Clinical Relevance of Physical Chemistry

Ian R. Tebbett, Paul Doering and Randy Hatton

College of Pharmacy and Shands Hospital, University of Florida, Health Sciences Center, P.O. Box 100485, Gainesville FL 32610-0485

PROLOGUE

Pharmaceutics I is a physical pharmacy course presented to pharmacy students in the first professional year at the University of Florida. In order to better illustrate the clinical relevance of physical chemical concepts, we have relied on the use of case studies and clinical examples originating from questions submitted to the Drug Information Center at this university hospital. This article is an example of our approach to teaching this material, with particular reference to the concepts of acid-base, partitioning and solubility. By emphasizing the clinical relevance of chemical concepts, we have found that the students are more receptive to this course and retain the information for much longer.

COURSE INFORMATION

The following is an abstract of lectures in the course Pharmaceutics I, which is essentially a physical chemistry course given to students entering their first professional year of the BS and PharmD programs in the College of Pharmacy at the University of Florida. The course reviews aspects of molecular structure, mathematical fundamentals and pH, and introduces the concepts of partitioning, solubility, colligative properties and thermodynamics. The technical information is taken from Martin’s Physical Pharmacy (1) and Remington’s Pharmaceutical Sciences(2) which are recommended texts. Having spent two years taking prepharmacy courses, the entering students are anxious to learn about pharmacology and therapeutics. To be met with the above list of topics often begs the question “Why do I need to know this?” In order to explain the relevance of physical chemical parameters to the practice of pharmacy, we have relied heavily on the use of case studies supplied by the drug information service at the University of Florida. The Drug Information and Pharmacy Resource Center (DIPRC) receives an average of 15 questions per day from health professionals all over Florida. These originate from pharmacists, physicians, nurses, dentists, and others trying to improve the care given to their patients by solving a variety of drug related problems. Answering the questions often calls upon direct knowledge of, or research into, one or more basic science concepts. The drug information service is therefore a valuable resource for clinical examples to be used for the illustration of basic science concepts. The following discusses the principles of solubility and partitioning and the influence of pH on both properties. The concept of a tablet dissolving in the stomach contents, passing into the more basic ileum and partitioning across intestinal membranes adds clinical relevance to this material.

ACIDS, BASES AND pH

The Bronsted-Lowry theory of acids and bases defines an acid as a substance, charged or uncharged that is capable of donating a proton: and a base is a substance charged or uncharged that is capable of accepting a proton from an acid. Acidic substances only behave as acids in the presence of a base, and a basic substance only behaves as a base when in the presence of an acid. Most drugs are weakly acidic or weakly basic when dissolved in water and their relative strengths are associated with their tendency to give up and take on protons. Hydrochloric acid is a stronger acid than acetic when dissolved in water since it more readily dissociates, giving up its proton. However the strength of an acid varies in different solvents, for example hydrochloric acid is a weak acid in glacial acetic acid and acetic acid is a strong acid in liquid ammonia. Consequently the strength of an acid depends not only on its ability to give up a proton but also on the ability of the solvent to accept it. This is referred to as the basic strength of the solvent.

The mechanism by which an acid transfers a proton to a base is called dissociation or ionization. Acids and bases are crudely classified as strong or weak depending on the completeness of the ionization process (extent of ionization). Strong acids are completely ionized in aqueous solution for example HNO₃, HCl, HClO₄ and H₂SO₄ and weak acids are partially ionized in water e.g., H₃BO₃, HCN, H₂S. The same holds true for strong and weak bases respectively. By the Bronsted Lowry definition, most pharmaceuticals can be considered as being weak acids or weak bases. Examples of acidic drugs include: amobarbital, aspirin, ibuprofen, penicillins. Atropine, codeine, epinephrine,
gentamicin and streptomycin are examples of bases. Amphoteric compounds are those which are capable of both donating and accepting a proton i.e., possessing both acidic and basic properties, for example morphine. Other drugs such as steroids and vitamins A, D and E do not have groups which ionize significantly in solution and are therefore not considered as having acidic or basic properties.

IONIZATION CONSTANTS
Weak acids and bases are incompletely or slightly ionized in solution. The extent of ionization is described by the equilibrium ionization constant, K.

For an acid; \[ \text{HA} = \text{H}_2\text{O} \leftrightarrow \text{H}_3\text{O}^+ + \text{A}^- \]

\[ K = \frac{[\text{H}_3\text{O}^+][\text{A}^-]}{[\text{HA}][\text{H}_2\text{O}]} \quad \text{Or} \quad K_a = \frac{[\text{A}^-][\text{H}_3\text{O}^+]}{[\text{HA}]} \]

[H$_2$O] is included in the ionization constant $K_a$ as [H$_2$O] can be treated as though it were a constant. It is more usual to refer to the ionization constant in terms of the $pK_a$ which is defined as $pK_a = -\log_{10}K_a$.

Similarly for a base where; \[ \text{BOH} + \text{H}_2\text{O} \leftrightarrow \text{OH}^- + \text{BH}^+ \]

\[ K_b = \frac{[\text{OH}^-][\text{BH}^+]}{[\text{BOH}]} \]

For strong acids, $K_a > 1$ or $pK_a < 0$ and for strong bases, $K_b > 1$ or $pK_b < 0$. Also $pK_a + pK_b = pK_w = 14$. Therefore if $pK_a$ is known for a base we can calculate $pK_b$ for the conjugate base. However if given the $pK_a$ for an unknown drug, we must decide from inspection of other chemical or structural data if the drug is an acid or a base, before using the $pK_a$ value in calculations. The $pK_a$ indicates the chemical or structural data if the drug is an acid or a base, unknown drug, we must decide from inspection of other

REAL AND IDEAL SOLUTIONS
In an ideal binary system, the molecules of the two components interact with each other in exactly the same way as if each component was in the pure state. This implies the complete uniformity of cohesive and adhesive bonds. In such a case, the properties of the solution are associated with the properties of the two pure components and are proportional to the mole fractions of each component present in the solution. However a non ideal solution such as H$_2$SO$_4$ in water has properties which are far from the mean of the properties of pure H$_2$O and pure H$_2$SO$_4$. The relationship between vapor pressure and mole fraction is defined by Raoults law. For an ideal binary solution, the vapor pressure of each component ($p_1$ or $p_2$) is equal to the vapor pressure of the pure component (p°) multiplied by its mole fraction (n).

$p_1 = p^°_1n_1$ and $p_2 = p^°_2n_2$

Therefore $P_{total} = p_1 + p_2.$

Unfortunately, most solutions of pharmaceutical relevance are non ideal (real solutions). In such solutions, it is found that the partial pressures are not directly proportional to the mole fraction. Experimentally observed vapor pressures may be lower than the theoretical value, i.e., show a negative deviation from Raoults law. This behavior results because the adhesive forces between the two different molecules are greater than the cohesive forces between the molecules in the pure liquids. Conversely, if the cohesive forces between the molecules of the pure components are greater than the adhesive forces between pairs of unlike molecules, positive deviation from Raoults law occurs. Most pharmaceutical solutions involve polar aqueous or alcoholic solutions which are hydrogen bonded. These can give either positive or negative deviations when fully miscible, depending on the nature of the solute. When miscibility is only partial or solubility is low, positive deviations occur.

A pair of liquids are said to be miscible if they form a single liquid phase when mixed in any proportion. Many pairs of liquids are only partially miscible. These are binary systems in which positive deviations from Raoults law are so great that the two liquids are completely dissolved in each other when one liquid is in considerable excess, but form two liquid phases when the two pure liquids are mixed in comparable proportions.

EFFECT OF pH ON SOLUBILITY OF ACIDS AND BASES
As previously discussed, many drugs are weakly acidic or basic. Such drugs are ionized at certain pH values and unionized at others. Acidic drugs ionize in base conditions, and basic drugs ionize in acid conditions. In each case the charged ion is more
soluble in water than the unionized drug. The uncharged drug is more soluble in organic solvents. If the pH of the solution changes the solubility of the drug may change. This effect is illustrated by the following example:

**Question:** Why can fosphenytoin be given IM and phenytoin cannot?

**Background:** Fosphenytoin (Cerebyx by Parke-Davis) was approved in 1996 as a prodrug of phenytoin that can be used both IV and IM for the treatment and prevention of seizures. Injectable phenytoin sodium injection has been on the market for many years for IV use. It cannot be given IM because of erratic absorption. Injectable phenytoin sodium has limited aqueous solubility. Phenytoin sodium injection USP 50 mg/mL is an aqueous vehicle of 40 percent propylene glycol and 10 percent ethanol at a pH of 12. The high pH is required because of the poor solubility (at a lower pH). This dosage form is irritating when given IV. It may cause tissue damage if it extravasates. Rapid administration can cause cardiovascular collapse, which has been attributed to the propylene glycol vehicle. IM administration has erratic absorption and is painful. These problems are most likely caused by crystallization of phenytoin at the IM site secondary to differences in tissue pH.

**Answer:** Fosphenytoin is a phosphate ester prodrug of phenytoin that is converted to phenytoin in the plasma by phosphatases i.e., phenytoin is liberated from the prodrug by breakdown of the ester linkage. The phosphate ester of phenytoin is 4400 times more soluble in an aqueous solution compared with phenytoin. The injection is an aqueous solution buffered to a pH of 8.6 to 9 (.i.e., closer to physiologic pH and therefore less likely to cause muscle irritation). Unlike phenytoin, fosphenytoin can therefore be given IM and results in 100 percent bioavailability of the phenytoin.

**DISSOLUTION RATES**

Chemicals including drugs do not dissolve in solvents instantly. Appreciable time is required for the process of dissolution. When a particle of a drug is introduced into water, the molecules at the surface of the particle dissolve and saturate the diffusion layer. The diffusion layer consists of tightly bound molecules of water which are not easily disrupted by stirring. In order for more of the drug to dissolve from the surface of the particle the dissolved drug must diffuse out of the diffusion layer, through the less tightly bound water to the bulk (stirred solution). The rate of dissolution is given by the Noyes-Whitney equation. This takes into account the two processes necessary for dissolution to occur, i.e., saturation and diffusion.

\[
dw/dt = k(Cs - Ct)
\]

where \( dw \) is the amount (in moles or mg) of drug going into solution in time \( dt \), \( k \) is a time dependent constant, \( Cs \) is the saturated solubility of the compound and \( Ct \) is the concentration at any time \( t \). The constant \( k \) is proportional to the diffusion coefficient (D) of the drug in the solvent (a measure of how fast the drug molecules diffuse through the solvent), and the area of solid drug exposed to the solvent. But, the constant \( k \) is inversely proportional to the thickness of the immobilized layer of solvent at the surface of the drug. The dissolution rate is important in determining the extent of absorption of drugs from orally administered tablets, suspensions and capsules. If the dissolution rate is slow, the extent of absorption may be limited.

**EFFECT OF PARTICLE SIZE**

Small particles have an increased rate of dissolution relative to that of larger particles for two reasons: Increased surface area to volume ratio and increased number of surface defects and cracks. A large number of surface defects and cracks mean that molecules are less tightly bound to each other. This results in each of the solid particles having a lower crystal lattice energy than corresponding perfect crystals. Surface cracks also increase the surface area of the crystals. Some very poorly soluble drugs may have little efficacy unless the particle size is very small or micronized (<25µm). An example is hydrocortisone cream compounded with micronized hydrocortisone which is more effective than products with the same weight of larger particles. Antifungal therapy with oral griseofulvin is much more effective if the tablets are made with micronized griseofulvin. Conversely, Macrobid is a preparation containing macrocrystalline nitrofurantoin which is used to slow the rate of absorption. Although absorption is decreased, the area under the concentration/time curve is the same as that produced with normal sized particles. The rate of absorption of the smaller particles however is so rapid that the resulting peak blood concentrations cause the patient to experience nausea and vomiting. Other drugs for which particle size is important include digoxin, phenytoin, steroids and anticoagulants. Preparations of these drugs, especially tablets, which contain a wide range of particle sizes, may result in sub-therapeutic blood levels. They may also result in marked changes in blood levels if the patient has a habit of switching between name brands and generic preparations of the same drug.

**EFFECT OF PROTEIN BINDING**

Many drugs are bound to plasma proteins. Serum albumin constitutes 60 percent of all the protein in plasma and is capable of binding molecules which are either positively charged, negatively charged or neutral. This type of complex formation may have a marked effect on the efficacy of the drug. The total solubility of the drug in plasma can be increased and the availability of the drug for transfer to the site of action is often reduced, depending on how tightly the drug is bound to the protein. If the patient has been taking a drug which binds to plasma protein for a period of time, a reservoir of drug will accumulate on the plasma protein. If the patient then takes another drug which is more strongly protein bound, a large amount of the first drug may be released into the circulation. This can lead to a potentially dangerous overdose situation. For example the anti-inflammatory agent phenylbutazone is strongly protein bound and can displace the anti-epileptic agent phenytoin. This interaction can be serious since phenytoin overdose can occur easily (narrow therapeutic window). Salicylic acid can also displace phenytoin from plasma proteins.

**PARTITIONING**

The Partition coefficient is a thermodynamic property of all compounds which are soluble to some extent in any pair of solvents in a ratio which reflects its relative affinity for each. One of the solvents is usually water and the other is an immiscible organic solvent such as ether, chloroform etc. The partition coefficient is important in pharmacy for the following reasons; estimating the ease of absorption of drugs across membranes; predictions of the pharmacological ac-
tivity of drugs; extraction of the drugs from aqueous solutions and biological media; estimating required amounts of preservatives for emulsions and other multiphase dosage forms. Drugs partition between aqueous and nonaqueous solvents. A compound which is ionized has a greater affinity for the aqueous phase than an unionized compound which will tend to move into the non organic phase. The degree of ionization depends on the pH.

For acids

\[ HA \leftrightarrow H^+ + A^- \]

unionized organic soluble

ionized water soluble

Similarly for bases

\[ BOH \leftrightarrow B^+ + OH^- \]

The partitioning of preservatives between aqueous and nonaqueous phases in emulsions and creams is a good example of the effects of pH on partitioning, and shows the importance of these considerations in the formulation of these products. Preservatives are compounds which prevent the growth of micro-organisms in liquid pharmaceuticals. These compounds may be either carboxylic acids or phenols which exert their antimicrobial effects only when the pH is low enough to produce a significant concentration of the unionized preservative. However the unionized preservative is also more lipid soluble than the ionized form. Thus at low pH values the unionized form partitions into the organic phase (where it is not needed since the microorganisms do not grow in this medium). At the same time the concentration of active preservative in the aqueous phase may be reduced below the minimum concentration required to inhibit microbial growth.

Similarly the partitioning of a drug from aqueous solution across biological membranes and tissues (lipid) is dependent to a large extent on the degree of ionization of a drug. Biological membranes are lipid-like (fatty) in nature. Acidic or basic drugs partition best across such membranes when the drugs exist in their neutral unionized forms. The pH of the environment to which the drug is exposed in the gastrointestinal tract changes as it proceeds from the stomach to the intestine, thereby affecting the dissociation of the drug. Hence the fraction of the drug present in its unionized form may change depending on the exact nature of the acidic or basic group(s). Thus the extent of absorption of the drug will also change depending on how far it has traveled along the GI tract. Acidic drugs are generally absorbed in the stomach, while basic drugs tend to be absorbed in the more basic small intestine. Excretion of drugs in urine is also affected by changes in urinary pH. Phenobarbital is excreted much more readily if the urine is made alkaline by means of a urinary alkalinizer such as potassium citrate.

The concepts of partitioning and solubility (sodium bicarbonate and calcium) can be further illustrated by reference to peritoneal dialysis. Peritoneal dialysis is an alternative to hemodialysis in patients with chronic renal failure. Patients can be maintained on Continuous Ambulatory Peritoneal Dialysis (CAPD) by means of a permanent catheter. Throughout the day, they infuse approximately 2 liters of dialysis solution that sits in their peritoneum and dialyses off “metabolic wastes.” The peritoneal membrane acts as the “dialysis membrane”, a highly vascular structure, and the blood and the dialysate are solutions on either side of it. The diffusion gradients between the blood and dialysate prevent the accumulation of uremic solutes. Dialysates, which are often dispensed from pharmacies, contain sodium, chloride, lactate, ionized calcium, magnesium, and glucose with an osmolality of 340 (compared with 280 to 300 for blood). Chronic renal failure (CRF) patients have hyperphosphatemia. There is no phosphate in the dialysate, as it is poorly dialyzed. These patients receive phosphate binders orally with their food (e.g., calcium carbonate) to prevent the phosphate from reaching the blood. CRF patients are also acidic, and lactate is added to the dialysate to help manage the patients metabolic acidosis. The lactate is absorbed and converted to bicarbonate in the liver. The glucose provides the osmotic gradient to pull off fluid (ultrafiltrate) and the higher the concentration of glucose the more fluid is removed with each dwell time. The sodium, chloride, calcium, and magnesium are added to prevent these important electrolytes from being removed by dialysis (i.e., maintain homeostasis). The concentration and electrolytes in dialysate can be manipulated based on the patient’s situation. For example, a hypokalemic patient can have potassium added to the dialysate to prevent removal or as a supplement.

Following the above discussion of electrolytes, students are asked the question; What is the maximum osmolality of a parenteral nutrition solution which can be given via peripheral vein? The question is put in the context of a pharmacist having received an order for a parenteral nutrition solution containing 15 percent dextrose and 4.25 percent crystalline amino acids. The order calls for this solution to be infused via the antecubital vein. After addition of electrolytes, trace elements, and the other ingredients the pharmacist is very concerned that the solution will be hyperosmolar and cause phlebitis. This scenario introduces the concept of osmolarity, isotonicity, and the consequences of infusing hypertonic solutions. Further, it would introduce the student to the clinical concept of parenteral nutrition which is explained in further detail later in the course.

**SUMMARY**

Pharmacy is a profession whose very foundation rests in the basic sciences. Students receive many hours of instruction in the basic sciences during their prepharmacy years and into their professional courses. Science is crucial to the understanding of dosage forms, drug manufacture, and drug action in the body. We must embrace rather than abandon the roots of our profession.

Unfortunately, basic science concepts are often taught without showing future application. Thus, students approach this mountain of information by memorizing formulae, facts, and chemical structures, with no real understanding of how this might apply to practice. Teaching that demands rote memorization to pass the course does not lend itself to long term retention.

Clerkship students are expected to have mastered the sum total (or at least the major points) of their professional curriculum by the time they enter the clinic. Unfortunately, many have only distant memory of ever taking biochemistry, pharmaceutics, or medicinal chemistry, to mention only a few subjects. Instead, they reply that they cannot possibly be expected to remember things from three years ago. If taught from the beginning in an applied fashion, there is greater likelihood that the student will have functional knowledge of a content area many years after first exposure. In the clerkship setting when the basic science principle is re-explained, this time in the context of a specific drug related
problem, a light seems to go on in the mind of the student. The look on their faces seems to say, “Now I get it!” Some will go so far as to comment that the point makes sense for the first time and should have been made in a patient context way back when it was first presented. If done this way, there would be more incentive to fully understand the concept and greater probability that the point will still be with the students several years later.

References