

Lesson 3: Calculations used when compounding medications

Pharmacists and pharmacy technicians all compound medications in one way or another, at least at some point in their careers, and you will try your hand at it soon, if you have not already. The most common compounding you are likely to do is preparation of intravenous (IV) solutions. This compounding is fairly straightforward and will involve primarily proportional calculations. There will be times when you will need to determine the osmolarity of an IV solution. Finally, you may need to change the concentration of an already-mixed IV solution, so you will need to know how to dilute or concentrate that solution.

You will likely also compound medications for topical application or administration via some body orifice. There are calculations you will need to perform to ensure that ingredients are properly weighed and that solutions for mucous membranes are isotonic, so they do not harm tissues. You may have to dilute or concentrate a topical or other compounded product. You will need to understand how buffers work, when they are needed, and be able to perform buffer solution calculations.

The purpose of this lesson is to review all of the calculations you will need in order to do those things just described, which include:

- proportional calculations
- determination of osmolarity
- isotonicity calculations
- dilution and concentration of previously-prepared medications
- aliquots
- buffer system calculations.

Common lingo used in the IV room

There are a few important terms that you need to become familiar with prior to moving on to calculations in this lesson. The first one is *stock solution*. A stock solution is the most concentrated form of a drug that you can put your hands on. Sometimes a stock solution will be pure drug in powder or crystalline form (I know, I know: it's not a solution then, but people may call it that, anyway). At other times it will be a liquid or a solid paste or cream.

The second term you will need to understand is the word *bag*. In the world of pharmacy, a bag is a flexible, soft plastic container filled with a sterile fluid (it looks vaguely like a heavy-duty, half-empty water balloon). Bags often have liquid forms of medication added to them (which are not-so-imaginatively referred to as *additives*), and the contents of the bag are then infused straight into a patient's vein (through tubing that is usually connected to a pump). Different sizes of bags will hold different volumes of fluid. Bag volumes used commonly contain 50ml, 100ml, 250ml, 500ml, or 1000ml amounts of fluid, commonly D5W or NS. Larger bags of fluid (250ml, 500ml, and 1000ml) will have medication added to them which will infuse in over a long period of time (hours), and are often referred to as *drips*. Little bags (50ml, 100ml bags) are often called IV "piggybacks," abbreviated IVPB, since they are piggybacked onto the tubing of a solution already infusing into the patient. Use of these small bags for medication administration has declined over the past decade in favor of syringes, which are placed in an pump for medication administration.

Another term you will need to know is *standard concentration*. A standard concentration is a set volume and concentration of a commonly-made medication. The medication concentration and volume is pre-determined by nursing and pharmacy, and then all bags of that medication are prepared based on the specified recipe. To illustrate how standard concentrations work, let's say that a physician decided that a patient needed an intravenously-administered drug called dopamine. The physician would just write the word "dopamine" on the order, plus the desired infusion rate, for example 5 mcg/kg/minute, and the pharmacy will automatically place 400mg of dopamine in a 250ml bag of D5W. Every institutional and home health care pharmacy will have available a list of standard concentrations for intravenous medication infusions. An example of a list of standard concentrations such as might be found in a hospital can be seen in the box below. Some standard concentrations are so standard between pharmacies that manufacturers have decided to prepare and market them commercially. For instance, when I was back in pharmacy school (yes, dinosaurs *were* extinct by then), we would prepare a lidocaine drip by placing 2g of lidocaine in a bag containing 500ml D5W. In the mid-'80s, manufacturers started selling a pre-mixed lidocaine bag at the same concentration, so if you work in a hospital pharmacy you will probably never need to mix this particular

lidocaine drip. It is important to understand what standard concentrations are, because a doctor or nurse may ask you to “double concentrate” a drip. This means you will have to prepare the drip at double the standard concentration.

An example of a list of standard concentrations for a hospital.

aminophylline	250mg/250ml D5W
dobutamine	250mg/250ml D5W
dopamine	400mg/250ml D5W
heparin	25,000 units/500ml D5W
insulin	25 units/250ml NS
lidocaine	2g/500ml D5W
magnesium	40g/500ml D5W
nitroglycerin	50mg/250ml D5W (glass bottle)
nitroprusside	50mg/250ml D5W (wrap)
oxytocin	30 units/1000ml
procainamide	1g/250ml D5W

Proportional Calculations

You will use proportional calculations *a lot* in pharmacy, especially in the IV room. This is great, because you already know how to do these types of calculations. Proportional calculations involve using an available drug concentration and a desired final drug amount (in either weight or volume) to determine the amount of each individual ingredient to add. Just like that. If you cook, you’ve probably done proportional calculations, even if you cook using only a can-opener and a microwave.

Red Alert!! An important message regarding proportional calculations. Some students try to do proportional calculations using a series of calculations that look like this:

$$\frac{a}{b} = \frac{x}{c} \quad \text{solving for } x \text{ by multiplying (a)(c) and dividing by (b)}$$

If this is the way you are used to doing proportional calculations, then realize that although you *can* get the correct answer this way, it is also possible to get the *incorrect* answer. This is particularly true if you don’t write out the units for (a), (b), and (c), and if there other variables such as (d) and (e) involved. Because you are dealing with medications that could harm and in some cases even kill patients if the dose is miscalculated, you *must* use a method that will allow you to get the right answer every time. If you didn’t learn about dimensional analysis in your high school mathematics classes, it would be in your best interest to learn it now. Dimensional analysis is a method of checking an equation or solution to a problem by the way you set up the dimensions (units of measurement). If the two sides of an equation do not have the same dimensions, the equation is wrong. If they do have the same dimensions, then the equation is set up correctly. (I learned about this in high school, but not by the fancy name. It was called the “make sure all your units cancel out, leaving the ones you want” method. I think. Or maybe Mr. Kays told us the name and I wasn’t listening. Always a possibility.) This is how it works:

1. Write out your final units (the units you would like to arrive at) on the right hand side of the page *first*. Leave a small space to the left, and then write an = sign.
2. On the left hand side of the page, begin to line up all of your available data. Be sure to include a unit for every number. If you’re dealing with more than one drug or drug strength, assign a drug name to all necessary units.
3. Flip-flop proportions as needed so that the units cancel out. Make sure that all possible units cross out. If you have done it correctly, you will end up with the same units in the numerator (and denominator, if appropriate) of the final units on the right-hand side of the equation. If you have additional units left that have not cancelled out, then you have missed an important dimension or included an unnecessary one.
4. Perform your calculations.

If you do this, you can feel comfortable that your answer is correct, as long as you punched the correct numbers on your calculator (“always double check,” a motto to live by...). You can see an example of the above steps in Lesson 2 and you will see more in this lesson. Again, this is called dimensional analysis and is vitally important if you intend to get the right dose to the patient. “First, do no harm.”

Back to proportional calculations in the IV room. Most commonly, you will usually be measuring out calculated volumes of stock solutions and adding them to some fluid (usually NS or D5W), producing more dilute solutions of drugs intended for administration to patients. Let’s look at some examples:

An easy example. You need to mix syringes filled with 1g cefazolin in 20ml diluent. Your stock solution contains 200mg cefazolin/ml. You want to know how many milliliters of the stock solution you will need to draw up and place in an empty, sterile 20ml syringe (and then you will add diluent to the syringe to fill it up the rest of the way to 20ml). Each of the steps in dimensional analysis is noted.

Step 1: write out your final units first

$$= \text{_____ ml cefazolin stock solution to add to each syringe}$$

Step 2: line up your available data

$$1000\text{mg} \quad \frac{200\text{mg}}{\text{ml}} \quad = \text{_____ ml cefazolin stock solution to add to each syringe}$$

Step 3: flip-flop proportions where necessary to ensure that units cancel out

$$1000\text{mg} \quad \frac{1 \text{ ml}}{200\text{mg}} \quad = \text{_____ ml cefazolin stock solution to add to each syringe}$$

Step 4: perform your calculations:

$$1000\text{mg} \times \frac{1 \text{ ml}}{200\text{mg}} = 5 \text{ ml cefazolin stock solution to add to each syringe}$$

You will then add an additional 15ml of D5W or NS, or whatever the diluent used for your standard concentration, to make a total of 20ml in each syringe.

A more complicated example. Your pharmacy’s standard dopamine drip concentration is 400mg/250ml D5W. You receive a request from the nurse to “double concentrate” the solution. This means you will want to double the concentration (i.e., multiply the numerator by 2 *or* divide the denominator by 2). First, you will need to choose the final volume that you will mix. From your available bag sizes, let’s say you decide to use a 100ml bag of D5W, because using less drug is cheaper. Dopamine is available in your pharmacy as a stock solution of 80mg/ml in 10ml vials. You will need to calculate how much dopamine stock solution to add to your 100ml bag of D5W in order to produce a 100ml bag of the correct concentration of dopamine. SS = stock solution

Step 1: write out your final units first

$$= \text{_____ ml of dopamine 80mg/ml stock solution 100ml}$$

Step 2: Assemble your data. You know that your usual concentrate is 400mg/250ml, that you need to double this concentration, that your stock solution is 80mg/ml and that you are going to place the contents in a 100ml bag.

$$\frac{400 \text{ mg}}{250 \text{ ml}} \quad 2 \quad \frac{80 \text{ mg SS}}{\text{ml}} \quad 100\text{ml} \quad = \text{_____ ml of dopamine 80mg/ml stock solution 100ml}$$

Step 3: flip-flop proportions where necessary to ensure that units cancel out

$$\frac{400 \text{ mg}}{250 \text{ ml}} \times 2 \times \frac{1 \text{ ml SS}}{80 \text{ mg}} \times 100 \text{ ml} = \underline{\hspace{2cm}} \text{ ml of dopamine 80mg/ml stock solution 100ml}$$

Step 4: perform your calculations:

$$\frac{400 \text{ mg}}{250 \text{ ml}} \times 2 \times \frac{1 \text{ ml SS}}{80 \text{ mg}} \times 100 \text{ ml} = 4 \text{ ml of dopamine 80mg/ml stock solution}$$

In the problems at the end of this lesson, you will not need to write out all the steps. Instead, you will write out the final step, realizing that you have done the first three steps in your head as you wrote the fourth step down.

Osmolarity

Osmolarity is an important factor to consider when mixing solutions for instillation into body fluids, particularly blood or eye fluids. You may remember studying passive diffusion across a membrane, in general chemistry, and how fluid amount will change on each side of a membrane in an attempt to preserve particulate concentration (as long as the membrane is permeable to the fluid). As noted in Lesson 2, the total number of particles in a given fluid is directly proportional to its osmotic pressure, therefore we measure the particles in milliosmoles. The term “osmolarity” is used to describe the number of milliosmoles in a given amount of solution: one liter.

Infusion of solutions into the bloodstream that have greater or fewer solute particles than the blood will cause fluid to shift between the blood cells and the serum, in an attempt to equilibrate the particulate distribution. When you infuse a solution intravenously into a patient, it would be ideal to match the blood osmolarity (around 300 mOsmol/L) as closely as possible. An osmolarity quite a bit lower (i.e., more dilute) than the blood osmolarity will cause the red blood cells to take on extra fluid in an attempt to equilibrate osmolarity on either side of the blood cell membrane. If they swell too much, they will burst, spilling their contents into the serum and, at least with the red blood cells, making them unavailable for oxygen transport. An osmolarity quite a bit higher (i.e., more concentrated) than the serum would result in a fluid shift from within the blood cell to outside the membrane, causing the cell to shrink (crenation) and interfering with its ability to perform its usual physiologic functions. Because osmolarity is used here in the context of body fluid, rather than just any ol’ solution, it is given a special name: *tonicity*. You should use the terms *hypotonic* rather than *hypo-osmotic*, *hypertonic* rather than *hyperosmotic*, and *isotonic* rather than *iso-osmotic*, whenever you are referring specifically to the osmolarity of body fluids, although in practice, people tend to use them interchangeably.

To calculate the osmolarity of a solution, you will need to be given a solution concentration, be able to locate the molecular weight of the solution concentration, and be able to figure out the species, just as you did in Lesson 2. The only thing different in milliosmoles versus osmolarity calculations, is that in osmolarity you will always normalize the volume to one liter.

Let’s look at an example. We’ll calculate the osmolarity of D5W (5% dextrose in water).

Step 1: write out your final units first

$$= \frac{\hspace{2cm}}{\text{L}} \text{ mOsmol}$$

Step 2: line up your available data

$$\frac{5 \text{ g dextrose}}{\text{dL}} \quad \frac{180 \text{ mg dextrose}}{\text{mmol}} \quad \frac{1000 \text{ mg}}{\text{g}} \quad \frac{1 \text{ mOsmol}}{\text{mmol}} \quad \frac{10 \text{ dL}}{\text{L}} = \frac{\hspace{2cm}}{\text{L}} \text{ mOsmol}$$

Step 3: flip-flop proportions where necessary to ensure that units cancel out

$$\frac{5 \text{ g dextrose}}{\text{dL}} \quad \frac{\text{mmol}}{180 \text{ mg dextrose}} \quad \frac{1000 \text{ mg}}{\text{g}} \quad \frac{1 \text{ mOsmol}}{\text{mmol}} \quad \frac{10 \text{ dL}}{\text{L}} = \frac{\hspace{2cm}}{\text{L}} \text{ mOsmol}$$

Step 4: perform your calculations:

$$\frac{5\text{g dextrose}}{\text{dL}} \times \frac{\text{mmol}}{180\text{mg dextrose}} \times \frac{1000\text{mg}}{\text{g}} \times \frac{1\text{ mOsmol}}{\text{mmol}} \times \frac{10\text{ dL}}{\text{L}} = 278 \frac{\text{mOsmol}}{\text{L}}$$

This compares favourably to the osmolarity of blood.

Often a calculated osmolarity will differ slightly from a measured osmolarity. This is because bonding forces may fractionally affect the species, rendering it slightly above or below a whole number.

Isotonicity

As mentioned previously, it is desirable to match the tonicity of body fluids as closely as possible when administering a drug into that body fluid. Solutions which are not isotonic with the body fluid produce a painful stinging sensation when administered. Isotonicity is most commonly taken into account in the preparation of eye drops and nasal solutions.

To ensure isotonicity, you will need to be able to equate everything administered into the body to sodium chloride, since sodium chloride is the major determinate of blood and body fluid osmolarity.

So, when faced with an isotonicity problem you will need to know:

- the amount of drug in whatever amount of solution you're making
- the sodium chloride equivalent [E] for that drug*
- the concentration of NaCl nearest to blood concentration; this is called "normal saline" and is 0.9% NaCl.

What is a sodium chloride equivalent? Well, if you were to make up a solution of normal saline (isotonic to body fluids) and then add the drug to it, you would end up with a solution that was hypertonic compared to body fluids, because you would have around 310 mOsmol/L contributed by the normal saline, plus the particulates that the drug you added would contribute. It would be best if you could add saline in a concentration that was just hypotonic enough so that when you added the drug, the resulting osmolarity of the solution would be around 310 mOsmol/L: isotonic. What you need to figure out is what amount of sodium chloride the drug you are adding is *equivalent* to. In other words, if you add the amount of drug to the diluent, you will get a certain osmolarity, let's say x mOsmol/L. How much sodium chloride would you add to the same volume of diluent in order to produce the same osmolarity (x mOsmol/L)? This is what you want to know. Once you know this, you can add the drug and then just the right amount of sodium chloride in order to produce an isotonic solution. The relationship between the amount of drug that produces a particular osmolarity and the amount of sodium chloride that produces the same osmolarity is called the sodium chloride equivalent, which many people call the "E value" for short.

How can you determine a sodium chloride equivalent for a drug? The absolute best way is to examine the difference between the freezing point of the drug and normal saline. Both osmotic pressure and freezing point are driven by the number of particles in the solution, so measuring the one can tell you the other. But you likely don't have the equipment or the time (or the interest) to do this when you get a prescription for an eye drop to be compounded and the patient is not-so-patiently waiting for you to mix it. Fortunately, there are several excellent lists of sodium chloride equivalents for many drugs. By far the most extensive list is in the most recent version of Remington: The Science and Practice of Pharmacy (which everyone calls "Remington's" for short) so if you do any compounding of eye or nasal solutions, you should have a copy of this.

What if the drug listed isn't in any of your resources? You can do a literature search to see if someone has published this information but, failing that, there is a way to guestimate the E-value. It won't be perfectly spot on, but it will be close enough. For the drug you want to compound, you will need to find out the molecular weight and figure out the number of ions into which the drug could potentially dissociate (this is called "i," for ionization). If it doesn't dissociate, then $i = 1$. Since normal saline is around 80% ionized, you will add 0.8 for each additional ion (beyond 1) into which the drug dissociates. Thus a drug dissociating into two ions would have an i of 1.8, once dissociating into 3 ions have an i of 2.6, etc. The rest is simple. The relationship between NaCl's molecular weight and its i , and the drug's molecular weight and its i , can be expressed mathematically, thus:

$$E = \frac{58.5}{i}$$

MW (of drug)/i

You will find the numbers easier to punch through your calculator if the equation is rearranged:

$$E = \frac{(58.5)(i)}{(\text{MW of drug})(1.8)}$$

Anyway, once you know the amount of drug, its E-value, and the volume you will make, you will need to follow these steps:

1. calculate total amount of NaCl needed for the product (i.e. multiply NS concentration by the desired volume)
2. multiply total drug amount in g by [E]
3. subtract 2. from 1. to determine the total amount of NaCl left to add.
4. Complete calculations needed to determine amount of other ingredients that need to be added.

An example. A prescriber orders tobramycin 1% ophth sol, 10ml. You have tobramycin 40mg/ml preservative-free injectable solution on your shelf, as well as some sodium chloride in crystalline form. The Merck Index tells you that tobramycin's MW = 468, so you calculate the E to be 0.07 (or you look in the calculations textbook).

1. $\frac{0.9 \text{ g}}{100\text{ml}} \times \frac{1000\text{mg}}{\text{g}} \times 10\text{ml} = 90\text{mg}$ NaCl or equivalent needed for this product
2. $\frac{1\text{g}}{100\text{ml}} \times \frac{1000\text{mg}}{\text{g}} \times 10\text{ml} \times 0.07 = 7 \text{ mg}$ of NaCl equivalent accounted for by the tobramycin
3. $90\text{mg} - 7\text{mg} = 82\text{mg}$ NaCl needs to be added to the product.
4. determine amount of tobramycin stock solution to add

$$\frac{1000\text{mg}}{100\text{ml}} \times 10\text{ml} \times \frac{1\text{ml}}{40\text{mg}} = 2.5\text{ml}$$

Summary of procedure to mix this product: you will draw up 2.5ml of the tobramycin 40mg/ml stock solution, weigh out 82mg of NaCl crystals, qs to 10ml with water, and place the contents into an eye drop container, and jump up and down to shake well (just kidding about that last part).

Diluting and Concentrating

There will be times when you will want to dilute or to concentrate an already-prepared medication. Examples of such scenarios include a cream or eye drop that comes in a more dilute strength than what the prescriber desires, or an already-mixed IV product that requires an additive change. Your first impulse will be to use straight proportional calculations when you are diluting or concentrating a commercial preparation. You cannot do this, however, without algebraic modifications, because proportional calculations as shown above do not allow you to account for the volume of the more-concentrated or less-concentrated product that you are adding. I will illustrate this with an example.

You get a prescription from the physician specifying 30g of a hydrocortisone 2% cream. You have a 30g tube of hydrocortisone 1% cream, and a 30g tube of hydrocortisone 2.5% cream. You can't just squish some 1% cream into the tube of 2.5% cream, because you would end up with more than 30g. Instead, you need to mix appropriate amounts of each together in order to arrive at your 2% cream. (Now, I know that those of you who are pragmatists and extroverts would simply call the doc and ask him/her to change the prescription to 2.5%, but for argument's sake, let's pretend that the doc insists that he/she wants the 2% prep).

How do you do the calculations in order to determine the amount of ingredients to add? There are two methods, both of which basically do the same thing. The first method (algebraic) is able to mathematically represent what is done, in an intuitive sense. The second method (alligation) is not as intuitive, but is quicker and easier.

The algebraic method

In a nutshell, what you want to do is to begin with your initial concentration, remove part of it, and replace what you removed with the more concentrated product, thus arriving at the correct amount of the desired product concentration. So, let the games begin:

- d) let C_L = the concentration of the initial commercial product (or the product with the smallest concentration)
- e) let V_F = the desired final total volume or amount of product
- f) let C_H = the concentration of the stock solution (or stock product for those of you who can't bear to see me use the word "solution" to describe a cream) – this will be your most highly concentrated product
- g) let x = the volume of the stock solution that you need to add; this will, amazingly enough, also be the amount of the initial product that you need to remove
- h) let C_F = the concentration of the final desired pharmaceutical preparation

A very important point here is that concentrations C_L , C_H , and C_F all must be in the same units.

Again, what you want to do is start with your initial product concentration (C_L), remove part of it ($V_F - x$), replace that removed part with the SAME amount of the stock product ($C_H x$), and you will have the correct volume or amount (V_F) of your desired final concentration (C_F). Put all together, it looks like this:

$$C_L (V_F - x) + C_H x = C_F V_F \quad \text{That's it: now just solve for } x.$$

$$C_L V_F - C_L x + C_H x = C_F V_F$$

$$C_L V_F - C_F V_F = C_L x - C_H x$$

$$V_F (C_L - C_F) = x (C_L - C_H)$$

$$x = V_F \frac{(C_L - C_F)}{(C_L - C_H)}$$

This equation will work for all situations where you desire to dilute or concentrate a product and end up with the same amount or volume at which you started.

Let's go back to our hydrocortisone scenario for an example. You receive a prescription from a physician for hydrocortisone 2% cream, 30g. You have in your pharmacy a 30g tube of hydrocortisone 1% cream and a 30g tube of hydrocortisone 2.5% cream.

- C_L = 1% cream
- C_F = 2% cream a.k.a. what the doc wants
- C_H = 2.5% cream
- V_F = 30g
- x = amount of 2.5% cream to add

$$x = \frac{30g (1\% - 2\%)}{(1\% - 2.5\%)}$$

$$x = 20g$$

Therefore, you will add weigh out 20g of the hydrocortisone 2.5%. How do you figure out how much of the hydrocortisone 1% to add? Just subtract the amount of 2.5% cream from the total amount (30g) to obtain the amount of 1% to add (i.e. $30g - 20g = 10g$). Mix them thoroughly. You will now have 30g of a hydrocortisone 2% cream.

What if you don't need to end up with the same volume? For instance, what if the prescriber in the scenario above had wanted 50g of 2% cream? The equation is nearly identical, but you will need to make a minor modification to it.

To restate the situation, what you want to do is start with some volume (V_I) of your initial product concentration (C_L), and add the correct amount (x) of the stock product (C_H), to produce a product with the correct final

concentration (C_F) and volume ($V_I + x$, which I will call V_F). Notice that x is the volume of the more highly concentrated product.

$$C_L V_I + C_H x = C_F V_F \quad V_I = V_F - x; \text{ therefore substitute } V_F - x \text{ in place of } V_I$$

$$C_L (V_F - x) + C_H x = C_F V_F \quad \text{That's it: now just solve for } x$$

$$C_L V_F - C_L x + C_H x = C_F V_F$$

$$C_L V_F - C_F V_F = C_L x - C_H x$$

$$V_F (C_L - C_F) = x (C_L - C_H)$$

$$x = V_F \frac{(C_L - C_F)}{(C_L - C_H)}$$

Notice that this is the same equation as before. It is only the the number you will plug into this equation for V_F is a different number than the last problem. **This equation will work for all situations where you dilute or concentrate a product and end up with a different volume from what you initially had.**

e.g., suppose the prescriber above had wanted a total of 50g of hydrocortisone 2%:

$$x = \frac{50g(1\%-2\%)}{(1\%-2.5\%)}$$

$$x = \frac{-50g}{-1.5}$$

$$x = 33g$$

Remembering that x is the amount of the more highly concentrated product, you will mix 33g of the 2.5% cream with 17g of the 1% hydrocortisone to make 50g of 2% cream.

The nice thing about the algebraic method of dilution and concentration is that you do not have to memorize any equations. You just think what you need to do with each of the ingredients, and then set up your mathematical equation. You can use logic to reason your way through any problem in this way.

Some of you, however, may have mathophobia, or, more correctly, algebraophobia, so you will want to read on and learn about alligation, which is doing algebra without seeming to do algebra.

The alligation method

The only problem with alligation is that you can stare at it until you need a new prescription for your eyeglasses before you understand why it does what it does. It seems like voodoo. This will frustrate those of you who are inherently logical and desire your math to be that way, too. Some of you, however, will not care how alligation does what it does, as long as you end up with the right answer, in the quickest fashion. You don't mind a little memorization. So if you are this type of person, alligation is the method you will probably like best. Here's how it works.

Place the most concentrated product at the top. Place the least concentrated product at the bottom. Place the desired concentration in the middle, off a bit to the right side. If we use the hydrocortisone cream example from above, it will look like this:

2.5%
2%

1%

OK. Now start with the top number. Subtract the middle number from it and place the resulting number to the lower right of the middle number, at the same level as the bottom number.

2.5%
2%
1% **0.5 part** (i.e., $2.5 - 2 = 0.5$)

Look at the bottom number. Subtract it from the middle number and place the resulting number at the top, to the right of the top and middle number, like this:

2.5% **1 part** (i.e., $2 - 1 = 1$)
2%
1% 0.5 part

Calculate your total parts:

2.5% 1 part
2%
1% 0.5 part
 1.5 parts total

As you look at the diagram above, realize that the “1 part” is on the same level as the 2.5%, and that the “0.5 part” is on the same level as the 1%. This is not coincidental. Your final product will contain one part of the 2.5% cream and one-half part of the 1% cream.

Now you can do a proportional calculation to determine the volume of each medication that you will need:

$$\frac{1 \text{ part } 2.5\% \text{ cream}}{1.5 \text{ total parts}} = \frac{x \text{ grams } 2.5\% \text{ cream}}{30\text{g total cream}} \quad x = 20\text{g of } 2.5\% \text{ cream}$$

$$\frac{0.5 \text{ parts } 1\% \text{ cream}}{1.5 \text{ total parts}} = \frac{y \text{ grams } 1\% \text{ cream}}{30\text{g total cream}} \quad y = 10\text{g of } 1\% \text{ cream}$$

You will thus mix 20g of the 2% cream and 10g of the 1% cream. Notice that this is the same answer as that obtained by the algebraic method.

Of course you then want to know what you should charge for your laborious ministrations, but that’s an entirely different calculation.

If you want a different amount from that with which you started, the method is exactly the same. Let’s use the 50g amount that we used above:

2.5% 1 part
2%
1% 0.5 part
 1.5 parts

$$\frac{1 \text{ part } 2.5\% \text{ cream}}{1.5 \text{ total parts}} = \frac{x \text{ grams } 2.5\% \text{ cream}}{50\text{g total cream}}$$

$$\frac{1}{1.5} = \frac{x}{50\text{g}}$$

$$50\text{g} = 1.5x$$

$$33\text{g} = x$$

$$\frac{0.5 \text{ part 1\% cream}}{1.5 \text{ total parts}} = \frac{x \text{ grams 1\% cream}}{50\text{g total cream}}$$

$$\frac{0.5}{1.5} = \frac{x}{50\text{g}}$$

$$25\text{g} = 1.5x$$

$$17\text{g} = x$$

Note: using a method you do not understand is a good way to make errors. Using logic, as in the algebraic method, is less likely to create errors. If you have problems remembering each step of the alligation method, then use the algebraic method.

Aliquot Measurement Calculations

All balances have a point below which they cannot measure accurately. For instance, one brand of a torsion balance similar to one you will likely use in your compounding laboratory classes can measure amounts of drug down to 6 milligrams. Fancy electronic balances can measure as little as 10 mg, 1mg, or even 100 micrograms (the number below which they cannot measure reliably is usually inversely proportional to the price of the balance...). This cutoff point is called the *sensitivity*, although the United States Pharmacopoeia (USP) prefers use of the term *sensitivity requirement*, abbreviated SR, in order to distinguish the sensitivity range of a balance from garden-variety sensitivity. The sensitivity requirement will tell you two things: the minimum amount of drug you can weigh on that balance and the increments of the balance measure.

If you attempt to weigh something less than the sensitivity requirement on a balance, the balance will give you a reading of zero – the mass on the balance is too small for it to sense. Thus, if you attempt to weigh a 3mg drug dose on a balance with a sensitivity requirement of 10mg, the balance would read zero and you would not know whether you had 1 mg (one-third of the prescribed dose), 3 mg, 6 mg (twice the dose) or 9 mg (three times the correct dose). The dose you attempted to weigh would not be accurate. Similarly, if you attempted to measure 43.6 mg on a balance with a sensitivity requirement of 10mg, you would likely be off. Because the balance is only accurate to 10mg, increments, you will get a reading that tells you there is 0.04 gram or 0.05 gram, but it won't tell you if you have 0.0436 gram because it cannot sense differences in increments smaller than 10 milligrams. If you measured out 0.04 gram on such a balance, you might actually have anywhere between 0.035 and 0.045 gram. Thus, if you needed exactly 43.6 mg of substance, you would not get an accurate enough reading to tell you if you had that amount. *Accuracy* in measuring refers to how close the measurement is to what it should be.

In every device made, there is the propensity for error. Balances are no different. If you take the same amount of substance, say 100mg, and weigh it 100 times, you will not always end up with the same reading. Why not? Air pressure, humidity, temperature, dust, breezes, general machine crankiness – all these things can affect the way the balance “reads” the weight of a given drug. The variation in the measurement of the same substance amount is called precision. *Precision* refers to the reproducibility of a measure.

How are accuracy and precision different? It is easiest to answer this with an example. Suppose we take the scenario just described: we have 100 mg of a drug; we weigh it on the same balance 100 times, then calculate the mean and standard deviation (SD) of all those weights. Here are four possible situations (for you statistics gurus, we're going to assume normal distribution):

	mean ± SD	This is:
1	99.9 mg ± 1 mg	accurate (99.9 mg is extremely close to 100 mg) and precise (the SD is small: 95% of the measurements (2 SDs) fell between 97.9 and 101.9)
2	99.9 mg ± 11 mg	accurate (99.9 mg is extremely close to 100mg) but not precise (the SD is large: 95% of the data points (2 SDs) fell between 77.9 mg and 121.9 mg—that's a pretty wide range for the same thing measured 100 times)

3	92 mg \pm 1 mg	inaccurate (there is an 8% difference between the average measured weight and the “real” weight) but precise (the SD is small: 95% of the measurements (2 SDs) fell between 90 mg and 94 mg)
4	92 mg \pm 11 mg	inaccurate (there is an 8% difference between the average measured weight and the “real” weight) and imprecise (the SD is large: 95% of the measurements (2 SDs) fell between 70mg and 114mg – big spread)

You can see above that it would be absolutely unacceptable to have a large standard deviation, because with any one measurement you could be off by quite a bit, e.g., 20% (20mg) in the second example above. The industry standard (determined by the United States Pharmacopeia— USP) is that all balances must have a 5% or lower rate of error. What does this mean in English? One way to interpret this is if you have a known weight of something and measure it 100 times on your balance, 95 of those measures need to be spot on. Assuming that the five measurements that are off are still pretty close, you can see that your mean will be almost exactly the same as the true mean (great accuracy) and the standard deviation will be quite small – probably less than 1% of the mean – so you’ll have great precision.

This 5% rate of error is going to affect how small a quantity of substance you can weigh. You need to make sure that the potential inaccuracy of the sensitivity requirement is incorporated into your 5% potential for error. If your balance sensitivity requirement is 10mg and you weigh 10mg, you could be off by up to 10mg – a potential error rate of 100%. If you try to weigh 20mg, you can be off by as much as 10mg, making your potential error rate 10mg \div 20mg, or 50%. If you try to weigh 40 mg, you can be off by as much as 25% (10mg \div 40mg). It is not until you reach a weight of 200mg that your sensitivity requirement will be within the accepted 5% range of potential error (10mg \div 200mg = 0.05: 5%). Two hundred milligrams, then, would be the smallest amount of substance that you could weigh with a 5% or less margin of error. This amount is called the *minimum weighable quantity (MWQ)* and can be calculated by taking your balance’s sensitivity requirement and dividing it by 5%, thus:

$$\frac{SR}{0.05} = MWQ$$

MWQs for balances with a sensitivity requirement of 1mg, 6 mg, or 10 mg are 20 mg, 120 mg, and 200 mg, respectively.

In order to be able to weigh something accurately, then, you will need to weigh an amount that is at or above the minimum weighable quantity. How can you do this if the dose is below that quantity? You will need to use a nifty trick called the aliquot method of measurement.

Webster’s dictionary defines an aliquot as an adjective “designating a part of a number that divides the number evenly and leaves no remainder.” With aliquot calculations, then, you will multiply the amount of drug you need in each dosage form by a number that allows you to weigh at or above the minimum weighable quantity (this final number will thus be evenly divided by the correct dose – the aliquot – of drug). But wait, there’s more. You will also need to weigh a suitable amount of diluent (e.g., lactose – a popular diluent for solid dosage forms) such that the total amount of drug plus diluent *used for each dose* is higher than the minimum weighable quantity of your balance. Here’s how you do it.

Let’s say that you are using the old-fashioned mechanical torsion balances found in the laboratories of most cash-strapped pharmacy schools (the new electronic balances weigh over \$1000 apiece at this time – ouch!) These torsion balances have a sensitivity requirement of 6mg. The minimum weighable quantity is 120 mg (this obtained by dividing 6 mg by the acceptable error rate of 0.05). You get a prescription for a compounded drug containing 20 mg of drug in each solid dosage form. You decide to use lactose as a diluent after checking that the patient is not lactose-intolerant. This patient will take one capsule daily for 5 days, so you know you need to make 5 capsules. You cannot weigh 20mg on your balance with an error rate of 5% or less, nor can you weigh 100mg (the total amount of drug in all 5 capsules). What you will need to do is to take your 20mg and multiply it by some number that will allow you to weigh 120mg or more of drug. It’s probably easiest to choose the multiple of six, since that means you will weigh 120mg of drug and thus will have the least amount of wastage, but will have enough for one extra capsule, just in case of spillage. You weigh 120mg on your balance.

You now need to choose an amount of diluent that you will use. You can choose any amount as long as that amount meets each of two criteria. First, the total amount of drug and diluent in each dosage unit must weigh more than your minimum weighable quantity. In our example, then, we will need to measure enough diluent so that there is at least 100mg of diluent in each dosage form (100mg diluent + 20mg drug = 120 mg of drug in each dose – the minimum weighable quantity). Second, you cannot use more diluent in each dosage form than will fit into the dosage form container – in this case an empty gelatin capsule. The easiest thing to do is to determine the how much diluent needs to be added to the drug in order to meet your minimum weighable quantity for each dose, then multiply that number by the same multiple you used for the drug, which in this case is six. This means you will weigh 600mg (100mg x 6) of lactose on your balance.

Place the measured drug and lactose in a mortar and triturate well with the pestle. Weigh out 120mg of the resulting mixture and place in an appropriately-sized capsule shell. Do this 5 times and you're set.

To summarize the steps in aliquot calculations:

1. Identify the sensitivity requirement of your balance. Divide by 0.05 to determine the minimum weighable quantity.

$$\frac{SR}{0.05} = MWQ$$

2. Multiply the strength of each drug dose by a number that will produce a weighable quantity at or above the minimum weighable quantity.

$$(\text{drug dose})(\text{multiplication factor}) = \text{or} > MWQ$$

3. Choose an amount of diluent to weigh. The most logical way to choose the amount is to subtract the drug dose from the minimum weighable quantity and use this number for your diluent amount per dose, then multiply by the same factor as the one used in step #2.

$$(MWQ - \text{drug dose weight})(\text{multiplication factor}) = \text{total diluent amount to weigh}$$

4. Mix the drug and diluent well. Divide the total weight by the multiplication factor to see how much of the drug-diluent mixture to use for each dosage form

Buffer Systems

I think of a buffer as a cushion against something. This is certainly true of its role chemically. Buffer systems help to lessen the impact of too few or too many hydrogen ions, which could otherwise cause some drugs to degrade and some proteins to destabilize.

Buffer systems are commonly composed of either a weak acid and salt of the acid, or weak base and salt of the base. These solutions act as a cushion so that when a stronger acid or base comes into contact with a drug or protein, it is the buffer that absorbs or contributes the hydrogen ions, rather than the drug or protein.

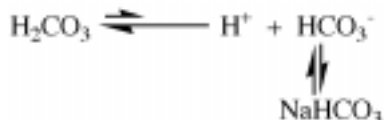
You carry around in your body one of the most sophisticated buffer systems known, so it will serve as a good illustration of how a buffer system works.

Your body's buffer system. The normal concentration of hydrogen ions in your extracellular fluid (blood and interstitial fluids) is 0.00004 mEq/L. You'll notice that this is pretty small in comparison with the concentration of sodium (~145 mEq/L) or even potassium (~4 mEq/L). What's even more amazing is that you ingest or produce around 80mEq of H⁺ ions daily. As you can imagine, adding that amount of hydrogen ions to your body could adversely affect your body functions if it weren't for the terrific buffer system you possess. How does it work?

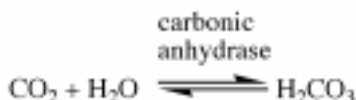
The hydrogen ions you ingest or produce combine in the bloodstream with bicarbonate ions (HCO₃⁻) to produce carbonic acid (H₂CO₃) which is a weak acid. Because the hydrogen ion is a stronger acid and bicarbonate a stronger base, carbonic acid doesn't dissociate very readily back into those two component parts; this keeps the hydrogen ion concentration low. Schematically, it looks like this:



The bicarbonate in your system occurs primarily as the sodium salt (NaHCO_3), which will dissociate readily to combine with hydrogen ions if the hydrogen ion concentration increases.

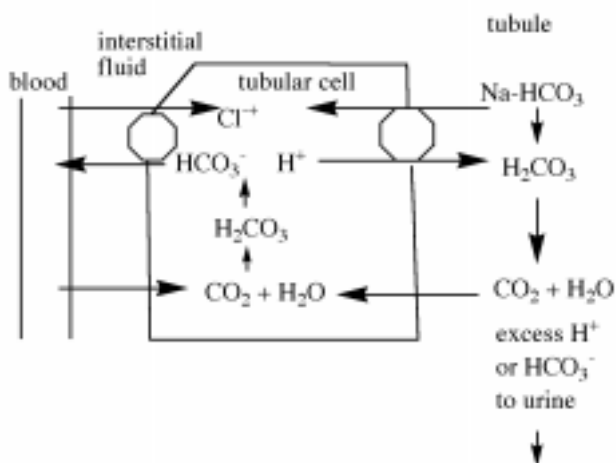


In addition to being formed from hydrogen ions and bicarbonate, carbonic acid will dissociate fairly readily to form water and carbon dioxide. When you exhale, you get rid of carbon dioxide. In order to have carbon dioxide to exhale, the body needs continuous formation of carbonic acid; the continuous formation of carbonic acid helps keep the hydrogen ion concentration low. Carbonic anhydrase can catalyze the conversion of carbon dioxide and water back to carbonic acid, where it could then theoretically dissociate back into hydrogen and bicarbonate, but for the most part the continually disappearing CO_2 pulls the equation toward production of more CO_2 rather than away from it.



Increased hydrogen ion concentration in the bloodstream directly increases the rate of breathing and so increases the amount of carbon dioxide that we “blow off” when we exhale.

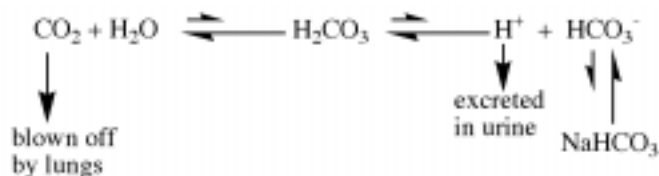
But that’s not all. The body has an additional way to deal with hydrogen ion excess. In the kidney, the bicarbonate is filtered into the tubules; most of it is reabsorbed into the renal tubular cells, so normally not much is excreted in the urine. Hydrogen ions are primarily secreted from the renal tubular cells out into the urine. In the urine, free bicarbonate and hydrogen ions combine, forming carbonic acid, which then dissociates to carbon dioxide and water. These are reabsorbed back into the renal tubular cell and turned back into carbonic acid by carbonic anhydrase. The carbonic acid dissociates into hydrogen ions and bicarbonate, which then quickly leave the cell, albeit in opposite directions. The bicarbonate is reabsorbed into the bloodstream and the hydrogen ions are pumped back out into the tubules, where they are then available to combine with more bicarbonate. The figure above provides a schematic illustration of this process.



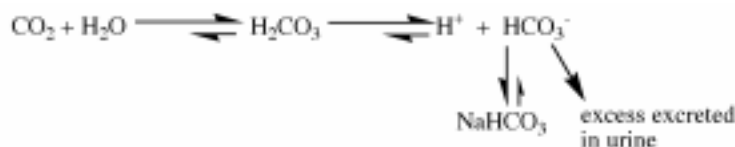
If there are more hydrogen ions pumped out into the lumen than there are bicarbonate ions to combine with them, the excess ions are excreted in the urine. The kidneys thus play a vital role in controlling the acid-base balance within the body by getting rid of excess hydrogen ions, which would otherwise lower the metabolic pH and interfere with normal cellular function in the body. If a person’s kidneys stop functioning, he or she will die within a couple of weeks unless dialysis (essentially an artificial kidney although it sure doesn’t look like one!) is started.

You can hopefully see what happens if something increases the hydrogen ion concentration in the bloodstream (we call this acidosis). The kidneys will start excreting excess hydrogen ions (it will take hours to days for the hydrogen ions to be excreted) and the lungs will blow off carbon dioxide (this happens within minutes to hours of a hydrogen

ion concentration increase), decreasing carbonic acid concentrations, which will stimulate increased formation from hydrogen and bicarbonate (the kidneys can make extra bicarbonate and the bones also store bicarbonate).



If the hydrogen ion concentration gets too low, and there is a bicarbonate excess, then less carbonic acid is formed, more bicarbonate is excreted by the kidneys, and more bicarbonate is incorporated into bones, so alkalosis is controlled by the buffer system, too.



Here you can see how a weak acid buffer (carbonic acid) and the salt of the acid (bicarbonate – this is the conjugate base of carbonic acid) can help the body to resist increases or decreases in hydrogen ion concentration. In the relationship between carbonic acid, the hydrogen ion, and the bicarbonate, there exists an equilibrium, represented by the arrows



This equilibrium is constant: if the hydrogen ion concentration increases, then the concentration of bicarbonate increases and together these increase the concentration of carbonic acid. As discussed in Lesson 2, this constant, represented as K, defines the relationship:

$$K = \frac{[\text{H}^+][\text{HCO}_3^-]}{[\text{H}_2\text{CO}_3]}$$

This means that if the hydrogen and bicarbonate concentrations increase (the top part of the above equation), so does the carbonic acid concentration (the bottom part of the above equation); ditto for a decrease in each, and so K remains the same. To take this where we want it to go, we'll pull out the hydrogen ion to stand on its own,

$$K = [\text{H}^+] \frac{[\text{HCO}_3^-]}{[\text{H}_2\text{CO}_3]}$$

take the negative logarithm of each component,

$$\text{pK}_a = \text{pH} - \log \frac{[\text{HCO}_3^-]}{[\text{H}_2\text{CO}_3]}$$

and pull the pH (which can change) out to the other side of the equal sign to make the Henderson-Hasselbalch equation for weak acids:

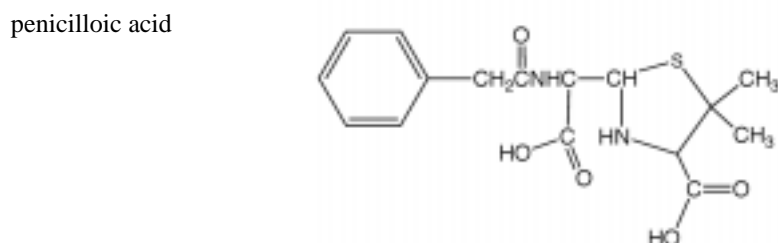
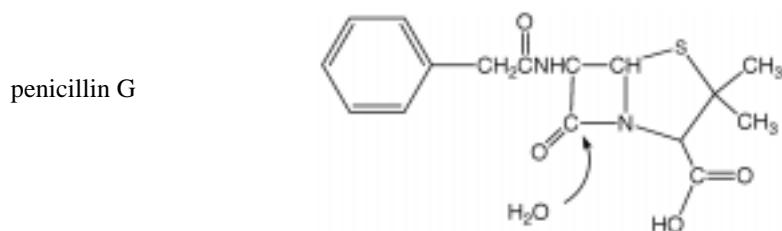
$$\text{pH} = \text{pK}_a + \log \frac{[\text{HCO}_3^-]}{[\text{H}_2\text{CO}_3]}$$

This tells you that if you make a change to the pH, the bicarbonate and carbonic acid concentrations will change accordingly. This acid-salt system thus bears the brunt of changes in the hydrogen ion concentration in the body, sparing other substances in the extracellular fluid (such as proteins, other electrolytes, and drugs) from being affected by the hydrogen ion. This is just one of several buffer systems in your body, but it is an important one and serves to illustrate how buffer systems work.

Use of buffers in pharmacy practice. When might you need to use a buffer? There are two common situations: when changes in the pH environment of a drug causes chemical degradation of a drug, and when application of an acidic or basic pH drug causes body tissue irritation. These situations are further explored below.

It is desirable to cushion a drug from the effects of changes in pH if the drug is susceptible to the effects of changes in hydrogen ion concentration. We call such drugs “pH labile.” Changes in pH can occur due to storage conditions or to the mixing of two pH-incompatible drugs

A classic example of a drug which can be inactivated over time during storage is penicillin (an antibiotic, as you probably know). Here, water acts as a stronger base than penicillin, causing hydrolysis of the beta-lactam ring (that’s the square structure in the middle of the molecule below); the beta-lactam ring is crucial to the penicillin’s ability to kill bacteria. Hydrolysis by water yields an inactive moiety, penicilloic acid.



It is for this reason that penicillin powder, reconstituted in water so that it can be given as an injection, has a citric acid-citrate buffer system. This buffer system runs interference for the antibiotic, attracting water by exchanging hydrogen ions more easily than the penicillin. This keeps the pH within a range of 6.0-6.8 and gives the drug a period of stability at room temperature of a day or a bit longer. Refrigeration will further slow down the hydrolytic activity of the water; refrigerated solutions will remain potent for a week.

Protein drugs are also susceptible to the effects of pH. Glutamine and asparagine can undergo hydrolytic deamidation.¹ Buffering of protein solutions containing these amino acid residues to a pH of 6.0 minimizes the deamidation. It is interesting that human chorionic gonadotropin a protein peptide used to induce ovulation in infertile women is buffered with monobasic and dibasic sodium phosphate and is stable after reconstitution for 30 days, when refrigerated. Menotropins, also a peptide hormone used along with human chorionic gonadotropin has no mention of a buffer in its formulation, is unstable in solution, and needs to have any unused portion discarded immediately after reconstitution. Nucleic acid-derived drugs are susceptible to hydrolysis and oxidation during

processing and storage.² Even in the solid state, proteins and peptides can destabilize due to a variety of factors such as storage temperature, residual moisture, and excipients; buffers can actually degrade proteins, if the effect of the system upon the drug in a variety of conditions is not well understood.³

A good, clinically important example of two pH incompatible drugs is penicillin derivatives and a class of antibiotics called aminoglycosides. These two classes of drugs can exert a synergistic effect (meaning that the antibacterial action of the two together is more effective than the sum of the action of each agent alone) and so are often given together to patients severely infected with certain bacteria. Drug concentrations of the aminoglycosides are often measured in the laboratory in order to ensure that an adequate concentration has been achieved to promote maximal bacterial killing, but that the concentration is not so high as to promote toxicity. If the blood drawn for laboratory assay is not promptly iced or placed in the freezer, and if concentrations of both drugs are relatively high, the acidic penicillin derivative will start degrading the basic aminoglycoside. If analysis of the concentration of the aminoglycoside shows it to be low, it is impossible to know whether that is because the blood concentration is truly low or if enough of the aminoglycoside has been inactivated during blood sample transit from patient to lab so that the blood concentration *appears* falsely low. This is frustrating. It is probably possible to add a buffer to the blood sample after the blood draw, but this is not routinely done.

The second situation where buffers are used is to protect body tissues which might be irritated by application of an acidic or basic drug. This situation usually involves localized application of a drug solution to a mucous membrane or infusion into a small vein. Here, the high concentration of the drug relative to the body fluid in the immediate environment can overwhelm the body's buffer system, rendering it incapable of preventing tissue irritation. Since hydrogen ions can stimulate pain-specific nerve receptors⁴ and promote tissue swelling,⁵ the patient will report pain upon application and will be unenthusiastic about reapplying the drug.

Buffering in each of these cases can help to decrease unwanted drug degradation or tissue irritation effects. Most of the time you will shoot for a solution buffered to:

- i) a pH within the range of 6.5-8.5 for eyes
- j) a pH within the range of 5.0-8.0 for nasal application
- k) a pH within the range of 5.0-8.0 for injection into a relatively small area such as an intramuscular injection or intravenous injection into a small vein
- l) a broader pH range such as 4-10 can be tolerated if the drug is infused into a large vein at a slow rate.

It may not be entirely possible to stay within these ranges, however, since some drugs will degrade if the pH of the drug's solution is raised or lowered into the comfort range. In this case a compromise pH will have to be determined.

Commonly used buffer systems include:

- sodium hydroxide (pH 11-13) and hydrochloric acid (pH 1-3), usually 0.1 or 0.2 N solutions. In addition to being used to increase solubility, these are used to raise and lower pH of solutions to the desired range to prevent tissue irritation upon instillation. These are the buffers used for drugs which are not pH labile.
- sodium citrate-citric acid. This is a high capacity buffer system and most useful for protecting pH labile weak acids. The system can be prepared for a pH range of 2.5-6.5. Penicillin and cefuroxime are two examples of drugs for which this buffer system is used.
- sodium acetate-acetic acid. pH range 3.6-5.6. acetic acid pK_a is 4.76 at 25°C. Useful for ophthalmic, mucous membrane, and parenteral solution buffering. Ciprofloxacin (pK_a s of 6 and 8.8) ophthalmic solution is buffered to a pH of 4.5
- sodium borate (0.05 M) - boric acid (0.2 M). pH range 6.8-9. boric acid pK_a 9.24 at 25°C. Used only for ophthalmic solutions as boric acid is toxic when administered parenterally.
- monobasic sodium or potassium phosphate (0.2 M), NaOH. pH range 5.8-8. Probably most widely used to buffer protein solutions.

Your challenge will be to figure out the amount of each part of the buffer solution in order to reach a desired pH. Fortunately, there are guidelines in the USP and in Judith Thompson's excellent text, "A practical guide to contemporary pharmacy practice." Still, you will need to understand the principles behind formulating buffer solutions. Henderson-Hasselbalch is a good mathematical tool for explaining these principles.

Buffer system basics. The concentration of hydrogen ions, which determines pH, can be represented by the ratio between an acid and its salt. You know that things that are acidic tend to have a low pH, so you can predict that pH will be inversely proportional to the percentage of a solution that is in the acid form compared to the salt form (i.e., as the acid form concentration goes up, the salt form concentration goes down and the pH drops). This can be represented semi-mathematically as

$$\text{pH is related to } \frac{[\text{salt}]}{[\text{acid}]}$$

with the brackets meaning “concentration of” and in this case we use the molar concentration of the chemical forms. The thing which drives the relationship between the salt/acid proportions and the pH is the acid’s pK_a . This goes into the relationship to give us the Henderson-Hasselbalch equation.

$$\text{pH} = \text{pK}_a + \log \frac{[\text{salt}]}{[\text{acid}]}$$

You know that when the pH is equal to the pK_a , the molar concentration of the salt form and the molar concentration of the acid form of the buffer acid-base pair will be equal: 50% of the buffer will be in salt form and 50% in acid form. Notice that the percentage of buffer in the acid form when added to the percentage of buffer in the salt form will always equal 100%. Therefore, if you have a solution with 90% in the salt form, then 10% will be in the acid form. If 60% of drug is in the acid form then 40% will be in the salt form. You know that the pK_a of the acid is a constant, so you can deduce that if you change the proportions of buffer in the salt and acid forms, it is the pH that will change. It is because of this that you can manipulate the ratios of the molar concentration of salt and the acid forms to produce a desired pH.

Let’s play with an example. You prepare a 0.2 M boric acid solution and a 0.05 M sodium borate solution. Let’s say that you would like to use these to prepare 100ml of a buffer. The pK_a for boric acid is 9.19. Now, you can’t just plop all of these numbers into Henderson-Hasselbalch like this:

$$\text{pH} = 9.19 + \log \frac{[0.05]}{[0.02]}$$

to determine the pH because this won’t tell you the effect on the pH of adding the differing *volumes* (i.e., milliliters) of the salt and the acid together. You will need to account for the volume of each in your equation. Let’s say that you decide to add 90ml of the 0.2M boric acid solution and 10ml of the 0.05M sodium borate. You know that a 0.2 M solution can also be expressed as a 0.2 mmol/ml solution and the 0.05 M solution is the same as a 0.05 mmol/ml solution. Thus, 90 ml of a 0.2 mmol/ml solution will give you 18 mmol of boric acid and 10ml of a 0.05 mmol/ml solution will give you 0.5 mmol sodium borate. It is these amounts that you can plug into Henderson-Hasselbalch.

$$\text{pH} = 9.19 + \log \frac{0.5}{18}$$

$$\text{pH} = 9.19 + \log 0.028 \qquad \log 0.028 = -1.56$$

$$\text{pH} = 9.19 - 1.56$$

$$\text{pH} = 7.6$$

Now let’s take the opposite proportions. Here we’ll add 10 ml of the 0.2M boric acid solution, which will be 2 mmol of boric acid, to 90 ml of 0.05 M sodium borate solution, which will yield 4.5 mmol of sodium borate.

$$\text{pH} = 9.19 + \log \frac{4.5}{2}$$

$$\text{pH} = 9.19 + \log 2.25 \qquad \log 2.25 = 0.352$$

$$\text{pH} = 9.19 + 0.352$$

$$\text{pH} = 9.5$$

Interestingly enough, the actual pHs that occur in each of the above scenarios are 7.4 and 9.1. It seems likely that there are other factors involved which will affect the final pH of a solution. Still, the numbers are relatively close to where you want them.

If we stand this equation on its head, we can manipulate the acid and salt proportions to give us a desired pH. Let's say that we want to make a buffer for a drug that can tolerate pHs down to 8.5, but won't be too stable if the pH goes lower. We will therefore want to make 100ml of a buffer solution that will be pH 8.5, using the same molar solutions as that shown above.

We will set x ml as our unknown volume for the boric acid 0.2 M solution. Because we know that the volume of the acid and the volume of the salt will always equal 100 ml, we can set the volume of sodium borate 0.05 M solution as 100-x. Because it makes the math easier, we will again consider that a 0.2 M solution is the same as a 0.2 mmol/ml solution and a 0.05 M solution the same as a 0.05 mmol/ml solution. Now we just have to solve for x.

$$8.5 = 9.19 + \log \frac{(0.05)(100 - x)}{(0.2)(x)}$$

$$-0.69 = \log \frac{5 - 0.05x}{0.2x} \quad \text{take the antilog of each side}$$

$$0.2 = \frac{5 - 0.05x}{0.2x}$$

$$0.04x = 5 - 0.05x$$

$$0.09x = 5$$

$$x = 56 \text{ ml boric acid}$$

One would thus theoretically mix 56 ml of the 0.2 M boric acid solution with 44 ml of the 0.05 M sodium borate solution to make a buffer with a pH of 8.5.

How would this buffer solution stand up to the addition of something that would otherwise change the pH? Let's say that I'm sloppy when mixing this buffer solution and accidentally drop in a half milliliter of 0.1 M sodium hydroxide. This would mean that we would be introducing 0.5 ml x 0.1 mmol/ml NaOH = 0.05 millimoles. In water, this amount of solution has a pH somewhat higher than 12. Let's see what it will do to the buffer.

Starting from the situation just outlined above, we have a pH of 8.5, a pK_a of 9.19. There are 56 ml of 0.2 mmol/ml boric acid, which means there are 11.2 mmol in the 100ml buffer. There are 44 ml of 0.05 mmol/ml sodium borate, which means that there are 2.2 mmol in the 100ml buffer. This gives us the following relationship:

$$8.5 = 9.19 + \log \frac{2.2\text{mmolNaB}}{11.2\text{mmolBA}}$$

where NaB stands for sodium borate and BA stands for boric acid. If 0.05 millimoles of NaOH is added to this solution, it will cause an equivalent number of millimoles of boric acid to convert to sodium borate.

$$\text{pH} = 9.19 + \log \frac{2.2\text{mmolNaB} + 0.05\text{mmolNaB}}{11.2\text{mmolBA} - 0.05\text{mmolBA}}$$

$$\text{pH} = 9.19 + \log \frac{2.25}{11.15}$$

$$\text{pH} = 9.19 + \log 0.202$$

$$\text{pH} = 9.19 - 0.69$$

$$\text{pH} = 8.5$$

You can see that an amount of sodium hydroxide that would change the pH of water from 7 to 12 would not affect the buffer solution. If addition of a small amount of a strong acid or base does not appreciably change the pH of the buffer solution, you can see how the addition of a drug (which will be either a weak acid or a weak base) to the buffer solution would have a negligible impact upon the pH. The drug would thus be protected from pH changes by the buffer and the buffer would protect the proteins of mucous membranes from the otherwise potentially irritating weakly acidic or basic drug.

References

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Lesson 3 practice questions

1. Proportional Calculations

1a. Ferrous sulfate, the most commonly prescribed form of iron, is available as 5 grain tablets which contain 20% elemental iron. The US recommended dietary allowance (RDA) of elemental iron for a pregnant female is 30mg. What percent of the US RDA will a pregnant woman receive when she ingests a 5 grain tablet?

_____ % RDA

1b. A 16-pound child with meningitis is prescribed ampicillin IV 200mg/kg/day in 4 divided doses. Ampicillin comes in vials containing 125mg, 250mg, 500mg, and 1gm of powder. Each vial can be reconstituted to produce a maximum concentration of 30mg/ml. Please calculate the dose, identify which vial you will use to reconstitute, and how many ml of the solution you will place in the syringe for the nurse to administer.

_____ mg/dose

_____ mg vial

_____ ml of 30mg/ml concentration

1c. A physician has ordered that 20mEq of potassium be administered to a patient as a potassium bolus. Based on the patient's serum potassium concentration, administration literature recommends a maximum concentration of 40mEq/L and a maximum infusion rate of 10mEq/hour. You notice that the patient's current bag of D5-1/2NS w/10mEq of KCl, set to run at 125 ml/hr, has 800ml remaining.

Calculate whether or not you can use the patient's current bag of fluid to infuse this potassium, per literature recommendation.

_____ I can use the current bag for infusion

_____ I cannot use the current bag for infusion

Either using the current bag for infusion, or using another bag (100ml, 250ml, 500ml, or 1000ml) for infusion, please show how you will mix the solution, how fast the drip rate will be, and the time you anticipate the potassium will finish infusing, assuming you will start the potassium infusion at 8pm. Your stock solution is KCl 2mEq/ml.

1d. While in hospital, a patient is receiving penicillin G 5 million units IV q6h (antibiotic), furosemide 40mg po qd (a diuretic), and K-Dur 20mEq po qd (a potassium supplement). Knowing that the penicillin G is being administered as the potassium salt, you check your references and note that there is 1.7mEq potassium in each million units of penicillin. How many mEq of potassium is this patient receiving daily?

_____ mEq potassium

2. Osmolarity

2a. D5-0.45NS with KCl 20mEq/L is a solution commonly infused in hospitalized patients. Please determine the osmolarity.

MW: dextrose = 180, Na = 23, Cl = 35.5, K = 39

_____ mOsmol/L

2b. How much sodium acetate 16.4% would you add to a liter of 1/2 normal saline in order to produce an isotonic solution? MW sodium acetate ($\text{NaC}_2\text{H}_3\text{O}_2$) is 82; MW NaCl is 58.5.

_____ ml sodium acetate

How many mEq of sodium are now in that liter of fluid? How many grams?

_____ mEq, _____ g sodium

2c. A physician orders magnesium sulfate to be administered at a rate of 2g/hr to a patient experiencing premature labour. The pharmacy sends up 500ml of a 2% solution. What is the osmolarity of this solution? MW MgSO_4 = 120

_____ mOsmol/L

How many mEq/hr of magnesium will this patient receive?

_____ mEq/hr

3. Isotonicity

3a. An ophthalmologist near your pharmacy swears by tropicamide 2% solution as a mydriatic for his patients. Tropicamide is available commercially as a 0.5% and 1% solution, so you decide to humour him (or her) by mixing it special, figuring that you can charge a healthy compounding fee in the process. The trick is to make a isotonic solution. You decide to make a 30ml vial. The E value for tropicamide is 0.11. Please calculate how much tropicamide, and how much sodium you will add to each 30ml vial before qs'ing to 30ml with water.

_____ mg tropicamide

_____ mg NaCl

3b. You have been asked to prepare 20ml of naphazoline 0.5% ophthalmic solution in a sodium chloride base. You have naphazoline HCl, USP (MW 246.74), which has a sodium chloride equivalent value of 0.27. How much naphazoline will you measure, how much sodium chloride, and approximately how much water will you add. Assume that no other substances will be added.

3c. Now you have to make 30ml of a 1% atropine solution in a boric acid base. The MW of atropine sulfate is 694.82 and of boric acid is 61.84. The sodium chloride equivalents are 0.13 and 0.50, respectively. How much atropine sulfate, how much boric acid, and how much water will you add? (just to confirm, you will *not* be adding any sodium chloride)

4. Diluting and Concentrating

4a. A physician orders Benylin DM® cough syrup, 4oz., 1 tsp q6h prn cough, for a child. Benylin DM® is a preparation containing 10mg of dextromethorphan (a cough suppressant) in each 5ml. You only carry Delsym® in your pharmacy, which contains 30mg dextromethorphan/5ml. Rather than adjust the dose (hey, that's not until lesson 4!), you decide to dilute some Delsym® with some cherry syrup, so as to arrive at the same concentration as the Benylin DM® (and make it more tasty in the process...). How much Delsym® and how much cherry syrup will you use?

_____ ml Delsym®

_____ ml cherry syrup

4b. You have been asked to mix 10ml of fortified tobramycin eye drops, 1%, for a patient. you have the commercially-prepared Tobrex® 0.3% 10ml on your shelf. You also have some preservative-free tobramycin 40mg/ml solution. Please explain how you will mix this preparation:

I will withdraw _____ ml of Tobrex® solution from the Tobrex® container and replace it with _____ ml of tobramycin 40mg/ml solution.

4c. A pharmacist mixed a standard morphine sulfate intravenous infusion of 50mg morphine in 250ml D5W for a patient. Before the solution could be used, the order was discontinued. Rather than discard the solution, the pharmacist decided to use it to make some solution for patient-controlled analgesia (PCA) syringes, the usual concentration of which is 1mg/ml. How many milliliters of a 15mg/ml stock solution of morphine sulfate will the pharmacist have to add to the 50mg/250ml solution to produce a final solution with a concentration of 1mg/ml? (round to the nearest 0.2ml) How many *full* 50ml syringes will the pharmacist be able to make?

_____ ml

_____ syringes

5. Aliquot calculations

5a. You receive a prescription for vanadyl sulfate 10mg capsules. The patient is to take one daily for 3 months to see if it helps her diabetes. You order 25 grams of vanadyl sulfate hydrate from a chemical manufacturing company and decide to use lactose as the diluent. You will need to make 90 capsules. The sensitivity requirement of your balance is 10 mg.

5b. A patient wishes to take a natural form of estrogen to see if it helps with hot flashes, and wants it prepared in a capsule that she can take once daily. You can purchase soy isoflavones in powder form from a distributor. You and the prescriber decide on a dose of 80mg daily (this has been shown effective in clinical trials). You will use starch as the base since she is lactose-intolerant. You have a mechanical torsion balance with a sensitivity requirement of 6mg.

5c. You receive a prescription for an estrogen preparation that is to contain estriol 2mg, estrone 0.25mg and estradiol 0.25mg in a single capsule. Lactose is to be used as the base. The patient will take one daily. You need to prepare 92 capsules. The sensitivity requirement of your balance is 1 mg.

6. Buffers

You need to compound an ophthalmic solution of a beta-lactam antibiotic that is susceptible to hydrolysis and most stable when the pH of a solution is 5.0. You have decided to prepare a sodium acetate-acetic acid buffer solution. You place 0.6 ml of glacial acetic acid (99% acetic acid) in 99.4ml of water, giving you ≈ 100 ml of a 0.1 M acetic acid solution. You then weigh 820 mg of sodium acetate and add water to the 100ml mark, giving you 100ml of a 0.1 M sodium acetate solution. The pK_a of acetic acid is 4.76.

6a. If you were to add 5ml of a 0.1 M acetic acid solution to 5ml of a 0.1 M sodium acetate solution, what would be the pH of the resulting solution?

6b. Let's change the relative proportions of each constituent of the buffer solution. If you were to add 2ml of a 0.1 M acetic acid solution to 8ml of a 0.1 M sodium acetate solution, what would be the pH of the resulting solution?

These are both easy calculations since the molarity of the buffer system components are the same, but it gives you a chance to see how altering the proportions of the buffer system components will alter the pH. In the next question, you can see how much of each component you will need in order to make a buffer solution at the pH you want: 5.0

6c. What volumes of 0.1 M acetic acid and 0.1 M sodium acetate will you need in order to make 30ml of a buffer that has a pH of 5.0?

Lesson 3 practice question answers

1. Proportional Calculations

1a. Ferrous sulfate, the most commonly prescribed form of iron, is available as 5 grain tablets which contain 20% elemental iron. The US recommended dietary allowance (RDA) of elemental iron for a pregnant female is 30mg. What percent of the US RDA will a pregnant woman receive when she ingests a 5 grain tablet?

216 % RDA

$$\frac{5 \text{ gr FeSO}_4}{\text{tab}} \times \frac{64.8 \text{ mg}}{\text{gr}} \times \frac{0.2 \text{ mg Fe}}{1 \text{ mg FeSO}_4} \times \frac{\text{RDA}}{30 \text{ mg Fe}} = \frac{2.16 \text{ RDA}}{\text{tab}} = 216\% \text{ RDA}$$

1b. A 16-pound child with meningitis is prescribed ampicillin IV 200mg/kg/day in 4 divided doses. Ampicillin comes in vials containing 125mg, 250mg, 500mg, and 1gm of powder. Each vial can be reconstituted to produce a maximum concentration of 30mg/ml. Please calculate the dose, identify which vial you will use to reconstitute, and how many ml of the solution you will place in the syringe for the nurse to administer.

$$\frac{200 \text{ mg/kg}}{\text{dose}} \times \frac{1 \text{ day}}{4 \text{ doses}} \times 7.2 \text{ kg} = 360 \text{ mg/dose}$$

I would use the 500 mg vial and reconstitute to 30mg/ml (directions are on side of the vial)

$$\frac{360 \text{ mg}}{30 \text{ mg}} \times \frac{1 \text{ ml}}{1} = 12 \text{ ml of 30mg/ml solution to draw up in the syringe}$$

1c. A physician has ordered that 20mEq of potassium be administered to a patient as a potassium bolus. Based on the patient's serum potassium concentration, administration literature recommends a maximum concentration of 40mEq/L and a maximum infusion rate of 10mEq/hour. You notice that the patient's current bag of D5-1/2NS w/ KCl 10mEq, set to run at 125 ml/hr, has 800ml remaining.

Calculate whether or not you can use the patient's current bag of fluid to infuse this potassium, per literature recommendation.

X I can use the current bag for infusion

_____ I cannot use the current bag for infusion

There is currently 80% of the liter left, so in theory there should be 10mEq x 80% or 8mEq of KCl left in the patient's bag.

$$\frac{20 + 8 \text{ mEq}}{800 \text{ ml}} \times \frac{1000 \text{ ml}}{\text{L}} = 35 \frac{\text{mEq}}{\text{L}} \text{ this is below the 40mEq/L max, so OK}$$

$$\frac{28 \text{ mEq KCl}}{800 \text{ ml}} \times \frac{125 \text{ ml}}{\text{hr}} = 4.4 \frac{\text{mEq}}{\text{hr}}, < \text{the max infusion rate of } 10 \frac{\text{mEq}}{\text{hr}}$$

Either using the current bag for infusion, or using another bag (100ml, 250ml, 500ml, or 1000ml) for infusion, please show how you will mix the solution, how fast the drip rate will be, and the time you anticipate the potassium will finish infusing, assuming you will start the potassium infusion now, at 8pm. Your stock solution is KCl 2mEq/ml.

a) amount of KCl to add: $\frac{1 \text{ ml}}{2 \text{ mEq}} \times 20 \text{ mEq} = 10 \text{ ml}$ of stock solution, which I will add directly to the bag that is hanging

$$\text{b) } 800 \text{ ml} + 10 \text{ ml} = 810 \text{ ml} \qquad 810 \text{ ml} \times \frac{1 \text{ hr}}{125 \text{ ml}} \approx 6.5 \text{ hours}$$

c) 8pm + 6.5 hours = 2:30am, anticipated finish time for the potassium infusion.

1d. While in hospital, a patient is receiving penicillin G 5 million units IV q6h (antibiotic), furosemide 40mg po qd (a diuretic), and K-Dur 20mEq po qd (a potassium supplement). Knowing that the penicillin G is being administered as the potassium salt, you check your references and note that there is 1.7mEq potassium in each million units of penicillin. How many mEq of potassium is this patient receiving daily?

$$\frac{54 \text{ mEq potassium}}{1.7 \text{ mEq K}} \times \frac{5 \text{ million units PCN}}{\text{dose}} \times \frac{4 \text{ doses}}{\text{day}} = 34 \frac{\text{mEq K}}{\text{day}}$$

34 mEq/day from penicillin + 20 mEq/day from potassium supplement = 54 mEq K/day

2. Osmolarity

2a. D5-0.45NS with KCl 20mEq/L is a solution commonly infused in hospitalized patients. Please determine the osmolarity.

MW: dextrose = 180, Na = 23, Cl = 35.5, K = 39

$$\text{dextrose osmolarity: } \frac{5000 \text{ mg}}{\text{dL}} \times \frac{10 \text{ dL}}{\text{L}} \times \frac{1 \text{ species}}{180 \text{ mg}} = 278 \frac{\text{mOsmol}}{\text{L}}$$

$$\text{saline osmolarity: } \frac{450 \text{ mg}}{\text{dL}} \times \frac{10 \text{ dL}}{\text{L}} \times \frac{2 \text{ species}}{58.5 \text{ mg}} = 154 \frac{\text{mOsmol}}{\text{L}}$$

$$\text{KCl osmolarity: } \frac{20 \text{ mEq}}{\text{L}} \times \frac{74.5 \text{ mg}}{\text{mEq}} \times \frac{2 \text{ species}}{74.5 \text{ mg}} = 40 \frac{\text{mOsmol}}{\text{L}}$$

$$\text{total} = 472 \frac{\text{mOsmol}}{\text{L}}$$

Facts and Comparison lists the measured osmolarity as 395 - 405 $\frac{\text{mOsmol}}{\text{L}}$

The difference in the calculated and actual numbers is due to bonding forces.

2b. How much sodium acetate 16.4% would you add to a liter of 1/2 normal saline in order to produce an isotonic solution? MW sodium acetate ($\text{NaC}_2\text{H}_3\text{O}_2$) is 82; MW NaCl is 58.5.

How many mEq of sodium are now in that liter of fluid? How many grams?

osmolarity

The definition of 1/2NS is that it is 1/2 the strength of normal saline: 1/2 of 0.9% = 0.45% saline

$$\frac{0.45 \text{ g NaCl}}{\text{dL}} \times \frac{10 \text{ dL}}{\text{L}} \times \frac{1 \text{ mol}}{58.5 \text{ g}} \times \frac{1000 \text{ mmol}}{\text{mol}} \times \frac{2 \text{ mOsmol}}{\text{mmol}} = 154 \frac{\text{mOsmol NaCl}}{\text{L}}$$

Blood osmolarity is 300-310 mOsmol/L so in order to be isotonic, you will need 310 – 154 = around 156 more milliosmoles. These will come from the sodium acetate.

$$156 \text{ mOsmol} \times \frac{1 \text{ mmol NaAc}}{2 \text{ mOsmol}} \times \frac{82 \text{ mg NaAc}}{\text{mmol}} \times \frac{1 \text{ g}}{1000 \text{ mg}} \times \frac{100 \text{ ml}}{16.4 \text{ g NaAc}} = 39 \text{ ml Na Ac}$$

The purists among you will say, “but you don’t have 310 mOsmol in a liter! It’s in 1039 ml!” This is true and why the upper end of the range was chosen. 310 mOsmol/1039 ml = 298 mOsmol/L \approx 300 mOsmol/L

milliequivalents

$$\frac{0.45 \text{ g NaCl}}{\text{dL}} \times \frac{10 \text{ dL}}{\text{L}} \times \frac{1 \text{ mol}}{58.5 \text{ g NaCl}} \times \frac{1000 \text{ mmol}}{\text{mol}} \times \frac{1 \text{ mEq}}{\text{mmol NaCl}} = 77 \frac{\text{mEq NaCl}}{\text{L}}$$

$$39 \text{ ml NaAcet} \times \frac{16.4\text{g NaAcet}}{100\text{ml}} \times \frac{1000\text{mg}}{1\text{g}} \times \frac{1 \text{ mmol}}{82 \text{ mg}} \times \frac{1\text{mEq}}{\text{mmol}} = \frac{78 \text{ mEq NaAc}}{\text{L}}$$

$$\begin{array}{rcl} 78\text{mEq Na Acetate} & = & 78\text{mEq Na} \\ 77\text{mEq NaCl} & = & \underline{77\text{mEq Na}} \\ \text{total:} & & 155\text{mEq Na} \end{array}$$

grams

NaCl is 39% sodium ($23/58.5 = 39\%$); Na Acetate is 28% sodium ($23/82 = 28\%$)

$$\begin{array}{rcl} 0.45 \text{ g NaCl/dL} \times 10 \text{ dL} & = & 4.5 \text{ g NaCl} \times 39\% = 1.755 \text{ g sodium} \\ 16.4\text{g NaAcet/100ml} \times 39\text{ml} & = & 6.396 \text{ g NaAcet} \times 28\% = \underline{1.79 \text{ g sodium}} \\ & & \text{total:} \quad 3.5 \text{ g sodium} \end{array}$$

Why would you want to know grams of sodium? Some patients are very sensitive to the osmotic effects of sodium (we call such individuals “salt sensitive”) and if they take in too much sodium, their blood pressure will climb. These patients need to limit their salt intake to no more than 2-3 grams of salt/day (this is called a “no-added-salt diet” and abbreviated NAS in a medical chart). You can see here that if such a patient were to receive the IV solution studied above, that person would exceed the recommended daily amount for sodium intake, possibly causing that person’s blood pressure to climb. High blood pressure is a strong risk factor for stroke and a relatively strong risk factor for heart attack and kidney disease. This wouldn’t mean that the patient couldn’t receive the sodium, but you would want to monitor the patient’s blood pressure and possibly give the patient a diuretic, which would cause him or her to increase urine production.

2c. A physician orders magnesium sulfate to be administered at a rate of 2g/hr to a patient experiencing premature labour. The pharmacy sends up 500ml of a 2% solution. What is the osmolarity of this solution? How many mEq/hr of magnesium will this patient receive?

osmolarity

A 2% solution is 2 g/dL. Since 500ml is 5 dL, you have 10g MgSO₄ in the bag.

$$10\text{g MgSO}_4 \times \frac{1 \text{ mol MgSO}_4}{120 \text{ g}} \times \frac{1000\text{mmol}}{\text{Mol MgSO}_4} \times \frac{2 \text{ mOsmol}}{\text{mmol MgSO}_4} = 165 \text{ mOsmol in 500ml}$$

Since osmolarity is mOsmol/L, we’ll multiply by two to get the osmolarity: $165 \times 2 = 312\text{mOsmol/L}$. This puts it on par with blood osmolarity, rendering this an isotonic solution.

milliequivalents

$$\frac{2 \text{ g}}{\text{hr}} \times \frac{1 \text{ mol}}{120 \text{ g MgSO}_4} \times \frac{1000 \text{ mmol}}{\text{mol}} \times \frac{2 \text{ mEq}}{\text{mmol}} = 33 \text{ mEq/hr}$$

3. Isotonicity

3a. An ophthalmologist near your pharmacy swears by tropicamide 2% solution as a mydriatic for his patients. Tropicamide is available commercially as a 0.5% and 1% solution, so you decide to humour him (or her) by mixing it special, figuring that you can charge a healthy compounding fee in the process. The trick is to make a isotonic solution. You decide to make a 30ml vial. The E value for tropicamide is 0.11. Please calculate how much tropicamide and how much sodium you will add to each 30ml vial before qs’ing to 30ml with water.

$$\text{a. } \frac{0.9 \text{ g}}{100\text{ml}} \times 30\text{ml} = 0.27\text{g (270 mg) NaCl in water in order to be isotonic}$$

$$\text{b. } 2\% = \frac{2 \text{ g}}{100\text{ml}} \times 30\text{ml} = 0.6\text{g tropicamide needed}$$

c. $0.6\text{g} \times 0.11 = 0.066\text{g}$ of NaCl accounted for by the tropicamide

d. $0.27\text{g} - 0.066\text{g} = 0.204\text{g}$ NaCl needed

summary: You will weigh out 0.6g of tropicamide powder 0.204g of NaCl crystals. You will place both of these in a beaker and qs (i.e. add enough water to make a total of) 30ml. This is assuming that tropicamide is soluble in water!

3b. You have been asked to prepare 20ml of naphazoline 0.5% ophthalmic solution in a sodium chloride base. You have naphazoline HCl, USP (MW 246.74), which has a sodium chloride equivalent value of 0.27. How much naphazoline will you measure, how much sodium chloride, and approximately how much water will you add? Assume that no other substances will be added.

1. $\frac{0.9\text{g}}{\text{dL}} \times \frac{1\text{dL}}{100\text{ml}} \times 20\text{ml} \times \frac{1000\text{mg}}{\text{g}} = 180\text{mg}$ NaCl or equivalent needed

2. $\frac{0.5\text{g naph}}{\text{dL}} \times \frac{1\text{dL}}{100\text{ml}} \times 20\text{ml} \times \frac{1000\text{mg}}{\text{g}} \times 0.27 = 27\text{mg}$ of NaCl equivalent by the naphazoline

3. $180\text{mg} - 27\text{mg} = 153\text{mg}$ NaCl needs to be added to the product.

4. determine amount of naphazoline HCl crystals to add

$$\frac{0.5\text{g naph}}{\text{dL}} \times \frac{1\text{dL}}{100\text{ml}} \times 20\text{ml} \times \frac{1000\text{mg}}{\text{g}} = 100\text{mg naphazoline HCL}$$

You will therefore weigh out 153mg of NaCl and 100mg of naphazoline. These should be placed into a sterile ophthalmic vial. You will then add enough water to make 20ml of solution (i.e., qs to 20ml with water).

Could you have done this using the osmolarity calculations similar to what was done in #s 1 and 2 above? Sure. You would get the same answer. But when you're dealing with such small amounts of drug, it is easier to use the method outlined above. You will find that the osmolarity calculations are most useful for medications that are administered intravenously in larger amounts of solution and that the sodium-chloride equivalent method outlined above works well for eye drops and nose drops/sprays.

3c. Now you have to make 30ml of a 1% atropine solution in a boric acid base. The MW of atropine sulfate is 694.82 and of boric acid is 61.84. The sodium chloride equivalents are 0.13 and 0.5, respectively. How much atropine sulfate, how much boric acid, and how much water will you add? (just to confirm, you will *not* be adding any sodium chloride)

1. $\frac{0.9\text{g}}{\text{dL}} \times \frac{1\text{dL}}{100\text{ml}} \times 30\text{ml} \times \frac{1000\text{mg}}{\text{g}} = 270\text{mg}$ NaCl equivalent needed

2. $\frac{1\text{g atropine}}{\text{dL}} \times \frac{1\text{dL}}{100\text{ml}} \times 30\text{ml} \times \frac{1000\text{mg}}{\text{g}} \times 0.13 = 39\text{mg}$ of NaCl equivalent for by the atropine

3. $270\text{mg} - 39\text{mg} = 231\text{mg}$ of the NaCl equivalent of boric acid needs to be added to the product.

$$231\text{mg NaCl} \times \frac{1\text{mg boric acid}}{0.5\text{mg NaCl}} = 462\text{mg boric acid to add}$$

4. determine amount of atropine crystals to add

$$\frac{1\text{g atropine}}{\text{dL}} \times \frac{1\text{dL}}{100\text{ml}} \times 30\text{ml} \times \frac{1000\text{mg}}{\text{g}} = 300\text{mg atropine}$$

You will therefore weigh out 462mg of boric acid and 300mg atropine. These should be placed into a sterile ophthalmic vial. You will then add enough water to make 30ml of solution (i.e., qs to 30ml with water).

4. Diluting and Concentrating

4a. A physician orders Benylin DM® cough syrup, 4oz., 1 tsp q6h prn cough, for a child. Benylin DM® is a preparation containing 10mg of dextromethorphan (a cough suppressant) in each 5ml. You only carry Delsym® in your pharmacy, which contains 30mg dextromethorphan/5ml. Rather than adjust the dose (hey, that's not until lesson 4!), you decide to dilute some Delsym® with some cherry syrup, so as to arrive at the same concentration as the Benylin DM® (and make it more tasty in the process...). How much Delsym® and how much cherry syrup will you use?

note: cherry syrup has a dextromethorphan concentration of 0mg/5ml

30mg/5ml		10 parts	<u>10 parts</u> = <u>x ml</u>	x = 40ml
	10mg/5ml		30 parts 120ml	
0mg/5ml		<u>20 parts</u> 30 parts		

you will therefore pour 40ml of Delsym® into a 4oz bottle and 80ml of cherry syrup to make 120ml of a 10mg/5ml cough syrup.

4b. You have been asked to mix 10ml of fortified tobramycin eye drops, 1%, for a patient. you have the commercially-prepared Tobrex® 0.3% 10ml on your shelf. You also have some preservative-free tobramycin 40mg/ml solution. Please explain how you will mix this preparation:

$$x = \frac{10\text{ml} (10\text{mg/ml} - 3\text{mg/ml})}{40\text{mg/ml} - 3\text{mg/ml}} = \frac{70\text{mg}}{37\text{mg/ml}} = 1.89\text{ml} \approx 1.9\text{ml}$$

You will withdraw **1.9 ml** of Tobrex® solution from the Tobrex® container and replace it with **1.9 ml** of tobramycin 40mg/ml solution.

Note: I have had to compound this medication in practice many times, so this is not just a textbook exercise.

I used the alligation method in problem #3a and the algebraic method in problem #3b. Your answers should be the same regardless of which method you use.

4c. A pharmacist mixed a standard morphine sulfate intravenous infusion of 50mg morphine in 250ml D5W for a patient. Before the solution could be used, the order was discontinued. Rather than discard the solution, the pharmacist decided to use it to make some solution for patient-controlled analgesia (PCA) syringes, the usual concentration of which is 1mg/ml. How many milliliters of a 15mg/ml stock solution of morphine sulfate will the pharmacist have to add to the 50mg/250ml solution to produce a final solution with a concentration of 1mg/ml? (round to the nearest 0.2ml) How many *full* 50ml syringes will the pharmacist be able to make?

14.3 ml

5 or 6 syringes (depending upon what you do with the leftover)

desired concentration = 1 mg/ml

starting solution = 0.2 mg/ml (50mg/250ml)

stock solution = 15 mg/ml

15mg/ml		0.8 parts
	1mg/ml	
0.2mg/ml		<u>14 parts</u> 14.8 parts

$$\frac{0.8 \text{ parts}}{14.8 \text{ parts}} = \frac{x \text{ ml}}{250 \text{ ml} + x}$$

$$14.8x = (250 \text{ ml} + x)0.8$$

$$14.8x = 200 \text{ ml} + 0.8x$$

$$14x = 200 \text{ ml}$$

$$x = 14.3 \text{ ml}$$

250ml + 14.3ml = 264.3ml = 5 full syringes, with some leftover (to which one could add 2.38 ml of the 15mg/ml stock solution and 33.3ml NS to make a sixth syringe)

5. Aliquot calculations

5a. You receive a prescription for vanadyl sulfate 10mg capsules. The patient is to take one daily for 3 months to see if it helps her diabetes. You order 25 grams of vanadyl sulfate hydrate from a chemical manufacturing company and decide to use lactose as the diluent. You will need to make 90 capsules. The sensitivity requirement of your balance is 10 mg.

$$\frac{10 \text{ mg}}{0.05} = 200 \text{ mg (the MWQ)}$$

$$0.05$$

total amount of vanadyl sulfate needed for 3 months (92 caps; will make 93 for wastage):

$$\frac{10 \text{ mg vanadyl}}{\text{capsule}} \times 93 \text{ capsules} = 930 \text{ mg vanadyl sulfate}$$

I will choose to add 190mg of lactose to each capsule in order to reach the MWQ for this balance.

$$\frac{190 \text{ mg lactose}}{\text{capsule}} \times 93 \text{ capsules} = 17,670 \text{ mg} = 17.67 \text{ grams lactose}$$

I will triturate these together and then fill the capsules with 200mg of the resulting product.

5b. A patient wishes to take a natural form of estrogen to see if it helps with hot flashes, and wants it prepared in a capsule that she can take once daily. You can purchase soy isoflavones in powder form from a distributor. You and the prescriber decide on a dose of 80mg daily (this has been shown effective in clinical trials). You will use starch as the base since she is lactose-intolerant. You have a mechanical torsion balance with a sensitivity requirement of 6mg.

$$\frac{6 \text{ mg}}{0.05} = 120 \text{ mg (the MWQ)}$$

$$0.05$$

total amount of soy isoflavone powder needed for 3 months (92 caps make 93 for wastage):

$$\frac{80 \text{ mg isoflavones}}{\text{capsule}} \times 93 \text{ capsules} = 7.440 \text{ grams isoflavone}$$

I will choose to add 40mg of cornstarch to each capsule in order to reach the MWQ for this balance

$$\frac{40 \text{ mg starch}}{\text{capsule}} \times 93 \text{ capsules} = 3.720 \text{ grams cornstarch}$$

I will triturate the cornstarch and isoflavones together and then fill the capsules each with 120mg of the resulting product.

5c. You receive a prescription for an estrogen preparation that is to contain estriol 2mg, estrone 0.25mg and estradiol 0.25mg in a single capsule. Lactose is to be used as the base. The patient will take one daily. You need to prepare 92 capsules. The sensitivity requirement of your balance is 1 mg.

1 mg = 20mg (the MWQ)
0.05

total amount of each ingredient needed for 3 months (92 caps; make 96 for wastage – why this number? When multiplied by 0.25, it comes out as a whole number; if it was a fraction of a mg, my balance could not accurately weigh that amount):

2mg estriol x 96 capsules = 192 mg estriol
capsule

0.25mg estrone x 96 capsules = 24 mg estrone
capsule

0.25mg estradiol x 96 capsules = 24 mg estradiol
capsule

I will choose to add 57.5 mg of lactose to each capsule in order to exceed the MWQ for this balance and to ensure that my #5 capsules are slightly packed.

57.5 mg lactose x 96 capsules = 5520 mg lactose = 5.52 g lactose
capsule

I will triturate the lactose and all 3 estrogen powders together and then fill the capsules each with 60mg of the resulting product.

6. Buffers

You need to compound an ophthalmic solution of a beta-lactam antibiotic that is susceptible to hydrolysis and most stable when the pH of a solution is 5.0. You have decided to prepare a sodium acetate-acetic acid buffer solution. You place 0.6 ml of glacial acetic acid (99% acetic acid) in 99.4ml of water, giving you ≈100ml of a 0.1 M acetic acid solution. You then weigh 820 mg of sodium acetate and add water to the 100ml mark, giving you 100ml of a 0.1 M sodium acetate solution. The pK_a of acetic acid is 4.76.

6a. If you were to add 5ml of a 0.1 M acetic acid solution to 5ml of a 0.1 M sodium acetate solution, what would be the pH of the resulting solution?

A 0.1 M acetic acid solution has 0.1 moles/L, which is the same thing as 0.1 mmol/ml. 5 ml of a 0.1 mmol/ml solution would give you 0.5 mmol acetic acid. The same thing is true for 5ml of a 0.1 M sodium acetate solution, since $0.1 \text{ moles/L} = 0.1 \text{ mmol/ml} \times 5\text{ml} = 0.5 \text{ mmol}$ of sodium acetate. This can now be plugged into Henderson-Hasselbalch.

$$pH = 4.76 + \log \frac{0.5\text{mmolNaAcetate}}{0.5\text{mmolAceticAcid}}$$

$$pH = 4.76 + \log 1 \quad \text{as you know, } 1 = 10^0, \text{ so } \log 1 = 0$$

$$pH = 4.76 = pK_a$$

I hope that this is comforting to you, since you know that when the $pH = pK_a$, the concentration of the ionized form is equal to the concentration of the unionized form (as it does here).

6b. Let's change the relative proportions of each constituent of the buffer solution. If you were to add 2ml of a 0.1 M acetic acid solution to 8ml of a 0.1 M sodium acetate solution, what would be the pH of the resulting solution?

You know that 2ml of a 0.1 M acetic acid solution will give you 2 millimoles, and 8ml of a 0.1 M sodium acetate solution will give you 8 millimoles.

$$\text{pH} = 4.76 + \log \frac{8\text{mmolNaAc}}{2\text{mmolAcetAc}}$$

$$\text{pH} = 4.76 + \log 4$$

$$\text{pH} = 4.76 + 0.6$$

$$\text{pH} = 5.4$$

These are both easy calculations since the molarity of the buffer system components are the same, but it gives you a chance to see how altering the proportions of the buffer system components will alter the pH. In the next question, you can see how much of each component you will need in order to make a buffer solution at the pH you want: 5.0

6c. What volumes of 0.1 M acetic acid and 0.1 M sodium acetate will you need in order to make 30ml of a buffer that has a pH of 5.0?

Let x = volume of acetic acid you will need, so $30-x$ = the volume of sodium acetate you will need.

$$5.0 = 4.76 + \log \frac{(0.1 \text{ mmol/ml NaAc})(30 \text{ ml} - x \text{ ml})}{(0.1 \text{ mmol/ml AcetAc})(x \text{ ml})}$$

$$5.0 - 4.76 = \log \frac{(0.1)(30-x)}{0.1x}$$

$$0.24 = \log \frac{3 - 0.1x}{0.1x} \quad \text{take the antilog of each side}$$

$$1.73 = \frac{3 - 0.1x}{0.1x}$$

$$0.173x = 3 - 0.1x$$

$$0.273x = 3$$

$$x = 10.989 \approx 11\text{ml}$$

Therefore, if you mix 11ml of 0.1 M acetic acid with 19 ml of 0.1 M sodium acetate, you will have 30ml of a buffer solution of pH 5.0