

Remington: The Science and Practice of Pharmacy

Volume I

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Volume I

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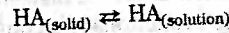
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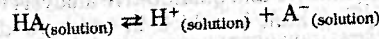
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process. The first example is the acid, HA, that is relatively insoluble in water. Its two-step dissolution can be represented as



followed by



The equilibrium constant for the first step is the solubility of HA ($K_S = [HA]_{(solution)}$), just as was developed earlier when no chemical reaction took place, and the equilibrium constant for the second step is the dissociation constant of the acid is

$$K_a = \frac{[H^+][A^-]}{[HA]}$$

Since the total amount of compound in solution is the sum of nonionized and ionized forms of the acid, the total solubility may be designated as $S_{i(HA)}$, or

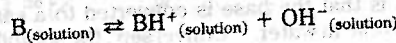
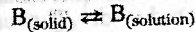
$$S_{i(HA)} = [HA] + [A^-] = [HA] + K_a \frac{[HA]}{[H^+]} \quad (8)$$

Since $K_S = [HA]$, Eq 8 becomes

$$S_{i(HA)} = K_S \left(1 + \frac{K_a}{[H^+]} \right) \quad (9)$$

Equation 9 is very useful since it equates the total solubility of an acid drug with the hydrogen-ion concentration of the solvent. If the water solubility, K_S , and the dissociation constant, K_a , are known, the total solubility of the acid can be calculated at various hydrogen-ion concentrations. Equation 9 demonstrates quantitatively how the total solubility of the acid increases as the hydrogen-ion concentration decreases (that is, as the pH increases).

It is possible to develop an equation similar to Eq 9 for the solubility of a basic drug, B, such as a relatively insoluble nitrogenous base (an alkaloid, for example), at various hydrogen-ion concentrations. The solubility of the base in water may be represented in two steps, as



Again, if K_S is the solubility of the free base in water and K_b is its dissociation constant

$$K_b = \frac{[BH^+][OH^-]}{[B]}$$

the total solubility of the base in water $S_{i(B)}$ is given by

$$S_{i(B)} = [B] + [BH^+] = [B] + \frac{K_b[B]}{[OH^-]} = K_S \left(1 + \frac{K_b}{[OH^-]} \right) \quad (10)$$

It is convenient to rewrite Eq 10 in terms of hydrogen-ion concentration by making use of the dissociation constant for water

$$K_w = [H^+][OH^-] = 1 \times 10^{-14}$$

basic drug there should be a pH at which maximum solubility occurs where this solubility remains the sum of the solution concentrations of the free and salt forms of the drug at that pH. Using a basic drug, B, as the example, this would mean that a solution of B, at pH values greater than the pH of maximum solubility, would be saturated with free-base form but not with the salt form and the use of Eq 11 would be valid for the prediction of solubility. On the other hand, at pH values less than the pH of maximum solubility, the solution would be saturated with salt form and Eq 11 is no longer really valid. Since in this situation the total solubility of the base, $S_{i(B)}$, is

$$S_{i(B)} = [B] + [BH^+],$$

where the subscript, s, designates a solution saturated with salt, the correct equation to use at pH values less than the pH maximum would be

$$S_{i(B)} = [BH^+]_s \left(1 + \frac{[OH^-]}{K_b} \right) = [BH^+]_s \left(1 + \frac{K_w}{K_b[H^+]} \right) \quad (12)$$

A relationship similar to Eq 12 likewise can be developed for an acidic drug at pH s greater than its pH of maximum solubility.

Effecting Solution of Solids in the Prescription Laboratory

The method usually employed by the pharmacist when soluble compounds are to be dissolved in water in compounding a prescription requires the use of the mortar and pestle. The ordinary practice is to crush the substance into fragments in the mortar with the pestle and pour the solvent on it, meanwhile stirring with the pestle until solution is effected. If definite quantities are used, and the whole of the solvent is required to dissolve the given weight of the salt, only a portion of the solvent should be added first and, when this is saturated, the solution is poured off and a fresh portion of solvent added. This operation is repeated until the solid is dissolved entirely and all the portions combined. Other methods of effecting solution are to shake the solid with the liquid in a bottle or flask or to apply heat to the substances in a suitable vessel. Substances vary greatly in the rate at which they dissolve some are capable of producing a saturated solution quickly others require several hours to attain saturation. All too often, in their haste to prepare a saturated solution, pharmacists fail to obtain the required degree of solution of solute.

With hygroscopic substances like pepsin, silver proteol compounds and some others, the best method of effecting solution in water is to place the substance directly upon the surface of the water and then stir vigorously with a glass rod. If the ordinary procedure, such as using a mortar and pestle, is employed with these substances, gummy lumps are formed which are exceedingly difficult to dissolve.

The solubility of chemicals and the miscibility of liquid are important physical factors for the pharmacist to know, as they often have a bearing on intelligently and properly filling prescriptions. Mainly for the information of the pharmacist the USP provides tabular data indicating the degree of solubility or miscibility of many official substances.

Determination of Solubility—For the pharmacist and pharmaceutical chemist the question of solubility is of paramount importance. Not only is it necessary to know solubility

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