

Lesson 2: Understanding expressions of drug amounts

All pharmaceutical preparations have some sort of ingredient amount associated with them, which many health care professionals refer to as “strength.” This term is sometimes used incorrectly as you can see in the box below. Drug amounts in products containing only one drug are quite easy to understand, since the units are most often metric (e.g., 250mg/capsule, 0.5g/tablet) or less often expressed in grains (with which you are now familiar, of course!). The following information is meant to give you some background on other ways drug amounts are expressed.

Strength, potency, and effectiveness

- Strength is the amount of drug in a given dosage form, for example, 500 mg/tablet.
- Potency refers to the relative strengths of medications that can produce the same effect. The drug with the lowest strength to produce the effect is said to be the most potent. Strength is often used interchangeably with potency, but they are not the same thing. Potency starts with the effect and examines the relative strengths of different drugs able to produce that effect, while the word “strength” itself does not imply anything about effect.
- Effectiveness refers to the percent of patients who will have a desired response to a drug. Strength can be confused with effectiveness when a patient asks if one drug is stronger than another. What the patient really wants to know is whether one drug is more likely to produce a desired effect compared to the other.

Units

Some drugs strengths are expressed in terms of units of activity according to some biologic assay. Common drugs for which units are used include penicillin, insulin, bacitracin, heparin, nystatin, polymixin, and vitamins A, D, and E. Metric equivalency to units varies, with each drug using a “unit” system of measurement having its own conversion factor. For example:

- penicillin 400,000 units = 250mg
- nystatin 4400 units \approx 1mg
- insulin 100 units/ml of insulin suspension. Therefore 1 insulin unit = 10 μ L of insulin suspension
- vitamin A 1 unit = 0.3 μ g of all-*trans* retinol, 0.344 μ g of all-*trans* retinol acetate, or 0.6 μ g of beta carotene; here you can see that the unit conversion varies with the form of vitamin A used

You do not need to memorize these unit equivalents, since you will rarely ever need to convert. If you do need to convert in practice, you can look the conversion up (AHFS Drug Information is a good source of information about unit equivalents; Facts and Comparisons also contains some information).

Parts

Parts indicate amount proportions. Parts are most often used for medication compounding to indicate the *relative* amounts of each ingredient. Parts themselves are unitless, because *you* decide what the units will be. Just remember that you must use the same units for each ingredient (e.g., you can’t use grams for one ingredient and ounces for another). It will be easiest to choose grams as the unit if you are dealing with a solid ingredient and milliliters if you are dealing with liquid since most of your measuring instruments will use metric units.

For an example, consider the following recipe for an antacid powder:

calcium carbonate	
magnesium oxide	5:1:4:3
sodium bicarbonate	
bismuth subcarbonate	
dissolve in 8 ounces of water and drink prn indigestion	

Notice that the parts are separated with a colon. You will assume that the order of each number corresponds to the order of the list of ingredients. Thus, there are 5 parts of calcium carbonate, 1 part of magnesium oxide, 4 parts of sodium bicarbonate, and 3 parts of bismuth subcarbonate.

The easiest way to make this would be to mix 5 g of calcium carbonate, 1g of magnesium oxide, 4g of sodium bicarbonate, and 3g of the bismuth subcarbonate, for each dose. The patient may, however, need more than one dose, so you may decide to mix a 300g supply. In this case, you will use the parts to tell you the ratio of the

ingredients. You know that $5+1+4+3 = 13$ total parts, and you know that the total weight is 300g. Now you can just use simple proportions to solve the amounts for each:

$$\text{e.g., } \frac{5 \text{ parts Ca(CO}_3)_2}{13 \text{ parts total}} = \frac{x}{300\text{g}} \quad x = 115 \text{ g calcium carbonate}$$

$$\frac{1 \text{ part MgO}}{13 \text{ parts total}} = \frac{y}{300\text{g}} \quad y = 23 \text{ g magnesium oxide}$$

$$\frac{4 \text{ parts NaHCO}_3}{13 \text{ parts total}} = \frac{z}{300\text{g}} \quad z = 92 \text{ g sodium bicarbonate}$$

$$\frac{3 \text{ parts (BiO)}_2\text{CO}_3}{13 \text{ parts total}} = \frac{w}{300\text{g}} \quad w = 69 \text{ g bismuth subcarbonate}$$

Occasionally, you will see a number followed by the term “ppm.” This stands for “parts per million” and is most often used to indicate the amount of trace substances in water. The standard dilution for fluoride added to a municipal water source, for example, is 1ppm. In every 1,000,000ml of water, therefore, there is 1g of fluoride. You get the idea.

Concentration

Liquid and topical preparation strengths are called concentrations and involve two numbers written in fraction form. The numerator will always tell you the amount of the drug that is the denominator, which is a given volume of drug plus vehicle. Put more simply, concentration tells you how much drug there is in a given dosage form amount.

Liquids are expressed as weight/volume (w/v) with the weight being the amount of drug and the volume representing a specific volume of drug and vehicle. An example of this type of concentration is Benadryl elixir. If you look on the side of the bottle, you will read that it has a concentration of 12.5mg/5ml. This means that 5ml of the elixir will contain 12.5mg of diphenhydramine (the active ingredient).

Solid topical medication concentrations are usually expressed as weight/weight (w/w), with the numerator representing the weight (mass) of drug present in the denominator, which is a total weight of drug plus vehicle. An example is nystatin cream, which is available in a concentration of 100,000 units/g. This means that there are 100,000 units of nystatin in each gram of cream that you squeeze out of the tube.

Rarely, you will see liquid forms of drugs expressed as volume/volume (v/v), with the first volume number expressing the volume of liquid medication added, and the second volume number representing the total volume of medication plus vehicle. An example is ethanol 10ml/100ml, where 10ml of absolute ethanol (i.e., 100% ethanol) is added to enough water (around 90ml, although bonding forces may fractionally affect the volume of the water) to make a total of 100ml of fluid.

Although all concentrations are expressed as weight/weight or weight/volume, you will most often see the solid topical (i.e., things applied to the outside of the body) medications expressed as percentage strength and infrequently as ratio strength. Percentage strength and ratio strength are just two different ways of expressing the same thing that standard weight/weight or weight/volume concentration expresses and are explained next.

Percentage Strength

Medication concentrations are often written as a number followed by a percent sign (e.g., 2%), which implies a specific weight/volume concentration of g/100 units. For a liquid, the units will be milliliters (e.g., 5% = 5g/100ml). In a solid, the units will be grams, so percentage would imply g active medication/100g total dosage form. For instance, a common OTC cream is hydrocortisone 1%. This means that there is 1 gram of hydrocortisone in each 100 grams of cream. An example of a liquid product is Hibiclens, a topical antiseptic. If you read the fine print on the bottle, you will notice that it “contains 4% w/v” chlorhexidine gluconate. Thus, there are 4g of chlorhexidine gluconate in every 100ml of Hibiclens solution. Almost all topical products (e.g. creams, gels, pastes) are expressed in percentage strength.

A special type of percentage is the mg%. This means mg/100ml or mg/100g. You will rarely encounter this expression in a commercial product, but will see it frequently used to express laboratory values (i.e., the numbers that are generated after analysis of the constituents in someone's blood). For instance, creatinine (a byproduct of muscle breakdown that can provide an indication of how well a person's kidneys are working) is often reported as "1.0 mg%" and sometimes as "1.0 mg/dL," both of which mean that there is 1.0 mg of creatinine in every 100ml of serum.

Ratio Strength

Ratio strength can be used to describe the concentration of a dilute solution. In ratio strength, the first number is a 1 and it is followed by a colon and then another number, e.g., 1:100. These can be read as parts (e.g., 1 part in 100 parts). You assign the units. The units are always grams or milliliters, depending upon whether you are dealing with a w/w or w/v preparation. Thus a 1:100 ratio strength would mean a solution with 1g in 100ml, or it might mean a solid preparation, say 1g of drug in 100g of ointment. You will use the word "in" to verbally express the relationship between the two numbers. Thus, an epinephrine 1:1000 ratio strength solution would be pronounced epinephrine "one in one thousand" and would refer to a solution that contains 1 gram of solute in every 1000ml of solution.

Solubility Ratios

A solubility ratio, more commonly just called solubility, is the maximal amount of a solute (hereafter referred to as a drug, since that's what we pharmacists care about) that will go into solution in a given amount of solvent. Once that maximal solubility is reached, addition of more drug will result in precipitation of that drug out of the solution, which you will see as a layer of crystals or crud at the bottom of the container holding the solution. You can find the solubility of each drug in references such as the United States National Formulary or, if you don't know anyone rich enough to afford this, in the Merck Index. The American Hospital Formulary Drug Information text also lists solubility ratios for some drugs. Solubilities are most often expressed in one of two ways.

- As a concentration. This will be the easiest kind of solubility for you to deal with. For example, ceftriaxone, an injectable antibiotic, is stated to have a solubility in water of 400mg/ml at 25°C (room temperature). This means that if you try to place 500mg in 1ml at 25°C, you will get a layer of stuff at the bottom of the vial.
- Qualitatively. Drugs will be described in words, rather than numbers. For example, cefazolin, another antibiotic, is described as "freely soluble" in water. This can be frustrating when a physician is on the phone asking if a patient who cannot swallow a tablet could instead receive the drug in liquid form and you find that not only is there no liquid form but that the drug is "slightly soluble" in water. What does this mean? Fortunately, there are guidelines that will give you a rough conversion of the qualitative term to a quantitative term.

<i>description</i>	<i>parts of solvent to one part of drug</i>
very soluble	less than 1
freely soluble	1-10
soluble	10-30
sparingly soluble	30-100
slightly soluble	100-1000
very slightly soluble	1000-10,000
insoluble (also practically insoluble)	>10,000

Similar to ratio strength, the units are always grams for solids and milliliters for liquids.

Reading this, you would see that the "freely soluble" cefazolin would allow 1 gram to be placed in between 1 and 10 milliliters, but the "slightly soluble" allopurinol that the physician called you about would need to be in a much more dilute solution. One gram could only be placed with confidence in one liter of water since the drug is soluble in somewhere between 100 and 1000 milliliters, but you don't know where in that interval the maximum solubility really is (fortunately, because you paid attention in your compounding class, you can come up with an alternative way to formulate the liquid so that your patient will not have to swallow such a large volume for each dose!).

One thing that you need to be aware of is that a solubility ratio may look a lot like a ratio strength, but the two are actually different. A solubility ratio of 1:3 is not the same as a ratio strength of 1:3. The difference between the two is explained here.

In a solubility ratio, the colon should be read as “to.” This will be more familiar to you if you have used the term “one-to-one” in a sentence to indicate that equal amounts of each ingredient are present (here you are actually using neither a ratio strength or a solubility ratio but is instead an indication of parts: proportions. Confusing? You bet!). A preparation with a solubility of 1:3 would be read as, “ a solubility of one to three,” and would indicate that you have one gram of drug and 3 grams of solvent mixed together. This is different from a ratio strength of 1:3 which would mean you have 1 gram of drug *in* 3 grams of solution (i.e., drug plus solvent). A drug made at its solubility ratio of 1:2 would have a ratio strength of 1:3.

So how do you tell the difference between the two when you see a 1:x term on a prescription or exam? The trick lies in looking or listening for the words “solubility of” *before* the expression to know that you are dealing with one part solute plus x parts of solvent; look for the word “solution” or “preparation” *after* the expression to indicate that you are dealing with a ratio strength problem, and thus will need one part of solute *in* x parts of solvent. This will be very tricky to sort out because colloquially, you have probably heard someone say that something has a “one-to-one ratio” (which as just mentioned means neither ratio strength nor solubility expression but actually refers to proportionate parts). You may therefore want to equate the word “to” with the ratio strength preparation. Avoid this tendency.

Burows solution (aluminum acetate) is an example of a medication with a ratio strength. It comes as a packet of powder (12.5g) that the instructions tell you to place in a container and qs to 500ml with water (i.e., add water until you reach the 500ml line of the container) in order to produce a 1:40 solution. Basically, then, you will have a final solution containing 1 gram of aluminum acetate *in* every 40 milliliters of Burows solution (expressed in ratio strength). Equal parts of this same Burows solution and some glycerin can then be mixed together to make a preparation that softens ear wax. The components of this ear wax softener are expressed as proportionate parts: one part burows and one part glycerin (i.e., Burows-glycerin 1:1).

A final note about seeing numbers separated by colons. There were three things reviewed here which involved drug amounts expressed as numbers separated by colons. These were parts, ratio strength, and solubility expression. If you find yourself getting confused by them, just remember that they are all a way of expressing drug and diluent proportions. You will use these proportions as tools to determine the correct amounts of drug to add when compounding a medication for a patient. Just be aware of the “to” (parts, solubility expression) and the “in” (ratio strength) difference between interpreting these.

Proof Strength

Taxes on alcoholic beverages are determined by the proof strength of the alcoholic beverage. Any given proof volume of alcohol will be composed of 50% water and 50% alcohol. Thus, proof strength of an alcoholic beverage will always be twice the amount of the percent strength (v/v). Forty proof vodka contains 20% v/v alcohol. Forty-eight proof whisky will contain 24% v/v alcohol. You get the picture. Most alcoholic beverage labels nowadays specify alcohol content by percentage strength. Some labels still list the proof strength but most of these labels also have the percentage strength listed as well.

Specific Gravity

You will remember the concept of density from your general chemistry course. Density is the weight (mass) of any given substance that occurs in a given volume, and is key to understanding specific gravity. It seems funny to include information about specific gravity in a chapter that introduces expression of drug amounts, mainly because specific gravity is a unitless number. It is important for you to understand the concept, however, and there is a clinical area where you will see specific gravity used routinely.

First, the concept. Specific gravity is the ratio of the mass (weight) of any given volume of solid or liquid, to the mass of the same volume of water. To calculate specific gravity of any given substance, you will need to choose a given volume and then weigh it. The resulting number, expressed as weight/volume, is placed in the numerator position of a fraction, and the weight of the same volume of water is placed in the denominator position. You will then divide one by the other and end up with a number referred to as the specific gravity of that tested solution.

e.g., 1 liter of 5% dextrose in water (D5W) weighs 1.02 kg

$\frac{1.02 \text{ kg/L (D5W)}}{1.0 \text{ kg/L water}} = 1.02$, which is the specific gravity of (D5W)

Notice that specific gravity has no units (because the units in numerator and denominator cancel each other out). Liquids and solids are always compared to the same volume of water, and gasses are compared to the same weight of hydrogen.

One place you will see specific gravity used in practice is in the IV admixture room. There is a machine which can be programmed to mix various IV fluids together into one bag. The correct amount of the IV fluid to be added is not determined by volume, but by weight, so the specific gravity of each IV fluid to be added needs to be programmed into the machine. The specific gravity of most of the commonly-used IV fluids is noted on a sheet of paper which accompanies the machine, so you don't have to go through the tedious business of finding out the specific gravity yourself. If you ever have an uncommon fluid, however, you will need to know how to determine the specific gravity. In this case it's time to get out the balance.

You will also see specific gravity used in the clinical setting, primarily in the analysis of urine. Since urine is mostly water with only a few particulates, the specific gravity is usually around 1.005. An increase or decrease in specific gravity can aid in diagnosis of certain medical disorders

Molarity

The preceding sections have dealt primarily with drug amounts expressed using the metric system. The remainder of this lesson will acquaint you with other ways in which drug concentrations in a solution are expressed/measured. The first of these is an expression of drug amount in solution that you may be so familiar with that you shake your head to think it even needs review. It never hurts, though, to brush up on the conversion between solutions expressed in molar form (moles/L) and in metric form (e.g., g/L). Where will you see the use of molarity in pharmacy practice?

One of the places molarity is commonly used is in the reporting of laboratory values (the numbers that they get from analyzing blood drawn from a patient), since the introduction of standard laboratory units (Système International or SI units) worldwide. Like the metric system (and indeed many other basic concepts such as universal healthcare and a decent cup of tea), about the only place in the world that has not yet adopted these units is the United States. Therefore, whenever you read an article from a medical journal not printed in the US (and many that are), you will see numbers reported for a laboratory value that seem very strange when compared to the normal laboratory values that, believe me, you will know intimately by the end of your pharmacy school career. In order for them to make sense to you, you will need to convert them to numbers you know. Let's look at an example:

A normal serum calcium is reported in a European medical journal as 2.1 - 2.6 mmol/L. US laboratories normally report this range in mg/dL. What would the European range be if it were reported in units used in a US laboratory?

$$2.1 - 2.6 \frac{\text{mmol}}{\text{L}} \times 40 \frac{\text{mg}}{\text{mmol}} \times \frac{1 \text{ L}}{10 \text{ dL}} = 8.4 - 10.4 \frac{\text{mg}}{\text{dL}}$$

Note: in case you were wondering where I got the 40mg/mmol, it is the molecular weight of calcium. "But," I hear you cry, "the molecular weight of calcium is 40 g/mole!" Just remember that if you divide both numerator and denominator by the same amount, the weight will stay the same.

Thus:

$$1 \frac{\text{g}}{\text{mole}} = 1 \frac{\text{mg}}{\text{mmol}}$$

or, in this example:

$$40 \frac{\text{g}}{\text{mole}} = 40 \frac{\text{mg}}{\text{mmol}}$$

Remember this concept! It will help you greatly in practice, as well as in an exam situation.

Another place that you will see molarity used is in the "methods" section of journal articles that outline solutions used for assays, particularly where stability is measured. If you need to make a solution that is not commercially available, you will need to decipher this information in order to duplicate the product tested for stability that was reported in the journal article.

The final, and possibly most important place you will see molarity used, is in the calculations used to decide amounts of certain electrolytes (most commonly phosphate) to be added to a total parenteral nutrition (TPN) intravenous solution. Because phosphate is commonly ordered in millimoles, you will need to figure out how many millimoles of phosphate need to be added as either the potassium or sodium salt, before you can calculate how much potassium or sodium to add as the chloride salt. We will get into this in greater depth during the section on preparation of TPN solutions (Lesson 5).

You know what molarity is. Your main challenge on calculations involving molarity will be to get the units to convert correctly, since laboratory values and phosphate in intravenous nutrition will not involve moles/L but instead will involve mmol/L or even $\mu\text{mol/L}$, whereas you will be dealing with a molecular weight that is g/mole. It is best when dealing with these to think of molecular weight as really being mg/mmol, since that will be more helpful to you in these types of conversions. Several practice problems are included at the end of this lesson to reacquaint the rusty with these conversions.

Milliosmoles

Another way that drug amounts in solution can be expressed is as the number of particles in a given amount of solution. Remember that the number of particles in a given solution determines the osmotic pressure and will play an important role in the rate and extent to which those particles will diffuse across a membrane. This is a crucial consideration for solutions that are being infused into a patient's veins or into other body parts such as the eye, and will be dealt with in greater detail in the next lesson. For now, it is important that you understand how to convert between milliosmoles in a given solution and molecular weight of a given solution.

How do you determine milliosmoles? It is pretty straightforward. You need to determine first how many particles a given substance will dissociate into. Most substances are bonded pretty tightly (i.e., covalently) and so will not dissociate. But what if a substance is not bonded tightly? What if it can dissociate into separate particles? In this case you will need to determine how many particles it can break up into. The number of potential particles that a substance can break up into is called the *species*. The species can be calculated by separating the substance into its positive and negative parts, and then counting those parts. e.g.,

- NaCl species = $1 \text{ Na}^+ + 1 \text{ Cl}^-$ = 2
- CaCl_2 species = $1 \text{ Ca}^{++} + 2 \text{ Cl}^-$ = 3
- dextrose species = 1 dextrose = 1 dextrose is covalently bonded so doesn't separate into smaller particles
- Na Acetate species = $1 \text{ Na}^+ + 1 \text{ Acetate}^-$ = 2 acetate ($\text{C}_2\text{H}_3\text{O}_2$) is covalently bonded so doesn't separate into smaller particles

Note that moles look at the whole substance whereas osmoles look at the potential dissociation of that substance. Thus, in a given substance that does not dissociate, e.g., dextrose as seen above, the number of millimoles is equal to the number of milliosmoles (abbreviated mOsmol). But what if the substance can dissociate? In this case one millimole will equal the number of particles (milliosmoles) that the substance could potentially break up into. Thus one millimole of NaCl would be equivalent to 2 milliosmoles of NaCl. One millimole of CaCl_2 would be equivalent to 3 milliosmoles of that substance. Written differently:

- 1 millimole NaCl = 2 milliosmoles NaCl
- 1 millimole CaCl_2 = 3 milliosmoles CaCl_2
- 1 millimole dextrose = 1 milliosmole dextrose
- 1 millimole sodium acetate = 2 milliosmoles sodium acetate

You know by now that many solution concentrations are expressed as metric weight/volume. How can you determine the number of milliosmoles (i.e., species) in a given solution, if you are told the solution concentration? First set up the destination for your equation (where you want to end up):

$$= \underline{\hspace{2cm}} \text{ milliosmoles}$$

You should be able to calculate from the solution concentration the amount of drug in grams. Convert this to milligrams.

$$\text{mg drug} = \text{_____ milliosmoles}$$

You know that a mole is equal to the molecular weight in grams. Thus, a millimole is equal to the molecular weight in milligrams of a substance, so you can convert molecular weight in milligrams to millimoles.

$$\text{mg drug} \quad \times \quad \frac{1 \text{ mmol}}{\text{MW in mg}} = \text{_____ milliosmoles}$$

You also know that in a millimole, there will be a certain number of milliosmoles: usually 1, 2, or 3. This will set up the final part of your conversion.

$$\text{mg drug} \quad \times \quad \frac{1 \text{ mmol}}{\text{MW in mg}} \quad \times \quad \frac{\# \text{ mOsmol}}{\text{mmol}} = \text{_____ milliosmoles}$$

An example. Let's say that in one liter of solution you have nine grams of sodium chloride. You want to know how many milliosmoles that solution contains. Just plug the numbers into the equation above:

$$9000\text{mg NaCl} \quad \times \quad \frac{1 \text{ mmol}}{58.5 \text{ mg}} \quad \times \quad \frac{2 \text{ mOsmol}}{\text{mmol}} = 308 \text{ milliosmoles in that liter}$$

where each millimole of NaCl contains 58.5mg and 2 mOsmol.

You may be saying, "well, yeah, right, but how do I know whether something dissociates or not?" A reasonable guide is to remember that ions dissociate and so if you are given a drug, look for those ionic parts. It's pretty easy if you're given an electrolyte such as the NaCl in the example above. But what if you're dealing with a commonly-used drug? Common sense will get you far in this question, since many drugs are given as the single drug (which is usually covalently bonded) or else as the salt. If you see the salt form, then you can guess that the drug will dissociate. For example, how many milliosmoles would there be in each millimole of cefazolin sodium? You might guess two, because you know that the sodium is an ion and can dissociate into 1 particle of sodium and 1 particle of cefazolin. You would be correct. One millimole of ticarcillin disodium would contain three milliosmoles (one ticarcillin particle and two sodium particles).

Milliequivalents

As just discussed, ionic substances can dissociate or can remain bonded. There are many things which can affect the proportion of bonded and dissociated ions in a given solution and you will learn about these in your pharmaceutical chemistry course(s). The amount of an ionic substance in the body can be relayed as molecular weight (millimoles) or as the number of particles into which the substance could dissociate (milliosmoles) but neither of these expressions would adequately express the electrical activity of the ions, that is the number of positively charged ions, negatively charged ions, or bonded ions that are chemically neutral.

Why would you want to know the electrical activity of ions in the body? The quantity of ions inside a cell can directly affect how that cell works. For instance, electrical activity, determined by the amount of ions capable of conducting an electrical impulse (i.e., electrolytes), can affect how nerve impulses are conducted. The insides of nerve cells have a primarily negative charge, owing to a larger number of anions than cations residing inside the cell in the resting state. When an electrical impulse is propagated down the nerve, channels on the cell surface open and positively charged ions, particularly sodium and calcium, rush inside, raising the interior of the cell to a positively-charged state. The cations are then pumped out afterward, returning the cell to its negatively-charged resting state. It is easy to see how a low serum concentration of sodium would mean that fewer sodium ions would be available to rush inside the nerve cell as the message propagated, and the interior of the cell would not be raised to as high of a positively-charged state, slowing down conduction of the nerve impulse. Symptoms of a low sodium level include lethargy, weakness, muscle cramps, twitching, confusion, and seizures, all of which are associated with poor nerve cell conduction. (There are other symptoms as well, related to the effect upon milliosmoles in the blood as just

discussed). It is important to understand the electronic equivalence of the electrolytes in various places in the body in order to appreciate the effect of those electrolytes on body physiology and pathophysiology.

In order to convey the electrical activity of the ions in the body, pharmaceutical scientists have come up with an expression of ionic (electrical) equivalence. This expression defines the weight of a substance that can combine with *or replace* one gram atomic weight of hydrogen. Since hydrogen has a single charge, every ion with a single charge is considered equivalent. If the ion is bonded, then it is considered the same as a single charge. If an ion has a +2 charge, like calcium, then it is considered the equivalent of two hydrogen ions. With this definition, one equivalent of hydrogen = one equivalent of Na⁺ = one equivalent of Cl⁻ = one equivalent of NaCl (chemically neutral).

As previously stated, if you have a single charge, then the gram atomic weight of the ionic substance you are interested in will be electrically equivalent to the gram atomic weight of hydrogen. If you have more than one positive or negative charge in an ionic substance, then the molecular weight of that substance will need to be divided by the valence in order to be equivalent to the single charge of a hydrogen ion. Thus,

$$1 \text{ equivalent} = \frac{\text{molecular weight (g)}}{\text{valence}}$$

with the valence being considered "1" for substances that are in bonded form.

For example,

$$1 \text{ equivalent KCl} = \frac{39\text{g K} + 35.5\text{g Cl}}{1} = 74.5\text{g}$$

In the human body, the concentration of any drug in any given body fluid space is pretty small, and if expressed as weight per volume, is usually given in mmol/L or mg/L. Because of this, the ionic equivalence of electrolytes in the body to the hydrogen ion are also expressed as 1/1000 of an equivalent: a milliequivalent, abbreviated mEq. Thus,

$$1 \text{ mEq} = \frac{\text{molecular weight (mg)}}{\text{valence}}$$

And using an example:

$$1 \text{ mEq KCl} = \frac{39\text{mg K} + 35.5\text{mg Cl}}{1} = 74.5\text{mg}$$

Notice that you still end up with the number 74.5 whether you use the equivalent calculation or the milliequivalent calculation. Since the number on the left hand side of the equation (1) didn't change when the equivalent equation was changed to a milliequivalent equation, the number on the right side (74.5) should not change either, because both sides were divided by 1000. When converting from equivalents to milliequivalents and from grams to milligrams *at the same time*, the numbers stay the same: it is merely the units that change. As long as you make the same change to both sides of the equation, the numbers won't change. This has been stated before, but it is worth re-emphasizing.

You will see milliequivalents used when people express amounts of cations, particularly: sodium, potassium, calcium, and magnesium, and anions: chloride, acetate, and bicarbonate. The nifty thing about milliequivalents is that, as already stated, because they express molarity in terms of ionic equivalence, 1 mEq of KCl will equal 1 mEq of the potassium component and/or 1 mEq of the chloride component. So when a prof asks you how many mEqs of potassium there are in 3 mEqs of potassium chloride, it's a no-brainer: there are 3 mEqs of potassium. Before you dissolve into celebration that a concept in pharmacy school is actually straightforward, however, realize that the challenge of milliequivalents lies in conversion to weights. Fortunately, this isn't too difficult. As just outlined, all you need to know is the molecular weight and the valence (number of usable outer electrons), that each constituent of a compound has. To calculate the valence, as previously stated, simply divide a chemical compound up into its positive and negative components, and then count the number of *either* positive *or* negative charges (not both). Remember that if you are working with a compound that contains a substance with a *covalent bond* then you will need to consider the valence of the entire covalently-bound unit, rather than the individual positive and negative components.

Examples of covalently bonded units with a valence of 1 are:

- acetate ($C_2H_3O_2^-$)
- bicarbonate which everyone just calls “bicarb” (HCO_3^-)
- gluconate ($C_6H_{11}O_7^-$)
- lactate ($C_3H_5O_3^-$)
- phosphate in the dihydrogen form ($H_2PO_4^-$).

Examples of covalently-bonded units with a valence greater than one are:

- carbonate (CO_3^{--})
- phosphate in the monohydrogen form (HPO_4^{--})
- sulfate (SO_4^{--})

which all have a valence of 2, and

- citrate ($C_6H_5O_7^{--}$), with a valence of 3.

Now, how do you get from a certain amount of an ion in a metric weight, to that amount in milliequivalents? First set up the destination for your equation:

$$= \text{_____ mEq}$$

You should be able to calculate from the solution concentration the amount of drug in grams. Convert this to milligrams.

$$\text{mg drug} = \text{_____ mEq}$$

You know that a milliequivalent is equal to the molecular weight in milligrams, divided by the valence.

$$\text{mg drug} \times \frac{1 \text{ mEq}}{\text{MW in mg/valence}} = \text{_____ mEq}$$

And there you are. If you’re given the amount of an ion in mEq, you simply go the other way:

$$\text{mEq drug} \times \frac{\text{MW in mg/valence}}{1 \text{ mEq}} = \text{_____ mg drug}$$

An example. Let’s say that you want to know how many milligrams of sodium chloride there are in each mEq:

$$1 \text{ mEq NaCl} \times \frac{(23\text{mg Na} + 35.5\text{mg Cl})/1}{\text{mEq}} = 58.5 \text{ mg NaCl}$$

How many mg of $CaCO_3$ are in each mEq of $CaCO_3$?

$$1 \text{ mEq } CaCO_3 \times \frac{(40 \text{ mg Ca} + 60\text{mg } CO_3)/2}{\text{mEq}} = 50\text{mg } CaCO_3$$

How many mg of calcium are in each mEq of $CaCO_3$? To do this, you will need to remember that 1 mEq $CaCO_3$ = 1 mEq Ca

$$1 \text{ mEq Ca} \times \frac{(40\text{mg Ca})/2}{\text{mEq}} = 20\text{mg calcium}$$

Bottom line for dealing with milliequivalents:

When you convert in an equation, the conversion factor will be:

$\frac{\text{MW in mg/valence}}{\text{mEq}}$ if you are converting from mEq to mg, and

$\frac{\text{mEq}}{\text{MW in mg/valence}}$ if you are converting from mg to mEq

A note: During my pharmacy school career, I could become confused in a pressure situation about when to use valence and when to use species. One thing that finally helped me was to remember that milliequivalents almost sounds like milliequivalence. I also remembered that osmolarity and species both have an s near the beginning. It may sound stupid, but sometimes stupid things are the easiest to remember.

Normality

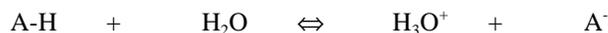
If you've taken general chemistry, then when you read the word "normality" you will likely think of the number of equivalents of solute in a liter of solution. Thus, a 0.25N KMnO_4 solution contains 0.25 equivalents of potassium permanganate in each liter of solution.

In the medical field, normality is defined a little differently. Solutions which are similar in milliequivalent content to physiological fluids are called "normal." Why? The normal concentrations of the electrolytes in serum are (ballpark) sodium 140 mEq/L, potassium 4 mEq/L, calcium 9 mEq/L, and magnesium 2 mEq/L. Add these all up and you get around 155 mEq of positive ions in each liter of serum. These are balanced by the same number of anions. This is considered the "normal" milliequivalence for electrical conductance and other physiologic functions. Anyway, the only fluid where you will see the term "normal" used regularly is with 0.9% sodium chloride solution. 0.9% saline contains 154 mEq of sodium and 310 milliosmoles in each liter, similar to serum ionic content and osmolarity (normal serum osmolarity: ~ 300 mOsm/L). Pharmacists call 0.9% NaCl solution "normal saline," and write it as "NS;" 0.45% NaCl solution "half-normal saline," and write it as "1/2 NS;" and 0.225% NaCl solution "quarter-normal saline," written as "1/4 NS."

pH and percent ionization

Many drugs have one (or more) chemical parts of their structure that are capable of donating or receiving a proton. Since hydrogen is the only substance with just one proton in its nucleus, it is more correct to say that many drugs have one (or more) parts of their structure that are capable of either donating or receiving a hydrogen ion. One common source of hydrogen ions is water, ubiquitous in the body and commonly used as a drug diluent. Those drugs with a moiety capable of donating or accepting a hydrogen ion can be represented in one of two ways, A or B.

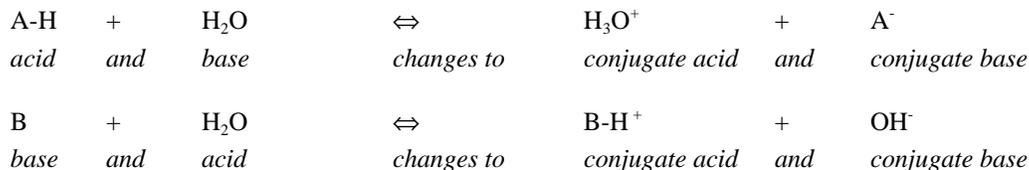
In situation A, the drug (referred to below as "A") has a hydrogen ion attached which it is willing to share (a chemical philanthropist!) with water, thus producing two slightly different compounds than those at the start.



In situation B, the drug (referred to below as "B") is willing to accept a hydrogen ion (a chemical non-profit organization) from water, thus producing two slightly different compounds than those at the start.



In both of these situations, you have a compound willing to give up a hydrogen ion and a compound willing to accept it, referred to as an acid and a base, respectively. Once these have combined or *conjugated*, you are left with two compounds, one of which has a negative charge and could thus accept a hydrogen ion (the conjugate base) and one that has a positive charge and thus might be willing to donate a hydrogen ion (the conjugate acid). The equations above could be represented with words, thus:

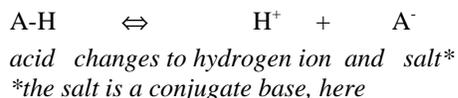


You will notice that the conjugate acid and conjugate base forms of the drugs carry charges and are thus often referred to as the *ionized* forms of the drugs; the acid or base forms are referred to as the *unionized* forms of the drugs. Conjugate acids or bases are usually combined with other substances in a solution to form a salt, increasing their solubility in aqueous solution, and thus many people will refer to the conjugate acid or conjugate base as the *salt form* of the acid or base. Recognize then, that the terms conjugate acid or base, ionic form, and salt form of a drug are all used fairly interchangeably to describe the right hand side of the above equations.

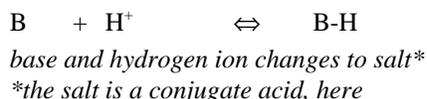
If you studied the different definitions of acids and bases in general chemistry, you may recognize what was just described as the Brönsted-Lowry theory, a model commonly used in pharmacy, which defines an acid as a proton donor and a base as a proton acceptor.

If an acid readily dissociates to donate a proton, it is called a strong acid. If it more reluctantly parts with the hydrogen ion then it is called a weak acid. If a base readily accepts a proton then it is called a strong base. If it more reluctantly accepts a proton then it is called a weak base.

Looking at the equation above, it is probably hard to think of water as being either an acid or a base, because we always think of water as being neutral. It is actually both a weak acid and a weak base. When it comes into contact with an acid that is stronger than it is, the acid will force an extra hydrogen ion upon the water. If it comes into contact with a base stronger than it is, the base will lure one of the hydrogens from the water molecule (possibly by promising it a better salary and benefits package). Either way, it is really the hydrogen atom that is the focus of attention with acid-base chemistry. If we remove the middleman of water in the equations above and concentrate just on the hydrogen ion, the equations will simplify to:



or better yet:
 $[\text{acid}] \rightleftharpoons [\text{H}^+] \text{ and } [\text{salt}]$
 with the brackets meaning "concentration of"



or better yet:
 $[\text{base}] \text{ and } [\text{H}^+] \rightleftharpoons [\text{salt}]$
 with the brackets meaning "concentration of"

As you can see above, there is a two-way arrow connecting each side of the equation. The acid-and-salt and base-and-salt will continuously trade the hydrogen ions back and forth between each other as if in some chemical ping-pong game. Because the exchange of the hydrogen ions is continuous, the concentration of drug in the unionized form (i.e., acid or base) remains constant as does the concentration of the salt form (i.e., conjugate acid or base/ionized form/salt form) and, of course, the concentration of hydrogen ions bouncing back and forth. Thus, in any given solution, the concentration of the acid form is at equilibrium with the concentration of the salt form (ditto for the base and salt of the base). Realize that just because the forms are in equilibrium does not mean that the fraction of the drug in the ionized form is equal to the fraction in the unionized form; these are usually unequal. The equilibrium (two-way arrow) is represented with the letter K, and is called K_a , or the equilibrium constant for the acid form. Mathematically, this can be represented as

$$K_a = \frac{[\text{salt}][\text{H}^+]}{[\text{acid}]}$$

If it helps you to remember the equation, consider that since you are talking about the K relative to the acid, the acid concentration should go into the denominator.

What if you're dealing with a base? You'll never find a pK_b in a reference book: only a pK_a . Realize that this is not the pK_a of the base, but is rather the pK_a of its conjugate acid, which is really the salt form. The equilibrium constant for a base, then, looks like this:

$$K_a = \frac{[\text{base}][\text{H}^+]}{[\text{salt}]}$$

In order to know which equilibrium constant to use, you will need to be told or to find out for yourself whether the drug you're dealing with is a weak acid or a weak base (most drugs are weak acids or weak bases since the body does not react well to administration of a strong acid or base!). We'll cover how to determine whether a drug is an acid or a base later in this section to preserve the flow of the current explanation.

Moving to the next derivation will be easier if the equations above are slightly rearranged.

dissociation constant for an acid:

$$K_a = [\text{H}^+] \frac{[\text{salt}]}{[\text{acid}]}$$

dissociation constant for a base:

$$K_a = [\text{H}^+] \frac{[\text{base}]}{[\text{salt}]}$$

So how does this all relate to pH? As you may know, the "p" in pH means "the negative logarithm of" and so pH means the negative logarithm of the hydrogen ion concentration ($\text{pH} = -\log[\text{H}^+]$). In order to get pH into the picture, then, we're going to have to take the negative logarithm of each of the parts. The negative logarithm of K_a is pK_a . Take the negative logarithm of everything in the equation, remembering to separate out the H^+ (since we're trying to see where pH fits into the equation). You now have:

for a drug that's a weak acid:

$$pK_a = \text{pH} - \log \frac{[\text{salt}]}{[\text{acid}]}$$

for a drug that's a weak base:

$$pK_a = \text{pH} - \log \frac{[\text{base}]}{[\text{salt}]}$$

Since pK_a is a constant, and we often wish to know the pH (or at least fiddle with it), the equations are more conveniently arranged as:

for a drug that's a weak acid:

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

for a drug that's a weak base:

$$\text{pH} = pK_a + \log \frac{[\text{base}]}{[\text{salt}]}$$

You will have seen these before. They are, of course, Henderson-Hasselbalch equations. You will see these on examinations in both your pharmaceutical chemistry course and also on the state licensing examination that you will take at the end of pharmacy school.

Take a moment to rest your eyes and stretch your fingers. Get out your calculator and plug some numbers into Henderson-Hasselbalch in its *raison d'être*, buffer solution component calculations, just to refresh your memory:

Calculate the pH of a buffer containing 0.01M lactic acid ($K_a = 1.38 \times 10^{-4}$) and 0.05 sodium lactate.

Did you get 4.6? If you didn't, then start by calculating the pK_a of acetic acid: the negative logarithm of 0.000138 (in case you're rusty here, you'll get some ionization constants in the practice problems at the end of this chapter so that you can practice using that log function on your calculator). Now plug it into the Henderson-Hasselbalch equation, thus:

$$\text{pH} = 3.9 + \log \frac{[0.05]}{[0.01]} = 4.6$$

We're going to work more with buffers in the next chapter, since these are important in ensuring stability when compounding pH labile drugs or administering drugs to pH-sensitive tissues. In this lesson, however, we're learning about drug amounts and so will now examine an important drug form amount called percent ionization. The reason

we needed to review all that stuff above (besides understanding the unit of pH) is because percent ionization is derived from Henderson-Hasselbalch.

Percent ionization. What is percent ionization and why do you need to learn it? First, there are *two vitally important principles for you to remember*:

- a) **Unionized drug goes through membranes.** In order for a drug to pass through a membrane (e.g., from the intestine through the gut wall for an oral drug, from the blood into the heart tissue cells for a cardiac drug), it must be unionized: in its acid or base form. Most membranes are largely composed of phospholipids; lipids tend to repel charged particles. In fact, most charged particles will need help to cross a membrane. Proteins within the cell membrane can create pores in the cell membrane, forming structural “gateways” to promote passive diffusion of ions; other proteins can also function as pumps to actively transport substances across the membrane. The size of the drug molecule will determine how much drug crosses the membrane through the pores (i.e., the bigger it is, the less likely to “make it through the gate”). The chemical configuration of the molecule will determine how much of the drug crosses the membrane via active transport.
- b) **Ionized drug is more soluble in water.** Most drugs are more highly soluble in water in their salt form. As the percent of drug in the salt form increases, solubility increases.

Drug delivery in the body, then, can be tricky. In order to get a maximum amount of drug into the body, you need to have it highly soluble in solution, i.e., in ionic form (salt). In order to get a maximum amount of drug to cross a membrane, however, it needs to be in unionized form (acid or base). *Memorize these two principles.*

Pharmaceutical chemists need to take pH and pK_a into account when coming up with drug formulations. A drug that is to be injected into the bloodstream must first be placed in a solution form. Therefore, *injected* drugs need to have maximal solubility.

Pharmaceutical chemists are also concerned with the solubility of *oral* medications, but an equal amount of consideration must be given to absorption from the gastrointestinal tract. Once a patient takes a drug orally, then the drug first goes into the stomach (pH 2-3), then to the intestine (pH 6-8), then into the blood (pH 7.35 – 7.4), through the liver (which can biotransform it, potentially changing its pK_a or even, more commonly, inactivate a portion of it), and eventually attach to or else enter a cell (pH 6.0 – 7.4); the attaching to or entering of the cell causes the pharmacologic effect. When the drug leaves the cell, it goes back into the blood and eventually reaches the urine (pH 5-7) or less commonly reenters the intestine and is excreted in the feces. It is thus helpful to be able to determine how much of the drug is ionized in any of these environments, since this will give you an idea of how much of the drug will get across the membrane. Injected drugs will also be absorbed through membranes but the pH ranges in the body fluids they are exposed to do not vary as greatly as those to which oral drugs are subjected. In either case, it is useful for people preparing medications to determine the percent of drug ionized so they can determine how well the drug will go into solution and how well it will cross membranes.

How is percent ionization determined? The fraction of drug ionized is determined by dividing the amount of drug in salt (ionized) form by the total amount of drug (unionized + ionized). This fraction is then multiplied by 100 to get the percent of drug ionized. Restated: the percent ionization is the fraction of the total amount of drug that is in the ionized form. Mathematically restated:

$$\% \text{ ionization of acidic drug} = 100 \times \frac{[\text{salt}]}{[\text{acid}] + [\text{salt}]}$$

Since the acid and salt concentrations will depend on the pH of the environment the drug is in, and the specific pK_a of the drug, the equation above, used alone, won't help you determine a percent ionization. You will need to rearrange Henderson-Hasselbalch to get to a more useful type of equation:

$$\text{pH} = \text{p}K_a + \log \frac{[\text{salt}]}{[\text{acid}]}$$

since $\log\left(\frac{1}{x}\right) = -\log(x)$:

$$\text{pH} = \text{p}K_a - \log \frac{[\text{acid}]}{[\text{salt}]}$$

rearrange for tidiness: $\log \frac{[acid]}{[salt]} = (pK_a - pH)$

take the antilog: $\frac{[acid]}{[salt]} = 10^{(pK_a - pH)}$

rearrange: $[acid] = [10^{(pK_a - pH)}][salt]$

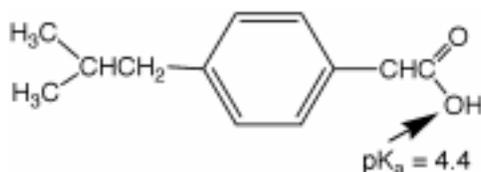
add salt to both sides: $[salt] + [acid] = [10^{(pK_a - pH)}][salt] + [salt]$

as $a + ax = a(1 + x)$, so: $[salt] + [acid] = [salt] [1 + 10^{(pK_a - pH)}]$

rearrange: $\frac{1}{1 + 10^{(pK_a - pH)}} = \frac{[salt]}{[salt] + [acid]}$

multiply by 100 for %: $\frac{100}{1 + 10^{(pK_a - pH)}} = 100 \times \frac{[salt]}{[acid] + [salt]} = \% \text{ ionization}$

Let's look at an example of a weak acid. Have you ever taken an over-the-counter (OTC) drug called ibuprofen? Trade names include Advil, Nuprin, and Motrin IB, but most people will purchase the generic since it's a lot cheaper. Chemically, it looks like this:



with the carboxylic acid moiety (COOH) the proton donor, which has a pK_a of around 4.4. What happens once it's swallowed? First it goes to the stomach. We'll assume the pH of the stomach is around 3.

pH of stomach around 3: $\frac{100}{1 + 10^{(4.4 - 3)}} = \text{you should get around 4\%}$

Not a large number. Most of the drug is in acid form and therefore could cross the stomach lining to enter the bloodstream; i.e., ibuprofen can be absorbed from the stomach. It really isn't appreciably absorbed from the stomach, though, either because the stomach is empty (faster transit time) or contains food, which may serve to buffer the drug's immediate environment.

Next the large intestine, assuming pH = 8: $\frac{100}{1 + 10^{(4.4 - 8.0)}} = > 99\%$

Most of the drug is in salt form and so shouldn't readily cross the intestinal lining and enter the bloodstream. This is not true in real life, however. About 80% of ibuprofen is absorbed. Why so much? Partly because there is a very large surface area in the gut, maximizing the amount of unionized drug coming into contact with the membrane. Partly because some absorption takes place in the duodenum, where the pH is lower (closer to 6) and more drug is unionized. There may be some that crosses the membrane via pores, since it is not a very large molecule (MW ≈ 187). The most likely reason that the drug is pretty well absorbed, though is by active transport across the gut wall.

Since the drug remains pretty much ionized in the blood stream, it wouldn't be expected to easily cross cell membranes. In general, it remains largely in the bloodstream (mainly because it binds to proteins in the blood, though) and is most effective in tissues that are well-supplied by the blood: aches in joints and muscles.

What if you have a weak base? Here, you want to know something similar to the definition of percent ionization in a weak acid, i.e.,

$$\% \text{ ionization of basic drug} = 100 \times \frac{[\text{salt}]}{[\text{base}] + [\text{salt}]}$$

but your starting equation is different. This means that the equation for determining percent ionization of a weak base will be different from that of a weak acid.

$$pH = pK_a + \log \frac{[\text{base}]}{[\text{salt}]}$$

rearrange:

$$pH - pK_a = \log \frac{[\text{base}]}{[\text{salt}]}$$

take the antilog:

$$10^{(pH-pK_a)} = \frac{[\text{base}]}{[\text{salt}]}$$

rearrange:

$$[\text{salt}][10^{(pH-pK_a)}] = [\text{base}]$$

add salt to both sides:

$$[\text{salt}] + [\text{salt}][10^{(pH-pK_a)}] = [\text{base}] + [\text{salt}]$$

as $a + ax = a(1 + x)$, so:

$$[\text{salt}] [1 + 10^{(pK_a-pH)}] = [\text{base}] + [\text{salt}]$$

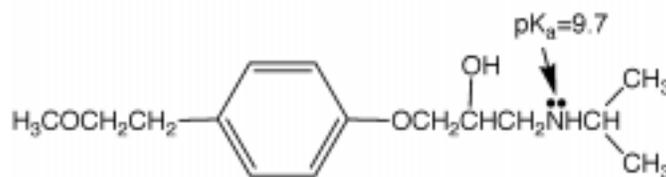
rearrange:

$$\frac{1}{1 + 10^{(pH-pK_a)}} = \frac{[\text{salt}]}{[\text{base}] + [\text{salt}]}$$

multiply by 100 for %:

$$\frac{100}{1 + 10^{(pH-pK_a)}} = 100 \times \frac{[\text{salt}]}{[\text{base}] + [\text{salt}]} = \% \text{ ionization}$$

Let's use this equation to determine percent ionization of a heart drug, metoprolol ($pK_a = 9.68$; it's a weak base so notice how the chemical form shown below is represented as a conjugate acid, since the pK_a is the negative log of the ionization constant for the *acid* form of the drug), in various environments.



metoprolol at physiologic pH

First the stomach, assuming $pH = 3$:

$$\frac{100}{1 + 10^{(3-9.7)}} \approx 100\%$$

Metoprolol thus would not be expected to be absorbed well from the stomach. It's not.

Next the large intestine, assuming $pH = 8$:

$$\frac{100}{1 + 10^{(8-9.7)}} \approx 98\%$$

Most of the drug is ionized and so shouldn't readily cross the intestine. It is well-absorbed, for reasons similar to

Is the pK_a of a drug and the pH of the environment the only thing that predicts a drug's ability to be absorbed? No. As mentioned previously, some drugs can go through membranes by actively being pumped from one side of the membrane to the other (active transport); in fact, we're finding out more and more that this is a primary determinant in a drug's ability to cross the gut wall. Drugs with a substantial lipid component can be absorbed directly across the lipophilic membrane (you will hear about partition coefficients in your pharmaceutical chemistry course). Other substances (e.g., blood proteins, divalent cations) in the environment can bind a drug, rendering it unavailable for crossing the membrane. Finally, the concentration gradient of a drug on either side of a membrane will influence migration of the drug across the membrane. For example, if a tablet has recently arrived in the intestine, then there will be a lot of drug in the intestine and little in the bloodstream across the membrane. As more drug is absorbed, the concentration in the intestine will decrease, decreasing the concentration gradient-dependent absorption.

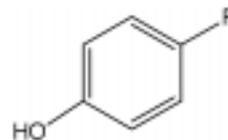
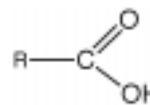
Where can you find out a drug's pK_a ? The most readily-available source for pharmacists is the product information leaflet that can be found accompanying the drug package. The American Hospital Formulary Service (AHFS) Drug Information reference notes the pK_a for many drugs and is probably the best single source available to the average pharmacist.

Acid or base? Before you can do percent ionization calculations, you need to first know whether the drug in question is an acid or a base. How can you determine this? The pK_a can provide some guidance. In general,

if pK_a is:	then the drug is a:
< 2	strong acid
4 - 6	weak acid and very weak base
8 - 10	very weak acid and weak base
> 12	strong base

But this still doesn't satisfactorily answer the question of whether a drug is an acid or a base, since pK_a s for drugs tend to be in the 2-10 arena (the body doesn't react well to the introduction of a strong acid or base) and as you can see above, a drug with a pK_a of 5 could be either a weak acid or a very weak conjugate base. In order to determine for yourself whether a drug is an acid or a base, you will need to look at the chemical structure itself. You will be looking for the presence of:

- a carboxylic acid group, which more happily gives up a proton and thus is weakly acidic, with a pK_a around 5; you saw this above on the ibuprofen molecule
- a) an amine group, which usually accepts a hydrogen ion and thus is a weak base (pK_a around 10 – see the metoprolol molecule above) *unless* it is part of an aromatic ring structure, which makes it less likely to accept a proton and thus renders it a very weak base (pK_a 5 or lower) or next door to a carbon that is double-bonded to an oxygen (same reason).
- a phenol group, which reluctantly gives up a hydrogen ion and is thus very weakly acidic (pK_a around 10); see the amoxicillin molecule for an example



Of course there are many exceptions, but this rule of thumb will work for many drugs.

Another clue that will tell you whether you are dealing with an acid or a base is to look at the salt in which the drug is given (many drugs are given in the salt form to increase solubility). In general, bases will be bound to things that will give up hydrogen ions easily, so if a drug is available in a phosphate (H_3PO_4), sulfate (H_2SO_4), hydrochloride, or maleate salt, it's probably a base. Weak acids, on the other hand, tend to give up a hydrogen ion, leaving a O^- portion and so are often balanced with a sodium ion. Thus if you see a sodium salt, it's a good bet that the drug you're working with is an acid.

Practical use of percent ionization. In order to increase solubility of drugs in solution (or even some drugs in powder or crystal form), manufacturers will add sodium hydroxide or hydrochloric acid, which will increase or decrease the pH of a solution. This will increase the percent ionization and therefore increase solubility. You will

need to measure the pH of the solution before you add the drug, and you will need to know the pK_a of the drug you're adding. For acids, raising the pH of the solution to approximately 2 units above the pK_a should give you nearly 100% ionization. For example, cefoperazone, an injectable antibiotic, has a pK_a of 2.55; the pH of the product has been adjusted to 4.5-6.5. The pK_a of ketorolac, an injectable pain medication, is 3.54 and the pH is adjusted to 6.9-7.9. The opposite is true for bases: lowering the pH of the solution to 2 units below the pK_a will give you nearly 100% ionization. For example, lidocaine is a weak base with a pK_a of 7.86. Because it is given as an injection, the pH is adjusted to around 4 to maximize solubility.

Relationship between changes in pH and changes in percent ionization

	<i>acids</i>	<i>bases</i>
	<i>% ionization</i>	<i>% ionization*</i>
pH 2 units above pK_a	99%	1%
pH 1 unit above pK_a	91%	9%
pH = pK_a	50%	50%
pH 1 unit below pK_a	9%	91%
pH 2 units below pK_a	1%	99%

*this is the percent ionization of the conjugate acid

Another place in which the concept of percent ionization is useful is in the acidification or alkalinization of urine in order to treat a disease or to promote the removal or retention of a drug.

Urinary acidifiers can be used to increase the antibacterial effect of some urinary tract infection agents. The main urinary acidifier is either potassium acid phosphate or a combination of sodium and potassium acid phosphates. Truth be told, these are used more often for their phosphate supplement properties than for acidifying the urine, but they do acidify urine and you will need to consider the effect on drug excretion if a patient is taking one of these products.

Urinary alkalinizers include sodium bicarbonate, potassium citrate, ammonium chloride, and various combinations of potassium or sodium citrate and citric acid. These agents can help to correct acidosis originating in the kidneys (called renal tubular acidosis), decrease uric acid crystallization (precipitation) in the urine, which could cause kidney stones (these are *very* painful, according to the patients I've talked to), and hasten the excretion of some drugs.

Lesson 2 practice questions

1. Units

a. A patient is receiving 1,000,000 units of procaine penicillin daily by deep intramuscular (IM) injection and needs to complete ten days of therapy. After three days, the patient has had enough of this (it hurts!) and requests an oral preparation. The physician agrees to this and calls you for a recommendation as to the equivalent amount to prescribe. You know that 250mg of penicillin VK is equivalent to 400,000 units of penicillin. Furthermore, you know that oral penicillin can be given for this type of infection in 2-4 divided doses/day. Your pharmacy carries 250mg and 500mg tablets. What will you recommend to the physician?

Circle the strength you will recommend: 250mg tablets 500mg tablets

You will recommend that the physician tell the patient to take the medication (circle one):

twice daily three times daily four times daily

How many tablets will you dispense? _____ tablets

b. A patient has been taking 10,000 IU of vitamin A daily as a supplement. This patient wishes to switch to beta carotene, a form of vitamin A that is available OTC in 15 mg capsules, and wants to know an equivalent dose. You know that vitamin A 1 unit = 0.3 μ g of all-*trans* retinol, 0.344 μ g of all-*trans* retinol acetate, or 0.6 μ g of beta carotene.

You recommend that she take _____ capsule(s) of beta-carotene daily.

2. Parts.

a. Note the amount of product and water in the following preparation:

How much Zephiran (benzalkonium chloride 1:750 solution), will you need to make one liter of a 1:3000 benzalkonium chloride solution for use as a wet dressing?

_____ ml Zephiran solution

_____ ml water

b. An old recipe for chapped hands calls for glycerin, alcohol, and rosewater, 1:1:8. A customer asks you to make some of this and gives you a used and cleaned 14oz baby oil squeeze container to put it in. You have a 100ml and 250ml graduated cylinder with which to measure your ingredients. How much of each ingredient will you mix in order to make a full bottle of this hand lotion?

c. The woman from question 2b is back. She liked the recipe for hand lotion that she found in her grandmother's household recipe book and now wants to try the Universal Liniment recipe for her joints. It calls for alcohol (16 parts), camphor (1 part), oil of peppermint (0.6 parts), and ammonia (0.4 parts). She would like a half pint. How much of each ingredient will you mix in order to make a full bottle of this liniment? You have 100ml, 50ml, 30ml, and 10ml graduated cylinders.

3. Please write down the concentrations and units for the following products:

a. clotrimazole 1% cream = _____ g clotrimazole/ _____ g total product

how much drug will a patient receive from each 5g applicatorful? _____ g

b. albuterol 0.083% solution for inhalation = _____ g albuterol/ _____ ml total product

how much drug will be in each 3ml container? _____ g albuterol

c. timolol ophth sol 0.25% = _____ g timolol/ _____ ml total product

how much drug will be in each 15ml bottle of solution? _____ mg

how much drug will the patient receive in each drop, assuming 20 drops/ml? _____

how much benzalkonium chloride, used at 0.1% concentration as a preservative, will the patient receive in each drop? _____ (please don't forget to note the units of the last two questions)

d. SSKI is short for "saturated solution of potassium iodide." Potassium iodide becomes saturated at a concentration of 1g/ml. What percentage strength is it? _____ %

A patient is instructed to dilute 0.3ml in one glass (assume 8oz) of water and drink QID. How much potassium iodide will the patient receive each day? _____ (please note units)

4. Please calculate the normal or therapeutic ranges in SI units of the following drugs or electrolytes from the normal or therapeutic ranges given in commonly-used U.S. units.

a. phenytoin (an anti-seizure medication). Therapeutic serum concentration range in US: 10-20 mg/L. The serum concentration values in Europe are given in units of $\mu\text{mol/L}$. Phenytoin MW: 252.

therapeutic phenytoin SI range: _____ $\mu\text{mol/L}$

b. theophylline (a medication used in patients with lung disease). Therapeutic serum concentration range in US: 10-20 mg/L. The serum concentration values in Europe are given in units of $\mu\text{mol/L}$. Theophylline MW: 180.

therapeutic theophylline SI range: _____ $\mu\text{mol/L}$

c. chloride. Normal serum concentration range in US: 95-105 mEq/L. The serum concentration values in Europe are given in units of mmol/L. Chloride MW: 35.5.

normal chloride SI range: _____ mmol/L

d. carbon dioxide. Normal serum concentration range in US: 22-28 mEq/L. The serum concentration values in Europe are given in units of mmol/L. CO_2 MW: 44.

normal CO_2 SI range: _____ mmol/L

e. phosphorus. Normal serum concentration range in US: 2.5-5.0mg/dL. The serum concentration values in Europe are given in units of mmol/L. PO_4 MW: 95.

normal P SI range: _____ mmol/L

f. calcium. Normal serum concentration range in US: 8.6 – 10.3 mEq/L. The serum concentration values in Europe are given in units of mmol/L. Ca MW: 40.

normal Ca SI range: _____ mmol/L

5. Milliosmoles. Calculate the number of milliosmoles in each of the following medications:

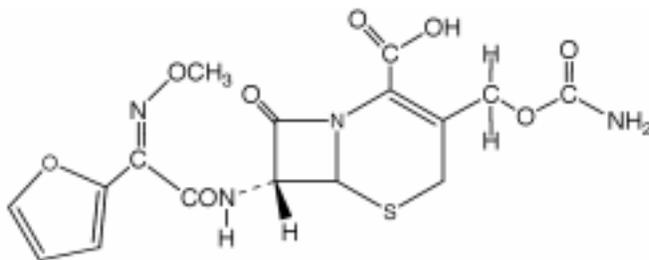
a. A 10ml syringe of 10% calcium chloride (CaCl₂). Ca MW 40, Cl MW 35.5.

b. A syringe containing 3.1g of ticarcillin disodium. ticarcillin MW 384, Na MW 23

c. A 500ml bag of D5W containing 2% magnesium sulfate. MW dextrose 180, MW Mg 24, MW SO₄ 96.

6. Acid-base and pK_a identification. For each of the following drugs, convert the dissociation constant into its pK_a, circle on the molecule where you think the proton is accepted or donated, then indicate whether you think the drug acts as an acid or a base.

a. Cefuroxime (an antibiotic)

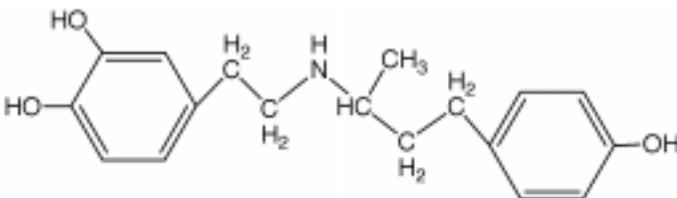


$$K_a = 3.55 \times 10^{-3}$$

*pK_a:

circle one: acid base

b. Dobutamine (increases the heart's ability to pump)

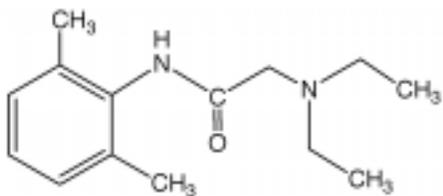


$$K_a = 3.98 \times 10^{-10}$$

pK_a:

circle one: acid base

c. Lidocaine (used for rhythm disturbances in the heart)

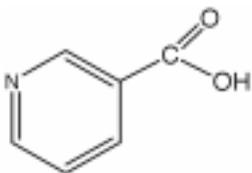


$$K_a = 2 \times 10^{-8}$$

pK_a:

circle one: acid base

d. Niacin (vitamin B-3; used for high cholesterol)

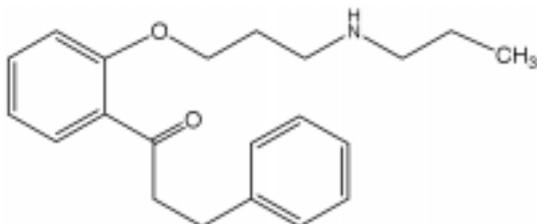


$$K_a = 1.41 \times 10^{-5}$$

pK_a:

circle one: acid base

e. Propafenone (used for rhythm disturbances in the heart)

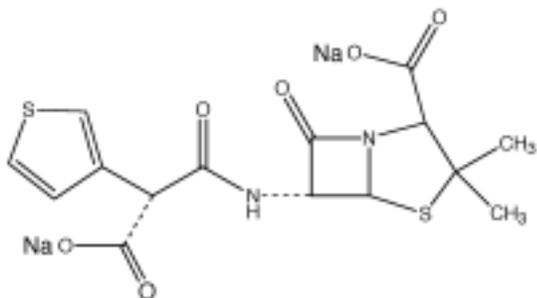


$$K_a = 1 \times 10^{-9}$$

pK_a:

circle one: acid base

f. Ticarcillin (an antibiotic)



$$K_a = 3.8 \times 10^{-4}$$

pK_a:

circle one: acid base

*If you are unsure how to do these K_a to pK_a conversions and you have a standard calculator (not a Reverse Polish Notation calculator), punch the log button on your calculator, enter 0.00355, hit the equal button, then multiply by -1 (or push the “change sign” button on your calculator).

6. Please determine the percent ionization for the following drugs:

a. clindamycin (a weak base, pK_a 7.45) injected into the bloodstream (pH 7.4)

b. ceftriaxone (a weak acid, pK_as of 3, 3.2, and 4.1 – you will use the lowest, since they are all in the same ballpark) injected into the bloodstream (pH 7.4)

c. paroxetine (a weak base, pK_a 9.9) in the intestine (pH 8). Would you expect this drug to be well absorbed from the gut?

d. pentobarbital (a very weak acid, pK_a around 8) injected into the bloodstream (pH 7.4)

e. phenobarbital (a very weak acid, pK_a 7.41) in the intestine (pH 8). Would you expect this drug to be well-absorbed from the gut?

f. timolol (a weak base, pK_a 9) placed in the eye (pH 7.4). Would you expect this drug to be well absorbed into eye tissues?

g. albuterol (a zwitterion with an amide constituent pK_a 9.3 and a phenol constituent pK_a 10.3) inhaled from the lungs (pH 7.4). Would you expect this drug to be well absorbed from the lungs?

h. methenamine mandelate (a very weak base, pK_a 4.8) excretion from the bloodstream (pH 7.4) into the urine (pH 5.0).

Would you expect it to stay in the urine or be reabsorbed into the bloodstream?

You could increase the retention of the methenamine in the urine if you (circle one) alkalinized
acidified the urine.

Lesson 2 practice question answers

1. Units

a. A patient is receiving 1,000,000 units of procaine penicillin daily by deep intramuscular (IM) injection and needs to complete ten days of therapy. After three days, the patient has had enough of this (it hurts!) and requests an oral preparation. The physician agrees to this and calls you for a recommendation as to the equivalent amount to prescribe. You know that 250mg of penicillin VK is equivalent to 400,000 units of penicillin. Furthermore, you know that oral penicillin can be given for this type of infection in 2-4 divided doses/day. Your pharmacy carries 250mg and 500mg tablets. What will you recommend to the physician?

$$\frac{1,000,000 \text{ units}}{\text{day}} \times \frac{250\text{mg}}{400,000 \text{ units}} \times \frac{1 \text{ day}}{2, 3, 4 \text{ doses}} = \begin{array}{l} 312.5\text{mg po BID} \\ 208.3\text{mg po TID} \\ 156.25\text{mg po QID} \end{array}$$

Circle the strength you will recommend: 250mg tablets 500mg tablets **250mg closest size to doses above**

You will recommend that the physician tell the patient to take the medication (circle one):

twice daily three times daily four times daily **250mg closest to 208mg**

How many tablets will you dispense? **21** tablets **3 doses/day x 7 remaining days = 21 tabs**

b. A patient has been taking 10,000 IU of vitamin A daily as a supplement. This patient wishes to switch to beta carotene, a form of vitamin A that is available OTC in 15 mg capsules, and wants to know an equivalent dose. You know that vitamin A 1 unit = 0.3µg of all-*trans* retinol, 0.344µg of all-*trans* retinol acetate, or 0.6µg of beta carotene.

You recommend that she take **1** capsule of beta-carotene daily.

Note: Even more accurate would be to take 1 capsule of beta-carotene every other day. If taken daily, the patient should check her skin daily for an orange or yellowish coloring, which would indicate too high of a dose.

BC = beta carotene; VA = vitamin A

$$\frac{10,000 \text{ IU VA}}{\text{day}} \times \frac{0.6\mu\text{g BC}}{1 \text{ IU VA}} \times \frac{1 \text{ mg}}{1,000 \mu\text{g}} = 6 \text{ mg BC}$$

2. Please note the amount of product and water in the following preparation:

How much Zephiran (benzalkonium chloride 1:750 solution), will you need to make one liter of a 1:3000 benzalkonium chloride (BAC) solution for use as a wet dressing?

$$\frac{250 \text{ ml Zephiran}^\circ \text{ solution}}{750 \text{ ml water}} \times \frac{1\text{g BAC}}{3000\text{ml}} \times 1000\text{ml} \times \frac{750\text{ml Zephiran}^\circ}{1\text{g BAC}} = 250\text{ml Zephiran}$$

1000ml of 1:3000 BAC solution - 250ml Zephiran[®] = 750ml water

b. An old recipe for chapped hands calls for glycerin, alcohol, and rosewater, 1:1:8. A customer asks you to make some of this and gives you a used and cleaned 14oz baby oil squeeze container to put it in. You have a 100ml and 250ml graduated cylinder with which to measure your ingredients. How much of each ingredient will you mix in order to make a full bottle of this hand lotion?

$$1 + 1 + 8 = 10 \text{ parts total} \qquad 14 \text{ oz} \times 29.6 \text{ ml/oz} = 414 \text{ ml total volume needed}$$

$$\frac{1 \text{ part glycerin}}{10 \text{ parts total}} = \frac{x \text{ ml glycerin}}{414 \text{ ml}} \quad x = 41 \text{ ml glycerin}$$

$$\frac{1 \text{ part alcohol}}{10 \text{ parts total}} = \frac{x \text{ ml alcohol}}{414 \text{ ml}} \quad x = 41 \text{ ml alcohol}$$

$$\begin{array}{l} \mathbf{8 \text{ part rosewater}} = \mathbf{\frac{x \text{ ml rosewater}}{414 \text{ ml}}} \quad \mathbf{x = 331 \text{ ml rosewater}} \\ \mathbf{10 \text{ parts total}} \end{array}$$

c. The woman from question 2b is back. She liked the recipe for hand lotion that she found in her grandmother's household recipe book and now wants to try the Universal Liniment recipe for her joints. It calls for alcohol (16 parts), camphor (1 part), oil of peppermint (0.6 parts), and ammonia (0.4 parts). She would like a half pint. How much of each ingredient will you mix in order to make a full bottle of this liniment? You have 100ml, 50ml, 30ml, and 10ml graduated cylinders.

$$\mathbf{16 + 1 + 0.6 + 0.4 = 18 \text{ parts total}} \quad \mathbf{8 \text{ oz} \times \mathbf{29.6 \text{ ml/oz}} = \mathbf{237 \text{ ml total volume}} \quad \mathbf{one-half \text{ pint} = 8 \text{ ounces}}$$

$$\begin{array}{l} \mathbf{16 \text{ parts alcohol}} = \mathbf{\frac{x \text{ ml alcohol}}{237 \text{ ml}}} \quad \mathbf{x = 211 \text{ ml alcohol}} \\ \mathbf{18 \text{ parts total}} \end{array}$$

$$\begin{array}{l} \mathbf{1 \text{ part camphor}} = \mathbf{\frac{x \text{ ml camphor}}{237 \text{ ml}}} \quad \mathbf{x = 13 \text{ ml camphor}} \\ \mathbf{18 \text{ parts total}} \end{array}$$

$$\begin{array}{l} \mathbf{0.6 \text{ parts peppermint oil}} = \mathbf{\frac{x \text{ ml peppermint oil}}{237 \text{ ml}}} \quad \mathbf{x = 8 \text{ ml peppermint oil}} \\ \mathbf{18 \text{ parts total}} \end{array}$$

$$\begin{array}{l} \mathbf{0.4 \text{ parts ammonia}} = \mathbf{\frac{x \text{ ml ammonia}}{237 \text{ ml}}} \quad \mathbf{x = 5 \text{ ml ammonia}} \\ \mathbf{18 \text{ parts total}} \end{array}$$

3. Please write down the concentrations and units for the following products:

a. clotrimazole 1% cream = **1 g** clotrimazole/ **100g** total product
how much drug will a patient receive from each 5g applicatorful? **50mg or 0.05g**

$$\frac{\mathbf{1 \text{ g clotrimazole}}}{\mathbf{100 \text{ g total product}}} = \frac{\mathbf{x}}{\mathbf{5 \text{ g product}}} \quad \mathbf{x = 0.05 \text{ g clotrimazole}}$$

b. albuterol 0.083% solution for inhalation = **0.083g** albuterol/ **100ml** total product
how much drug will be in each 3ml container? **2.5mg** albuterol

$$\frac{\mathbf{0.083 \text{ g}}}{\mathbf{100 \text{ ml}}} = \frac{\mathbf{x}}{\mathbf{3 \text{ ml}}} \quad \mathbf{x = 0.0025 \text{ g}}$$

c. timolol ophth sol 0.25% = **0.25 g** timolol/ **100ml** total product
how much drug will be in each 15ml bottle of solution? **37.5 mg**

$$\frac{\mathbf{0.25 \text{ g}}}{\mathbf{100 \text{ ml}}} = \frac{\mathbf{x}}{\mathbf{15 \text{ ml}}} \quad \mathbf{x = 0.0375 \text{ g}}$$

how much drug will the patient receive in each drop, assuming 20 drops/ml? **0.125mg**

$$\frac{\mathbf{37.5 \text{ mg}}}{\mathbf{15 \text{ ml}}} \times \frac{\mathbf{1 \text{ ml}}}{\mathbf{20 \text{ drops}}} = \frac{\mathbf{0.125 \text{ mg}}}{\mathbf{\text{drop}}}$$

how much benzalkonium chloride, used at 0.1% concentration as a preservative, will the patient receive in each drop? **0.05 mg**

$$\frac{\mathbf{0.1 \text{ g}}}{\mathbf{100 \text{ ml}}} \times \frac{\mathbf{1 \text{ ml}}}{\mathbf{20 \text{ drops}}} = \frac{\mathbf{0.00005 \text{ g}}}{\mathbf{\text{drop}}} = \frac{\mathbf{0.05 \text{ mg}}}{\mathbf{\text{drop}}}$$

d. SSKI is short for "saturated solution of potassium iodide." Potassium Iodide becomes saturated at a concentration of 1g/ml. What percentage strength is it? **100 %**

$$\frac{\mathbf{1 \text{ g}}}{\mathbf{1 \text{ ml}}} = \frac{\mathbf{100 \text{ g}}}{\mathbf{100 \text{ ml}}} \quad \mathbf{100 \text{ g/ml} = 100\%}$$

A patient is instructed to dilute 0.3ml in one glass (assume 8oz) of water and drink QID. How much potassium iodide will the patient receive each day? **1.2 g**

$$\frac{\mathbf{0.3 \text{ ml}}}{\mathbf{\text{dose}}} \times \frac{\mathbf{1 \text{ g}}}{\mathbf{\text{ml}}} \times \frac{\mathbf{4 \text{ doses}}}{\mathbf{\text{day}}} = \frac{\mathbf{1.2 \text{ g}}}{\mathbf{\text{day}}}$$

4. Please calculate the normal or therapeutic ranges in SI units of the following drugs or electrolytes from the normal or therapeutic ranges given in commonly-used U.S. units

a. phenytoin (an anti-seizure medication). Therapeutic serum concentration range in US: 10-20 mg/L. The serum concentration values in Europe are given in units of $\mu\text{mol/L}$. Phenytoin MW: 252. therapeutic phenytoin SI range: **40-80 $\mu\text{mol/L}$**

$$\frac{10-20 \text{ mg}}{\text{L}} \times \frac{1 \text{ mmol}}{252 \text{ mg}} \times \frac{1000 \mu\text{mol}}{\text{mmol}} = 39.7-79.4 \frac{\mu\text{mol}}{\text{L}}$$

b. theophylline (a medication used in patients with lung disease). Therapeutic serum concentration range in US: 10-20 mg/L. The serum concentration values in Europe are given in units of $\mu\text{mol/L}$. Theophylline MW: 180. therapeutic theophylline SI range: **55-110 $\mu\text{mol/L}$**

$$\frac{10-20 \text{ mg}}{\text{L}} \times \frac{1 \text{ mmol}}{180 \text{ mg}} \times \frac{1000 \mu\text{mol}}{\text{mmol}} = 55.6-111 \frac{\mu\text{mol}}{\text{L}}$$

c. chloride. Normal serum concentration range in US: 95-105 mEq/L. The serum concentration values in Europe are given in units of mmol/L. Chloride MW: 35.5. normal chloride SI range: **95-105 mmol/L**

$$\frac{95-105 \text{ mEq}}{\text{L}} \times \frac{1 \text{ mmol}}{35.5 \text{ mg}} \times \frac{35.5 \text{ mg/1 valence}}{\text{mEq}} = 95-105 \frac{\text{mmol}}{\text{L}}$$

d. carbon dioxide. Normal serum concentration range in US: 22-28 mEq/L. The serum concentration values in Europe are given in units of mmol/L. CO_2 MW: 44. normal CO_2 SI range: **22-28 mmol/L**

$$\frac{22-28 \text{ mEq}}{\text{L}} \times \frac{1 \text{ mmol}}{44 \text{ mg}} \times \frac{44 \text{ mg/1 valence}}{\text{mEq}} = 22-28 \frac{\text{mmol}}{\text{L}}$$

e. phosphorus. Normal serum concentration range in US: 2.5-5.0mg/dL. The serum concentration values in Europe are given in units of mmol/L. P MW: 31.

normal P SI range: **0.8-1.6 mmol/L**

$$\frac{2.5-5.0 \text{ mg}}{\text{dL}} \times \frac{1 \text{ mmol}}{31 \text{ mg}} \times \frac{10 \text{ dL}}{\text{L}} = 0.8-1.6 \frac{\mu\text{mol}}{\text{L}}$$

Note: most clinicians refer to this laboratory value as “phosphate.” As you can see, however, if it were truly phosphate (PO_4) that was measured in the bloodstream, the conversion would lead to an incorrect range when converted to SI units, because there are 95 mg of phosphate/mmol, whereas there are only 31mg of phosphorus. Do try to refer to the laboratory value as “phosphorus,” rather than “phosphate,” if you are interested in being accurate.

f. calcium. Normal serum concentration range in US: 8.6 – 10.3 mg/dL. The serum concentration values in Europe are given in units of mmol/L. Ca MW: 40.

normal Ca SI range **2.2-2.6 mmol/L**

$$\frac{8.6-10.3 \text{ mg}}{\text{dL}} \times \frac{1 \text{ mmol}}{40 \text{ mg}} \times \frac{10 \text{ dL}}{\text{L}} = 2.2 - 2.6 \frac{\text{mmol}}{\text{L}}$$

5. Milliosmoles. Calculate the number of milliosmoles in each of the following medications:

a. A 10ml syringe of 10% calcium chloride (CaCl_2). CaCl_2 MW 111. **CaCl_2 has a species of 3**

$$10 \text{ ml } \text{CaCl}_2 \times \frac{10 \text{ g } \text{CaCl}_2}{100 \text{ ml}} \times \frac{1000 \text{ mg}}{\text{g}} \times \frac{1 \text{ mmol}}{111 \text{ mg}} \times \frac{3 \text{ mOsmol}}{\text{mmol } \text{CaCl}_2} = 27 \text{ mOsmol}$$

b. A syringe containing 3g of ticarcillin disodium. ticarcillin MW 384, Na MW 23. **species = 3**

$$3\text{g ticar} \times \frac{1000\text{ mg}}{\text{g}} \times \frac{1\text{ mmol}}{430\text{ mg}} \times \frac{3\text{ mOsmol}}{\text{mmol}} = 21\text{ mOsmol}$$

c. A 500ml bag of D5W containing 2% MgSO₄. MW dextrose 180, MW Mg 24, MW SO₄ 96. **species = 3**

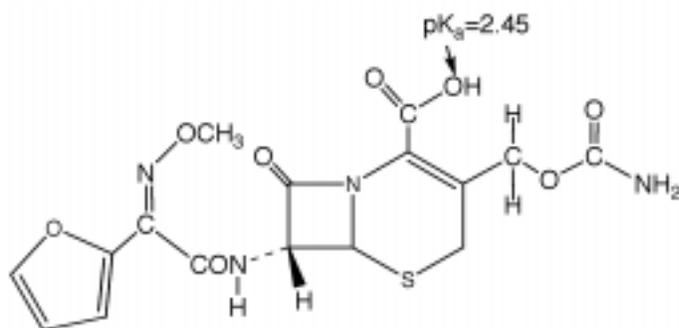
$$500\text{ml} \times \frac{5\text{g dextrose}}{100\text{ml}} \times \frac{1000\text{ mg}}{\text{g}} \times \frac{1\text{ mmol}}{180\text{ mg}} \times \frac{1\text{ mOsmol}}{\text{mmol dextrose}} = 140\text{ mOsmol}$$

$$500\text{ml} \times \frac{2\text{g MgSO}_4}{100\text{ml}} \times \frac{1000\text{ mg}}{\text{g}} \times \frac{1\text{ mmol}}{120\text{ mg}} \times \frac{2\text{ mOsmol}}{\text{mmol dextrose}} = 167\text{ mOsmol}$$

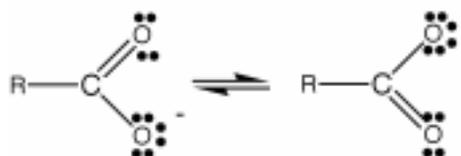
$$\text{total} = 307\text{ mOsmol}$$

6. Acid-base and pK_a identification. The pK_a is indicated at the site of proton donation or acceptance.

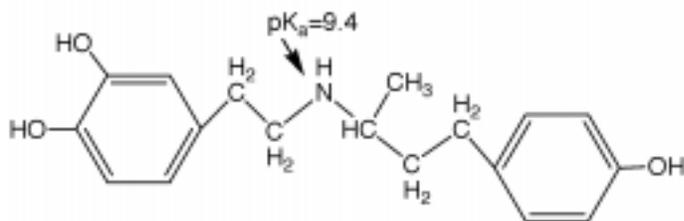
a. Cefuroxime (an antibiotic)



Cefuroxime, like many antibiotics, is a weak acid. The carboxylic acid group on it has a low pK_a, rather readily giving up the hydrogen. The resulting negative charge is shared between the two oxygens on the carbon, producing a relatively stable configuration.

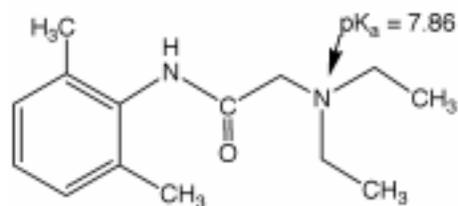


b. Dobutamine (increases the heart's ability to pump)



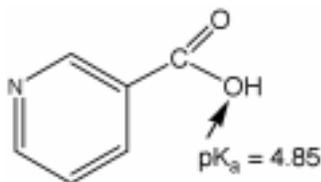
Dobutamine is a weak base. The amine group in the middle of the molecule rather readily accepts another hydrogen.

c. Lidocaine (used for rhythm disturbances in the heart)



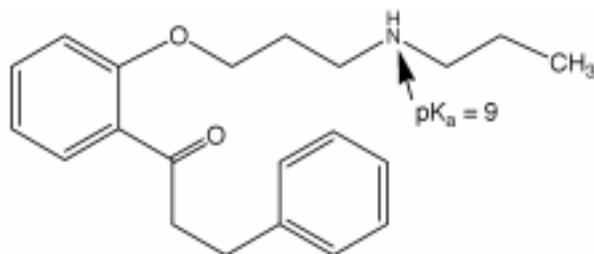
Lidocaine, like many of the heart drugs, is also a weak base. It may have been difficult for you to decide which nitrogen was the proton acceptor. The nitrogen nearest the ring structure is stabilized by that ring structure; acceptance of another hydrogen ion would make it no longer able to participate in resonance with the ring. Thus, the most likely candidate is the free and easy nitrogen further away from the ring. Here there is no resonance effect and so the nitrogen is available to accept a proton.

Niacin (vitamin B-3; used for high cholesterol)



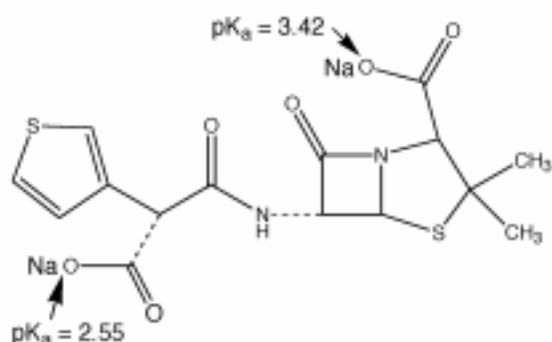
Another weak acid, weaker than cefuroxime above. The ring structure on the niacin shares a bit of the hydrogen's positive charge and so the molecule is less likely to want to donate the hydrogen compared to a carboxylic acid structure further from a ring structure.

Propafenone (used for rhythm disturbances in the heart)



Propafenone is a weak base, similar to the dobutamine and lidocaine above.

Ticarcillin (an antibiotic)



Ticarcillin is a weak acid. The difference in pK_a s between the two carboxylic acid moieties probably is the result of it being more difficult to lure a proton away from a molecule that has already lost one.

Notice how you can guesstimate the pK_a from the K_a since the first digit of the pK_a will always be the number of zeros you punch into your calculator, or one less than the power the 10 is to. Thus a K_a of something $\times 10^{-5}$ will always be 4.something. A K_a of something $\times 10^{-8}$ will always be 7.something. This is a no-brainer for you if you are comfortable with math, but if logs are not your friend, then knowing this will give you more confidence when you're doing K_a to pK_a conversions.

6. Please determine the percent ionization for the following drugs:

a. clindamycin (a weak base, pK_a 7.45) injected into the bloodstream (pH 7.4)

$$\frac{100}{1 + 10^{(7.4-7.45)}} = 53\% \text{ ionized}$$

b. ceftriaxone (a weak acid, pK_a s of 3, 3.2, and 4.1 – you will use the lowest, since they are all in the same ballpark) injected into the bloodstream (pH 7.4)

$$\frac{100}{1 + 10^{(3-7.4)}} = \sim 100\% \text{ ionized}$$

c. paroxetine (a weak base, pK_a 9.9) in the intestine (pH 8). Would you expect this drug to be well absorbed from the gut?

$$\frac{100}{1 + 10^{(8-9.9)}} = 99\% \text{ ionized}$$

You would not expect this drug to be well absorbed from the gut. Examining its structure, however, you would notice a prominent 3-ring structure forming the backbone of the molecule. This makes the drug reasonably lipophilic, which aids in absorption.

d. pentobarbital (a very weak acid, pK_a around 8) injected into the bloodstream (pH 7.4)

$$\frac{100}{1 + 10^{(8-7.4)}} = 20\% \text{ ionized}$$

e. phenobarbital (a very weak acid, pK_a 7.41) in the intestine (pH 8). Would you expect this drug to be well-absorbed from the gut?

$$\frac{100}{1 + 10^{(7.41-8)}} = 80\% \text{ ionized}$$

You would expect this drug to be absorbed from the gut, but not very rapidly. This is actually the case. It is interesting that absorption is better when this drug is rectally administered. The pH in the rectum is closer to physiologic pH (7.4).

f. timolol (a weak base, pK_a 9) placed in the eye (pH 7.4). Would you expect this drug to be well absorbed into eye tissues?

$$\frac{100}{1 + 10^{(7.4-9)}} = 98\% \text{ ionized}$$

You would not expect this drug to be well absorbed into eye tissues. Pharmacologic effect in the eye, however, can be measured in as little as 15 minutes after administration of the eye drop so there is probably some active transport of the drug occurring.

g. albuterol (a zwitterion with an amide constituent pK_a 9.3 and a phenol constituent pK_a 10.3) inhaled from the lungs (pH 7.4). Would you expect this drug to be well absorbed from the lungs?

Part of this drug will always be ionized, so you would not expect it to be well absorbed from the lungs. Again, there is pharmacologic effect seen within minutes of administration, so there is likely active transport of the drug occurring.

h. methenamine mandelate (a very weak base, pK_a 4.8) excretion from the bloodstream (pH 7.4) into the urine (pH 5.0).

in the bloodstream:		in the urine:	
$\frac{100}{1 + 10^{(7.4-4.8)}}$	=	<1% ionized	$\frac{100}{1 + 10^{(5-4.8)}}$ = 40% ionized

Would you expect it to stay in the urine or be reabsorbed into the bloodstream? **You would expect it to readily cross membranes from the bloodstream into the urine. Once there, you would not expect it to be readily reabsorbed from the urine back into the bloodstream.**

You could increase the retention of the methenamine in the urine if you (circle one) alkalized acidified the urine.

This makes sense since it would only increase the percent ionized in the urine.