
كلية الصيدلة
COLLEGE OF PHARMACY
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AL MUSTAQBAL UNIVERSITY
جامعة المستقبل

Liquid Dosage Form
Syrups (Monophasic Liquids)

Mohammed Albarki, BSPharm, PhD.

Syrups

In simple words: **syrup is sugar and water.**

Advantages:

1. The use of liquid is common due to **ease of administration**.
2. A drug in solution is **immediately available for absorption**. And in most cases, It is more rapidly and efficiently absorbed than a tablet or capsule.

Disadvantages:

1. Some drugs are **unstable**; this property is magnified when the drug is in solution.
2. **Special techniques** are required to solubilize poorly soluble drugs.

Syrup Dosage Form

- The final preparation must satisfy the requirements of pharmaceutical elegance with regard to taste, appearance, and viscosity.
- The formulation of solutions presents many technical problems to the industrial pharmacist. To solve these problems:
- A study of **solubility** and **stability** can be approached **scientifically.**
- **Flavoring and organoleptic** properties remain **subjective**.
- So successful formulation needs science and art.

Solubility

- The first consideration in syrup formulation is the **solubility** of additives in the solution.
- It studies whether or not the substance is **dissolved** in a given system and the **extent** to which it dissolves.
- The **equilibrium solubility** of the drug of interest should be:

1. Determined in a solvent **similar** to the one intended for use in the final product.
2. The effect of temperature on solubility should be studied **since** the final product is expected to be exposed to a wide range of temperature conditions during shipping and handling.
   - As a rule, a solution should be designed in which the solubility of the solute is not exceeded even at a temperature as low as **4˚C**.

Effect of pH on Solubility

- 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.
- **Dissociation** of weak acid can be written as:

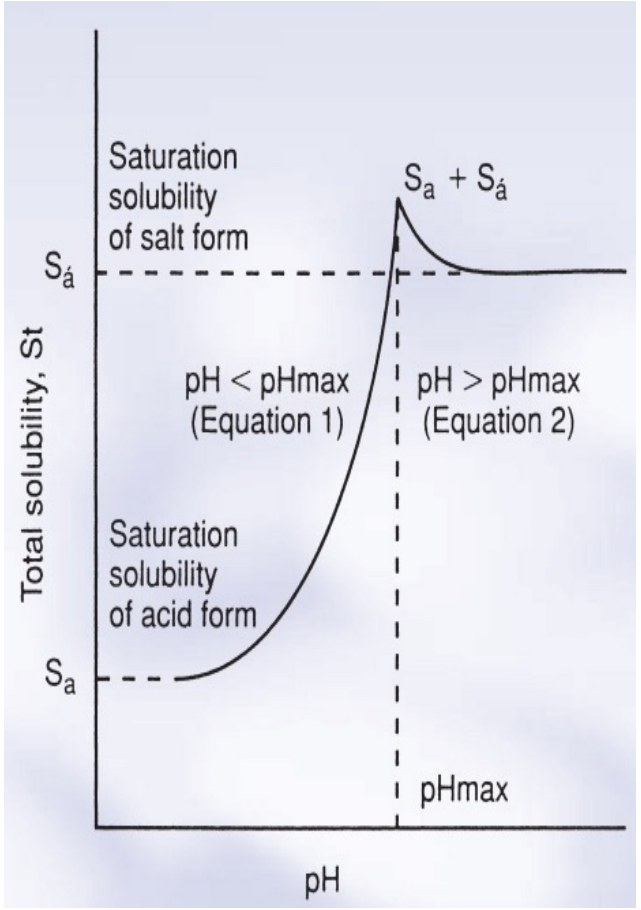
$$[DH] \overset{Ka}{\leftrightarrow} [D^-] + [H^+]$$

$$\text{Where } Ka = \frac{[D^-]\,[H^+]}{[DH]}$$

- If an **excess** acidic drug is added, the quantity of the acid in the solution is maximized and constant because of its saturation solubility (due to the excess amount).
- As the pH of the solution **increases** (becomes more basic, Decreases [H]), the quantity of drug in the solution increases **because** the water-soluble salt is being formed.

Effect of pH on Solubility

- There is a **certain pH value** at which the total solubility ($\mathbf{S_T}$) of the drug is saturated with respect to both the acid and salt. This pH is called the $\mathbf{pH_{max}}$.
- The solution can be saturated with respect to the **salt** at pH values higher than this, but not with respect to the acid (the original drug).
- 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} .This is illustrated in the following figure.



Effect of pH on Solubility

- 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 ([DH]) and salt ($[D^-]$)form. **Which is equal to total solubility (S_T)**

$$S_{(T)} \rightarrow S_T = [DH] + [D^-] \rightarrow \text{by substitution:}$$

$$S_T = [DH] + [DH]\frac{Ka}{[H^+]} \rightarrow [H^+] = \frac{[DH]K_a}{S_T - [DH]}$$

- This equation is the most useful equation in **determining** the solubility of weak acid at specific pH.

Effect of pH on Solubility: Example

- A pharmacist prepares a 3% solution of an acidic drug as a syrup and dispenses it to a 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:
- The molecular weight of the drug = 263 g/mol
- Solubility of the drug (free acid) (DH) = 3.1 mg/mL (0.0118 M) (how???)
- Ka = 5.86×10^{-6}

Solution:

- pH=6 then, $[H^+]=1\times 10^{-6}$.
- Now applying the equation : $S_T = [DH] + [DH]\frac{Ka}{[H^+]}$ → S_T= 0.0118 [1+(5.86×10^{-6})/(1×10^{-6})] → S_T=0.080 M

Effect of pH on Solubility: Example

- From this value, the pharmacist knows that at pH 6, a 0.080 M solution can be prepared.
- However, the concentration that should be prepared was 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 changes over time, resulting in the precipitation of the drug.
- The question is at what pH the drug will remain in the solution? This can be calculated using the : $[H^-] = \frac{K_a\,[DH]}{S_T - [DH]}$ → $[H^+]=6.7\times10^{-7}$ → **pH=6.17.** **[DH]=0.0118, S_T= 0.114**
- So, the pharmacist prepares the syrup adjusts the pH to **above 6.2** using a suitable buffer, and dispenses it to the patient.
- The above example gives interesting information concerning 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 **30 %** more drug going to the solution.

Effect of pH on Solubility

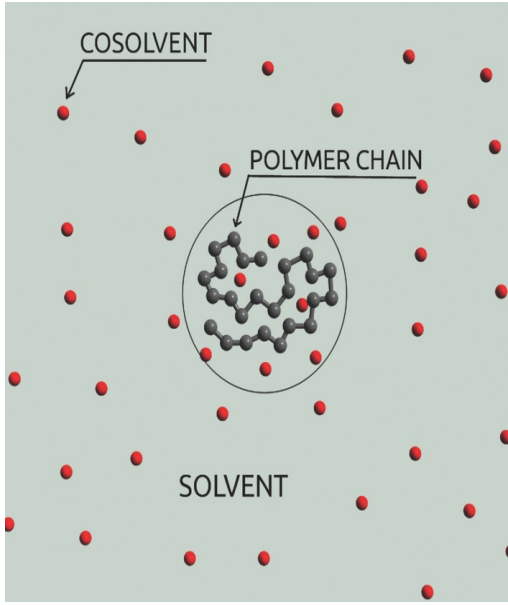
- **Note**: In selecting the pH for adequate solubility, several other factors should be considered.

1. The pH that satisfies the solubility must **not** conflict with other requirements, such as **stability** and **physiologic compatibility**.
   - **For Example**: 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).
2. Also: 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**.
   - This means that there are other means of enhancing solubility:➔

Enhancing Solubility of Non-Ionizable Drugs

A- Cosolvent

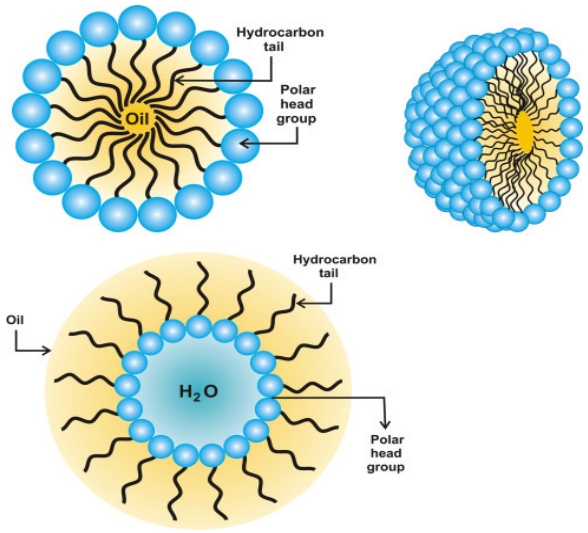
- The **solubility** of some drugs can be **increased** by the addition of a water-miscible solvent in which the drug has good solubility.
- This process is known as **cosolvency**, and the solvents used in combination with the original solvent are known as **cosolvent**.
- The cosolvent works by **reducing 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 the solubility of the drug but also to **improve** the solubility of other constituents such as flavors.



Enhancing Solubility of Non-Ionizable Drugs

B- Solubilization

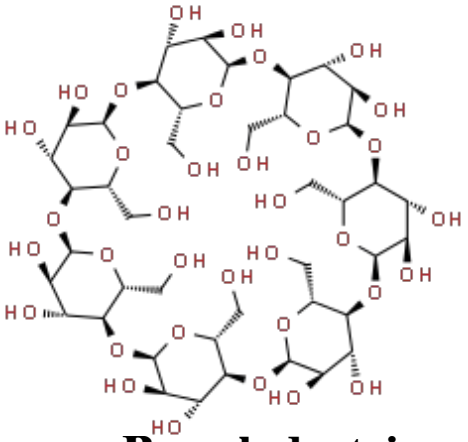
- It involves the use of **surface active agents** to form the **micelles**. Examples of surfactants are Span and Tween.
- However, sometimes the surfactants **may have a negative** effect on the formula and care should be taken to avoid such situations.
  - For Example: the activity of several preservatives and dyes, for example, has been found to **significantly decrease** in the presence of surfactants.



Micelle

C- Complexation

- It is a method to increase the solubility of certain drugs using suitable complexing agents, e.g. **cyclodextrin complexes**.



B-cyclodextrin

Enhancing Solubility of Non-Ionizable Drugs

D- Chemical Modification of the Drug

- Many poorly soluble drugs can be chemically modified into 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 biological activity and toxicity.
- This approach can be useful only if no other reasonable way is available.

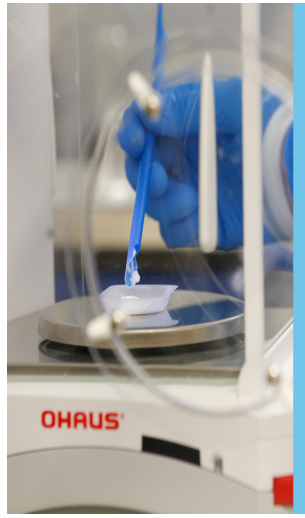
Syrup Component: Preservatives

- Microbial growth is one of the problems that may be encountered in liquid preparation.
- Numerous sources of contamination exist such as processing equipment, 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 the exosmotic 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 using a preservative or using 5-15% alcohol in the formula. The evaporation of ethanol is faster than that of water thus it evaporates and prevents bacterial growth.

Syrup Component: Preservatives

- The **selection of suitable preservatives** 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. It must be nontoxic, non-sensitizing, compatible with other formulation components, and acceptable with respect to taste and odor at the concentration used.



Choosing the Appropriate Antimicrobial Preservative for Compounded Medication

Syrup Component: 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 of 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 crystallizes on the cap of the bottle.
- Crystallization can occur with any variation of storage conditions (**cooling-heating cycle**) that might produce sucrose crystals.
- These crystals may act as nuclei initiating a type of **chain reaction** that would result in the 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.**

Syrup Component: Sweetening Agents

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

I. **Liquid glucose** which is a viscid liquid that imparts liquid formulations of both body and sweetness.

II. **Non-sugars** e.g., sorbitol, glycerin, propylene glycol, etc. However, these materials are **converted** to glucose inside the body.

III. **Non-glycogenetic** substances such as methyl cellulose (MC), and carboxymethyl cellulose (CMC)).
   - These materials are not hydrolyzed and not absorbed, and they are excellent syrup vehicles for medications intended for **diabetic patients**.

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

Syrup Component: Viscosity Enhancers

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

1. **Increasing** the sugar concentration *or*
2. Incorporation of **thickening agents** such as polyvinyl pyrrolidone and different cellulose derivatives like carboxymethyl cellulose (CMC).

- 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 of Syrup Dosage Form

- Generally, the stability of dosage forms decreases in the following order:
- Solids are more stable than suspensions which are more stable than solutions.
- **The stable liquid** should retain its viscosity, color, odor, clarity, and taste throughout its shelf life.
- A **freshly prepared** sample should serve as a reference standard for evaluation.
- So the company will keep a sample of their product in the desired conditions in order to be used as a reference.

Compounding Considerations

- **Equipment**
- 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 Considerations

- **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**.
- **Filling:**
- 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 the filling machine), the type of package into which the liquid is placed, and the required production output.