Syrups

The use of liquid is common due to ease of administration. It is more rapidly and efficiently absorbed than a tablet or capsule.

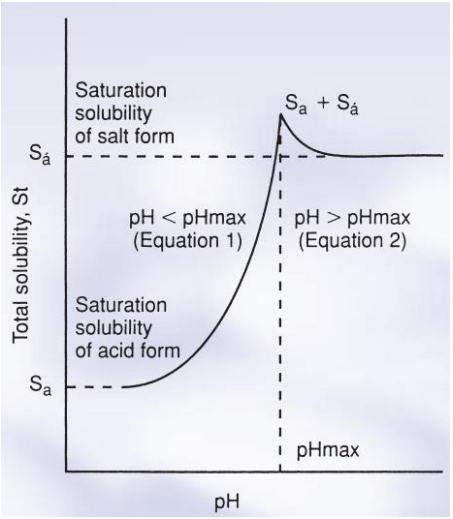
However, the formulation of solutions presents many technical problems to the industrial pharmacist. Some drugs are unstable; this property is magnified when the drug is in solution. Special techniques are required to solublize poorly soluble drugs. The final preparation must satisfy the requirements of pharmaceutical elegance with regard to taste, appearance, and viscosity.

The pH of the formula

A large number of drugs are either weak acids or weak bases. The solubility of these agents can be influenced by the pH of their environment.

The total quantity of a weak acid *in solution* (i.e. *soluble*) at a specific pH is the sum of the concentrations of both the acid and salt form. If excess acidic drug is added, the quantity of the acid in solution is maximized and constant because of its saturation solubility (due to the excess amount). As the pH of the solution increases, the quantity of drug in solution increases because the water-soluble salt is being formed.

There is certain pH at which the total solubility (S_T) of the drug is saturated with respect to both the acid and salt. This pH is called the pH_{max}. The solution can be saturated with respect to the **salt** at pH values higher than this, but not with respect to the acid. Also, at pH values less than pH_{max}, the solution can be saturated with respect to the **acid** but not to the salt. Therefore, the acid is preferred to be in a pH region above the pH_{max} whereas the salt is preferred to be in a pH region below the pH_{max}. This is illustrated in the following figure.



To calculate the total quantity of drug that can be maintained in solution at certain pH, the following two equations can be used, depending on whether the drug is a free acid or salt.

The equation of the acid is:

$$S_T = S_a\left(1+\frac{K_a}{[H^+]}\right)$$ (equation 1)

The equation of the salt is:

$$S_T = S'_a\left(1+\frac{K_a}{[H^+]}\right)$$ (equation 2)

Where:

S_T is the total molar solubility of the drug (acid and salt).

S_a is the molar solubility of the acid.

S'_a is the molar solubility of the salt.

EXAMPLE: A pharmacist prepares a 3% solution of an acidic drug as syrup and dispenses it to patient. A few days later the patient returns the syrup to the pharmacist because the product contains a precipitate. The pharmacist checks the pH of the solution and finds it to be 6. The information of interest on the drug includes the following:

Molecular weight of the drug is 263

Solubility of the drug (free acid) is 3.1 mg/mL

Ka is 5.86×10^{-6}

Sol.

Since S_a is ***molar*** solubility, then 3.1 mg/mL equals to 0.0117 M (*how? H.W.*)

pH=6 then, $[H^+]=1\times 10^{-6}$.

Now applying the equation 1:

$S_T= 0.0117\ [1+(5.86 \times 10^{-6})/(1\times 10^{-6})]$

$S_T=0.080$ M

From this value, the pharmacist knows that at a pH 6, a 0.080 M solution can be prepared. However, the concentration that should be prepared was a 3% (i.e., 0.114 M). Consequently, the drug will not be in solution at this pH. In fact, the pH might be all right initially but changed over time, resulting in precipitation of the drug.

The question is at ***what pH the drug will remain in solution?*** This can be calculated using the same equation:

$0.114=0.0117\{1+(5.86 \times 10^{-6})/[H^+]\}$

$[H^+]=6.7\times10^{-7}$

pH=6.17

So, the pharmacist prepares the syrup and adjusts the pH to above 6.2 using a suitable buffer, and dispenses it to the patient.

The above example gives an interesting information concerns the close relationship of pH to solubility. At a pH of 6, only a 0.080 M solution could be

prepared, but at a pH of 6.17 a 0.114 M solution could be prepared. In other words, a difference of 0.17 pH units resulted in:

$$\frac{0.114 - 0.080}{0.114} \times 100 = 30\%$$

30% more drug going into solution at the higher pH than at the lower pH. In other words, a very small change in pH resulted in about 30% more drug going into solution (30% difference in solubility!!).

If pH is critical to maintain drug solubility, the system must be adequately buffered.

Note: In selecting the pH for adequate solubility, several other factors should be considered. The pH that satisfies the solubility must not conflict with other requirements, such as stability and physiologic compatibility.

On the other hand, the pH adjustment for some drugs does not provide an appropriate means for achieving solution. In the case of very weak acids or bases, the required pH may be unacceptable in terms of physiologic considerations or owing to the effect of pH extremes on the stability of formulation adjuvants (e.g., sugars flavors, preservatives). In addition, the solubility of nonionizable drugs (nonelectrolyte) is unaffected by pH adjustment. If a solution is to be achieved in these cases, it must be done by the use of ***cosolvents, solubilization, complex phenomena, or chemical modification of the drug***.

1. Cosolvency: The solubility of some drugs can be increased by the addition of a water miscible solvent in which the drug has good solubility. This process is known as cosolvency, and the solvents used in combination with the original solvent are known as cosolvents. The cosolvent works by reducing interfacial tension between the aqueous solution and the hydrophobic solute.

Ethanol, sorbitol, glycerin, propylene glycol and several members of the polyethylene glycol represent the limited number of cosolvents that are both useful and safe in the formulation of aqueous liquids.

Cosolvents are employed not only to improve solubility of the drug, but also to improve the solubility of other constituents such as flavors. .

2. Solubilization: it involves the use of surface active agents to form the micelles. Examples of surfactants are Span and Tween.

However, some times the surfactants may have a negative effect on the formula and care should be taken to avoid such situations. The activity of several preservatives and dyes, for example, has been found to significantly decrease in the presence of surfactants.

3. Complexation: is a method to increase the solubility of certain drugs using suitable complexing agents, e.g. cyclodextrin complexes.

4. Chemical Modification of the Drug: Many poorly soluble drugs can be chemically modified to water soluble derivatives. For example, the solubility of betamethasone in water is 5.8 mg/100 ml. The solubility of its disodium phosphate ester is greater than 10 g/100 ml, an increase in solubility greater than 1500-fold.

However, this approach has severe practical limitations. New derivatives must have the same properties as the parent compound, including biologic activity and toxicity. However, this approach can be useful only if no other reasonable way is available.

Preservatives

Microbial growth is one of the problems that may be encountered in liquid preparation. Numerous sources of contamination exist such as processing equipments, containers, environment, packaging, operators and users. Examples of preservatives are ethanol, benzoic acid, benzyl alcohol, paraben and benzalkonium chloride.

Syrups containing 85% sugar resist bacterial growth (self preserving) due to osmotic effect on the bacteria. However, it is possible for surface dilution to take place as a result of solvent evaporation followed by condensation on the top of the liquid. This can be prevented either by suing a preservative or using 5-15% alcohol in the formula. The evaporation of ethanol is faster than that of water thus it evaporates to the surface of the solution preventing bacterial growth.

The selection of suitable preservative is based on many considerations, such as:

1. The preservative should prevent the growth of the microorganisms which are most likely contaminating the preparation.
2. The preservative should be soluble enough in water (*why?*).
3. The preservative has adequate stability and will not be reduced in concentration by chemical decomposition or volatilization during the desired shelf life of the preparation.
4. The proportion of preservative remaining undissociated at the pH of the preparation should make it capable of penetrating the microorganism and destroying it. Thus, it is meaningless to specify the preservative effective concentration unless the pH is mentioned and the undissociated concentration of the preservative (which is the active form) is determined.

Similarly, if a material in the formula interacts with the availability of the preservative, the concentration of the preservative may be misleading because it may not be a true indicator of its effectiveness. Many of the incompatible combinations that inactivate the preservative contain various cellulose derivatives, polyethylene glycols and tragacanth. That is why tragacanth cannot be incorporated with parabens.

Sweetening Agents:

Sweetening agents constitute the major portion of solid content in syrups. Sucrose is one of the most widely used sweeteners. It is water soluble with reasonable cost and stable in the pH range 4-8. It is frequently used in combination with sorbitol and glycerin to reduce its tendency for crystallization. One manifestation of sucrose crystallization is cap-locking which occurs when sucrose crystallize on the cap of the bottle.

If the syrup was completely saturated with sucrose, any variation of storage conditions (cooling-heating cycle) might produce sucrose crystals. These crystals may act as nuclei initiating a type of chain reaction that would result in separation of an amount of sucrose disproportionate to its solubility at the storage temperature. The syrup would then be very unsaturated & suitable for microbial growth.

Sometimes, sucrose may be replaced in whole or in part by:

I. Non-sugars e.g., sorbitol, glycerin, propylene glycol, etc. However, these materials converted to glucose in the body.

II. nonglycogenetic substances such as methyl cellulose (MC), carboxymethyl cellulose (CMC) or hydroxyl ethyl cellulose (HEC). These materials are not hydrolyzed and not absorbed, and they are excellent syrup vehicle for medications intended for diabetic patients. The viscosity of them is much like that of sucrose syrups**.**

New artificial sugars such as aspartame and saccharine are also used.

Viscosity Enhancers

It is desired sometimes to increase the viscosity of a liquid either to improve the palatability or to improve the pourability. This can be achieved by:

- Increasing the sugar concentration *or*
- Incorporation of thickening agent such as polyvinyl pyrrolidone and different cellulose derivatives like carboxymethyl cellulose.

Viscosity inducing polymers should be used with a degree of caution. They are known to form molecular complexes with a variety of organic and inorganic compounds, and in doing so, influence the activity of these compounds.

Stability:

Generally, the stability of dosage forms decreases in the following order: solids, suspensions, solutions. The stable liquid should retain its viscosity, color, odor, clarity and taste throughout its shelf life. A freshly prepared sample should serve as reference standard for evaluation.

Equipments:

Generally, the type of equipment used in the manufacture of oral solutions consists of mixing tanks equipped with a means of agitation, and a filtration system for the final clarification and/or sterilization of the solution.

All equipment must be thoroughly cleaned and sanitized (sterilized if possible) before use. Equipment and lines can be sterilized by such methods as alcohol, boiling water, autoclaving, steam, or dry heat.

Tanks are usually constructed of stainless steel and are usually jacketed to allow for heating or cooling of the contents. If tanks are used for the compounding of the bulk liquid, they have a built-in agitation system.

The liquid is then clarified by a filtration system, and the filtered solution is stored in an adjacent tank until released by the quality control department. The liquid may then be transported to the filling line.

Compounding Procedure

Dilute solutions, prepared from rapidly dissolving materials, are simply prepared by the addition of the solute to the solvent and agitating until the solution is homogeneous. When more concentrated solutions are being made, or when the solute is slowly dissolving, it may be advantageous to employ heat.

Packaging:

The specific method used for filling a pharmaceutical liquid varies greatly depending on the characteristics of the liquid (e.g., viscosity, foam producing qualities, and compatibility with filling machine), the type of package into which the liquid is placed, and the required production output.