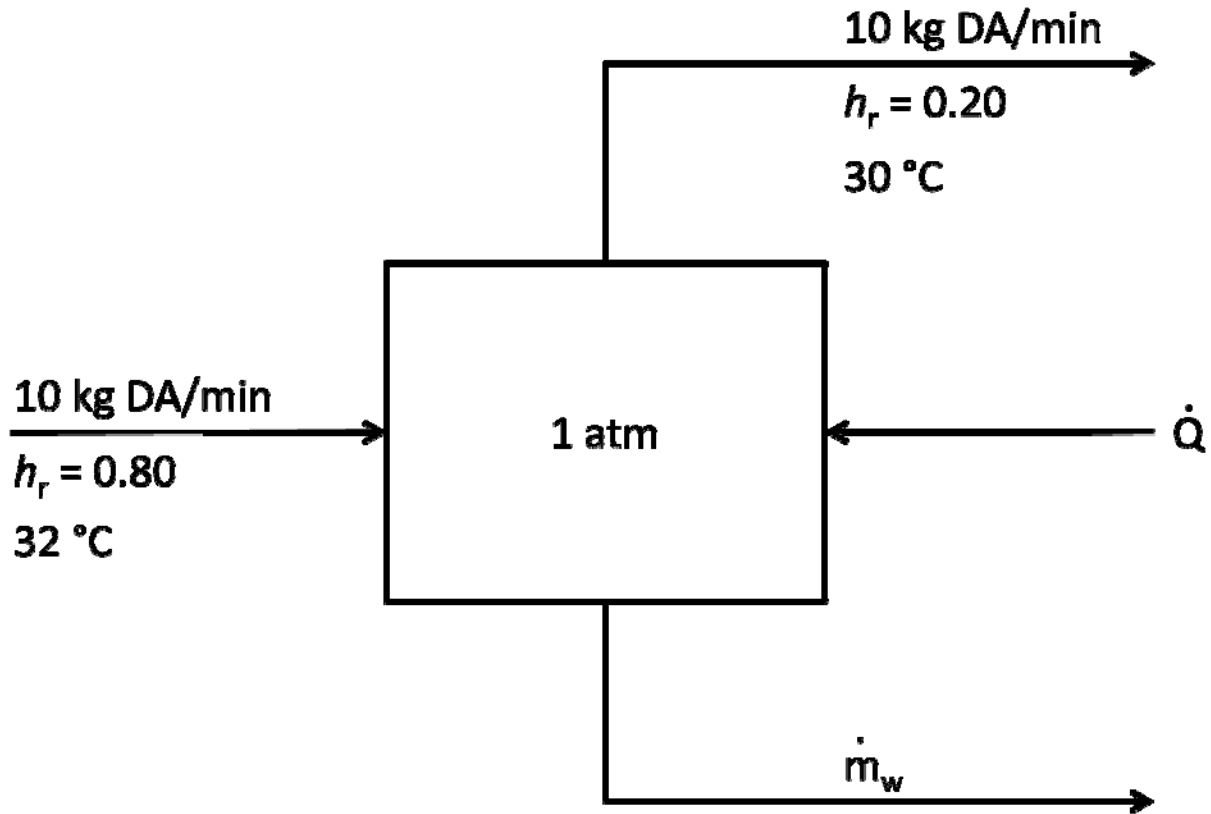
F&R 8.4d TB1.17 (Dehumidification of powders)

As anyone who has used a salt shaker on a summer day knows, powders will **clump** at high humidity. This is a problem in pharmaceutical processes where large amounts of powder must be used. Lactose powder, a common **filler** (volume increasing agent), flows best at 20% relative humidity. To obtain this, the air in the powder is supplied from a dehumidifier. If 10 kg DA/min of filtered room air at 32 °C enters with 80% relative humidity and exits at 30 °C with 20% relative humidity:

- (a) How much water is removed from the air per minute?
- (b) What is the **heat duty** in an hour of operation?

Solution

To begin any problem of this sort, the first step must be to draw and label a flow chart:



To produce this, the following assumptions were made:

1. Steady state
2. Open system
3. $P_{\text{throughout}} = 1 \text{ atm} / \Delta P = 0$
4. $\Delta \dot{E}_p = \Delta \dot{E}_k = \dot{W}_s = 0$
5. Exit streams are in thermal equilibrium

(a) Now, we perform mass analysis first (Determining flow rates, etc.). For this problem, this means solving for \dot{m}_w . To do this we set up our equation:

$$\dot{m}_{\text{in}} = \dot{m}_w + \dot{m}_{\text{out}}$$

The mass flow rates of water may be determined from the psychrometric chart after noting that we have the three intensive variables needed to fix the state of each stream (Relative humidity, temperature and pressure = 1 atm).

Consulting the psychrometric chart, we find the absolute humidities for the two vapor streams:

$$\begin{array}{l}
 T = 32 \text{ }^\circ\text{C} \\
 T = 30 \text{ }^\circ\text{C}
 \end{array}
 \left. \vphantom{\begin{array}{l} T = 32 \text{ }^\circ\text{C} \\ T = 30 \text{ }^\circ\text{C} \end{array}} \right\} \xrightarrow{\text{Figure 8.4-1}}
 \begin{array}{l}
 h_a (80\%) = 0.0275 \text{ kg/kg DA} \\
 h_a (20\%) = 0.0052 \text{ kg/kg DA}
 \end{array}$$

These we may then incorporate into our mass equation from previously:

$$10 \frac{\text{kg DA}}{\text{min}} \times 0.0275 \frac{\text{kg}}{\text{kg DA}} = \dot{m}_w + 10 \frac{\text{kg DA}}{\text{min}} \times 0.0052 \frac{\text{kg}}{\text{kg DA}}$$

$$0.275 \frac{\text{kg}}{\text{min}} = \dot{m}_w + 0.052 \frac{\text{kg}}{\text{min}}$$

$$\boxed{\dot{m}_w = 0.223 \text{ kg/min}}$$

(b) To obtain the heat duty, we write our energy equation, simplify it and expand it:

$$\Delta\dot{H} + \Delta\dot{E}_k + \Delta\dot{E}_p = \dot{Q} - \dot{W}_s$$

$$\dot{Q} = \Delta\dot{H}$$

$$\Delta\dot{H} = \sum_{\text{out}} \dot{m}\hat{H} - \sum_{\text{in}} \dot{m}\hat{H}$$

Now we construct our enthalpy table:

References: DA (0 °C, 1 atm), H₂O (L, 0 °C, 1 atm)

	m_{in}	H_{in}	m_{out}	H_{out}
Substance	(kg/min)	(kJ/kg)	(kg/min)	(kJ/kg)
Dry air	10	H_1	10	H_2
H ₂ O(l)	—	—	0.223	H_3

Now we obtain the enthalpies from the psychrometric chart:

$$\begin{array}{l}
 \hat{H}_1 = 90.3 \text{ kJ/kg DA} \\
 \hat{H}_2 = 42.6 \text{ kJ/kg DA}
 \end{array}
 \xrightarrow{\text{Figure 8.4-1}}$$

We have to use the heat capacity to obtain the enthalpy of the liquid water. Since our reference is liquid water at 0 °C. We assume it is in thermal equilibrium with the air exiting the system.

$$\hat{H}_3 = C_p \Delta T = 4.187 \frac{\text{kJ}}{\text{kg C}^\circ} \times (30 - 0) \text{ C}^\circ$$

$$\hat{H}_3 = 126 \frac{\text{kJ}}{\text{kg}}$$

Now the actual heat:

$$\dot{Q}_{\text{cond}} = 10 \frac{\text{kg}}{\text{min}} \times \hat{H}_2 + 0.223 \frac{\text{kg}}{\text{min}} \times \hat{H}_3 - 10 \frac{\text{kg}}{\text{min}} \times \hat{H}_1$$

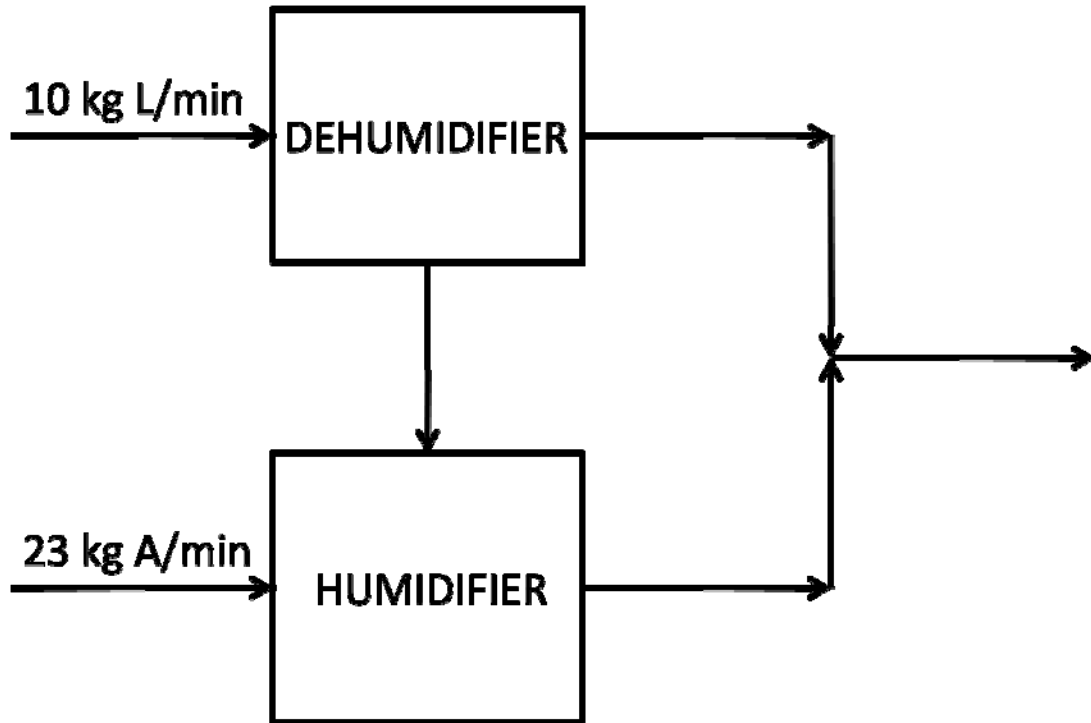
$$\dot{Q}_{\text{cond}} = 10 \frac{\text{kg DA}}{\text{min}} \times 42.6 \frac{\text{kJ}}{\text{kg DA}} + 0.223 \frac{\text{kg DA}}{\text{min}} \times 126 \frac{\text{kJ}}{\text{kg DA}} - 10 \frac{\text{kg DA}}{\text{min}} \times 90.3 \frac{\text{kJ}}{\text{kg DA}}$$

$$\dot{Q}_{\text{cond}} = -449 \frac{\text{kJ}}{\text{min}}$$

$$\boxed{\dot{Q}_{\text{cond}} = -7.48 \text{ kW}}$$

F&R 8.4d TB1.18 (Powder flows as a function of moisture)

Lactose and Avicel are the two **excipients**, or inactive ingredients in pharmaceutical preparations. At a pharmaceutical production plant it is required to dry the lactose powder and humidify the Avicel. An enterprising engineer seeking process elegance has determined to use the water from the dehumidifier to feed the humidifier, as shown below:



The air in the lactose powder enters at 80% relative humidity and leaves the condenser at 20% relative humidity, while the air surrounding Avicel enters the humidifier at 40% relative humidity and leaves at 80% relative humidity for optimal flow. Assume that air flow in the feed streams equals one tenth of the mass flow of each powder. Careful cooling ensures that the processes run at a constant 25 °C and 1 atm.

- What is the product composition and flow?
- How much water is leaving the condenser?
- How much water does the humidifier require? If the supply from the condenser isn't enough, how much makeup water is required?
- What are the heat duties of the condenser and humidifier (Assume humidifier feed meets requirement)? What is the energy gain/loss for the entire system?
- Is the reuse stream a good idea? List possible benefits and problems

Solution

This is a fairly involved mass and energy system analysis. The equations are overall simple, but an understanding of the system and its streams is required. Knowledge of the use of the psychrometric chart is also required.

For all of the solutions, we assume an open system at steady state.

(a) Determining the product of the mixing is very easy (by now):

$$\sum_{\text{in}} \dot{m} = \sum_{\text{out}} \dot{m}$$

$$\dot{m}_{\text{out}} = (10 + 23) \text{ kg/min} = 33 \text{ kg/min}$$

$$x_A = \frac{\dot{m}_A}{\sum \dot{m}} = \frac{23}{33} = \boxed{0.697}$$

$$x_L = 1 - x_A = 1 - 0.697 = \boxed{0.303}$$

(b) To determine the water leaving the condenser, we refer to the psychrometric chart and obtain the absolute humidities.

$$\left. \begin{array}{l} P = 1 \text{ atm} \\ T = 25 \text{ }^\circ\text{C} \end{array} \right\} \xrightarrow{\text{Figure 8.4-1}} \begin{array}{l} h_a (80\%) = 0.016 \text{ kg/kg DA} \\ h_a (20\%) = 0.004 \text{ kg/kg DA} \end{array}$$

Now a simple application of the mass equation shows the flow of water out:

$$\sum_{\text{in}} \dot{m} = \sum_{\text{out}} \dot{m}$$

$$1 \frac{\text{kg DA}}{\text{min}} \times 0.016 \frac{\text{kg}}{\text{kg DA}} = \dot{m}_{\text{cond}} + 1 \frac{\text{kg DA}}{\text{min}} \times 0.004 \frac{\text{kg}}{\text{kg DA}}$$

$$\dot{m}_{\text{cond}} = \boxed{0.012 \text{ kg/min}}$$

(c) We do the same thing again to determine the water flow in to the humidifier.

$$\left. \begin{array}{l} P = 1 \text{ atm} \\ T = 25 \text{ }^\circ\text{C} \end{array} \right\} \xrightarrow{\text{Figure 8.4-1}} \begin{array}{l} h_a (40\%) = 0.008 \text{ kg/kg DA} \\ h_a (80\%) = 0.016 \text{ kg/kg DA} \end{array}$$

$$2.3 \frac{\text{kg DA}}{\text{min}} \times 0.008 \frac{\text{kg}}{\text{kg DA}} = \dot{m}_{\text{humid}} + 2.3 \frac{\text{kg DA}}{\text{min}} \times 0.016 \frac{\text{kg}}{\text{kg DA}}$$

$$\dot{m}_{\text{humid}} = 0.0184 \text{ kg/min}$$

To answer the other part of the question, this is more than the humidifier supplies, so we will need a makeup stream of

$$\dot{m}_{\text{makeup}} = \dot{m}_{\text{humid}} - \dot{m}_{\text{cond}} = (0.0184 - 0.012) \text{ kg/min}$$

$$\dot{m}_{\text{makeup}} = 0.0064 \text{ kg/min}$$

(d) We begin with our energy analysis by taking the open system first law of thermodynamics and simplifying:

$$\Delta \dot{H} + \Delta \dot{E}_k + \Delta \dot{E}_p = \dot{Q} - \dot{W}_s$$

Assuming no shaftwork or kinetic/potential energy changes ($\Delta \dot{E}_k = \Delta \dot{E}_p = \dot{W}_s = 0$):

$$\dot{Q} = \Delta \dot{H}$$

$$\dot{Q} = \sum_{\text{out}} \dot{m} \hat{H} - \sum_{\text{in}} \dot{m} \hat{H}$$

We now have to set up our enthalpy table:

References: DA (0 °C, 1 atm), H₂O (L, 0 °C, 1 atm)

	m_{in}	H_{in}	m_{out}	H_{out}
Substance	(kg/min)	(kJ/kg)	(kg/min)	(kJ/kg)
Dry air	1	H_1	1	H_2
H ₂ O(l)	—	—	0.012	H_3

We refer to the psychrometric chart:

$$\begin{array}{l} \xrightarrow{\text{Figure 8.4-1}} \hat{H}_1 = 65.9 \text{ kJ/kg DA} \\ \hat{H}_2 = 34.7 \text{ kJ/kg DA} \end{array}$$

We have to use the heat capacity to obtain the enthalpy of the liquid water. Since our reference is liquid water at 0 °C:

$$\hat{H}_3 = C_p \Delta T = 4.187 \frac{\text{kJ}}{\text{kg C}^\circ} \times (25 - 0) \text{ C}^\circ$$

$$\hat{H}_3 = 105 \frac{\text{kJ}}{\text{kg}}$$

Now we add the values to our equation and determine heat flow:

$$\dot{Q}_{\text{cond}} = 1 \frac{\text{kg}}{\text{min}} \times \hat{H}_2 + 0.012 \frac{\text{kg}}{\text{min}} \times \hat{H}_3 - 1 \frac{\text{kg}}{\text{min}} \times \hat{H}_1$$

$$\dot{Q}_{\text{cond}} = 1 \frac{\text{kg DA}}{\text{min}} \times 34.7 \frac{\text{kJ}}{\text{kg DA}} + 0.012 \frac{\text{kg DA}}{\text{min}} \times 105 \frac{\text{kJ}}{\text{kg DA}} - 1 \frac{\text{kg DA}}{\text{min}} \times 65.9 \frac{\text{kJ}}{\text{kg DA}}$$

$$\dot{Q}_{\text{cond}} = -30 \frac{\text{kJ}}{\text{min}}$$

$$\boxed{\dot{Q}_{\text{cond}} = -0.5 \text{ kW} = -500 \text{ W}}$$

The humidifier method is the same but with different flows and enthalpies.

$$\Delta \dot{H} + \Delta \dot{E}_k + \Delta \dot{E}_p = \dot{Q} - \dot{W}_s$$

Assume $\Delta \dot{E}_k = \Delta \dot{E}_p = \dot{W}_s = 0$:

$$\dot{Q} = \Delta \dot{H}$$

$$\dot{Q} = \sum_{\text{out}} \dot{m} \hat{H} - \sum_{\text{in}} \dot{m} \hat{H}$$

Enthalpy table:

References: DA (0 °C, 1 atm), H₂O (L, 0 °C, 1 atm)

	m_{in}	H_{in}	m_{out}	H_{out}
Substance	(kg/min)	(kJ/kg)	(kg/min)	(kJ/kg)
Dry air	2.3	H_1	2.3	H_2
H ₂ O(l)	0.0184	H_3	—	—

Psychrometric chart:

$$\begin{array}{l} \xrightarrow{\text{Figure 8.4-1}} \hat{H}_1 = 45 \text{ kJ/kg DA} \\ \hat{H}_2 = 66.5 \text{ kJ/kg DA} \end{array}$$

The third specific enthalpy is the same as the water stream that is leaving the condenser.

$$\hat{H}_3 = 105 \frac{\text{kJ}}{\text{kg}}$$

Now we add the values to our equation and determine heat flow:

$$\begin{aligned} \dot{Q}_{\text{humid}} &= 2.3 \frac{\text{kg DA}}{\text{min}} \times \hat{H}_2 - \left[0.0184 \frac{\text{kg}}{\text{min}} \times \hat{H}_3 + 2.3 \frac{\text{kg DA}}{\text{min}} \times \hat{H}_1 \right] \\ \dot{Q}_{\text{humid}} &= 2.3 \frac{\text{kg DA}}{\text{min}} \times 66.5 \frac{\text{kJ}}{\text{kg DA}} - \left[0.0184 \frac{\text{kg}}{\text{min}} \times 105 \frac{\text{kJ}}{\text{kg}} + 2.3 \frac{\text{kg DA}}{\text{min}} \times 45 \frac{\text{kJ}}{\text{kg DA}} \right] \\ \dot{Q}_{\text{humid}} &= +47.5 \frac{\text{kJ}}{\text{min}} \end{aligned}$$

$$\boxed{\dot{Q}_{\text{humid}} = +0.8 \text{ kW} = +800 \text{ W}}$$

Finally, we can sum the two and obtain the overall heat flow for the system.

$$\dot{Q} = \sum \dot{Q} = (-500 + 800) \text{ W}$$

$$\boxed{\dot{Q} = +300 \text{ W}}$$

- (e) Possible problems include cross contamination and unsanitaryness. Benefits include solvent economy and certainty of composition of solvent.