



Lecture 1

Solution (Part 1)

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Overview

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- Dispersed Systems
- General Description of Solutions
- Advantages of Solutions
- Disadvantages of Solutions

Drug Solubility

- Solubility Definition
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- Factors Affecting Drug Solubility
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Learning Objectives

1. Differentiate between different types of dispersed systems and their main characteristics.
2. Define the various types of liquid dosage forms
3. List the advantages and disadvantages of solutions
4. Define solubility and describe how different factors increase or decrease solute solubility in a given solvent
5. Demonstrate how to enhance the solubility of therapeutic agents in a suitable solvent
6. Define dissolution and how to increase its rate



Introduction

Dispersed Systems

General Description of Solutions

Advantages of Solutions

Disadvantages of Solutions

Dispersed Systems

Definition

Dispersed systems consist of a *dispersed phase* distributed throughout a *continuous* or *dispersion medium*.

Based on the size of the dispersed phase, three types of dispersed systems are generally considered:

- (a) *molecular* dispersions
- (b) *colloidal* dispersions
- (c) *coarse* dispersions

Molecular dispersions are homogeneous in character and form true solutions. Colloidal and coarse dispersions are examples of heterogeneous systems.



Dispersed Systems

Classification

Class	Particle size	Characteristic of system	Examples
Molecular dispersion	< 1 nm	Invisible in electron microscope Pass through semipermeable membrane Undergo rapid diffusion	Oxygen molecules and glucose
Colloidal dispersion	1–500 nm	Invisible by ordinary microscope Visible in electron microscope Pass through filter paper Do not pass semipermeable membrane Diffuse very slowly	Colloidal silver sols, natural and synthetic polymers
Coarse dispersion	> 500 nm	Visible under microscope Do not pass through normal filter paper Do not pass semipermeable membrane Do not diffuse	RBCs, most Pharmaceutical suspensions and emulsions



General Description of Solutions

Definition

Pharmaceutical **solutions** may be generally defined as liquid preparations that contain one or more chemical substances dissolved in a suitable solvent or mixture of mutually miscible solvents.



General Description of Solutions

Classification

Because of a particular pharmaceutical solution's use, it may be classified as **oral**, **otic**, **ophthalmic**, or **topical**.

Still other solutions, because of their composition may be classified as other dosage forms:

- Aqueous solutions containing a sugar are classified as **syrups** (even though some syrups may contain some alcohol),
- Sweetened hydroalcoholic (combinations of water and ethanol) solutions are termed **elixirs**.
- Solutions of aromatic materials in alcohol are termed **spirits**.
- Solutions of aromatic materials in water are termed **aromatic waters**



General Description of Solutions

Classification

- Solutions prepared by extracting active constituents from crude drugs are termed **tinctures** (Tinctures may also be solutions of chemical substances dissolved in alcohol or in a hydroalcoholic solvent)
- Certain solutions prepared to be sterile and pyrogen-free and intended for parenteral administration are classified as **injections**.



Advantages of Oral Solutions

1. Therapeutic agents can easily be administered orally to provide systemic effect to individuals who have difficulty in swallowing, e.g. elderly patients, infants.
2. The therapeutic agent is dissolved in the formulation and is therefore immediately available for absorption. The bioavailability of pharmaceutical solutions is greater than that of suspensions or oral solid-dosage forms.
3. Taste-masking of bitter therapeutic agents may be readily achieved.



Disadvantages of Oral Solutions

1. Pharmaceutical solutions for oral administration are unsuitable for therapeutic agents that are chemically unstable in the presence of water.
2. The poor solubility of certain therapeutic agents may prohibit their formulation as pharmaceutical solutions.
3. Pharmaceutical solutions are expensive to ship and are bulky for the patient to carry due to the associated mass of the product.



Drug Solubility

Solubility Definition

Solubility Classification

Factors Affecting Drug Solubility

Solubility Enhancement

Dissolution

Solubility Definition

The solubility of an agent in a particular solvent indicates the maximum concentration to which a solution may be prepared with that agent and that solvent.

The solubility of a substance in a given solvent may be determined by preparing a saturated solution of it at a specific temperature and by determining by chemical analysis the amount of chemical dissolved in a given weight of solution.

The solubility may be expressed as grams of solute dissolving in milliliters of solvent (e.g. 1 g of sodium chloride dissolves in 2.8 mL of water) or expressed as percentage % (w/v, v/v, or w/w).



Solubility Classification

The expression "part" describes the number of millilitres (mL) of solvent in which 1 gram (g) of solid is soluble.

Classification	Parts of solvent required for one part of solute (between 15° C and 25° C)
Very soluble	less than 1
Freely soluble	from 1 to 10
Soluble	more than 10 to 30
Sparingly soluble	more than 30 to 100
Slightly soluble	more than 100 to 1000
Very slightly soluble	more than 1000 to 10.000
Practically insoluble	more than 10.000



Solubility Classification

High Solubility

In pharmaceutical solutions both the therapeutic agent and the excipients are legally required to be present in solution over the shelf-life of the formulated product.

One of the major challenges in syrup formulation is the attainment of homogeneity, due primarily to the limited aqueous solubility of the therapeutic agent.

When the aqueous solubility of the therapeutic agent is high at the selected pH of the formulation, the therapeutic agent may be readily incorporated into the vehicle and formulated as an oral solution.



Solubility Classification

Moderate Solubility

If the aqueous solubility of the therapeutic agent is moderate at the selected pH of the formulation (the aqueous solubility is less than the requested concentration of therapeutic agent) then the solubility must be enhanced using co-solvents or surfactants or other related methods.



Solubility Classification

Low Solubility

If the aqueous solubility of the therapeutic agent is low at the selected pH of the formulation (The difference between the aqueous solubility and the required concentration is too great to be bridged by the use of co-solvents and related methods or the concentration of co-solvents or surfactants in the solubilised formulation may be toxic when administered orally), then the drug may be formulated as an alternative-dosage form, e.g. a suspension.



Factors Affecting Drug Solubility

The solubility properties of drug molecules in a particular solvent system are dependent on several physicochemical properties including molecular weight, size, density, number of rotatable bonds, hydrogen bond donors and hydrogen bond acceptors.

Furthermore, the properties of the solid state, e.g. crystal habit, crystalline/amorphous properties, will also affect the solubility of the therapeutic agent.



Factors Affecting Drug Solubility

Chemical Substituent

The solubility of a therapeutic agent is directly affected by both the type of chemical substituent groups and the substituent position.

The solubility of therapeutic agents containing hydrophilic groups (e.g. OH, COO, ammonium ion) will accordingly be greater than those containing lipophilic substituent groups, (e.g. methyl, ethyl, ethoxy or chlorine) groups.



Factors Affecting Drug Solubility

Chemical Substituent

Table 13.3 SOLUBILITIES OF SELECTED ORGANIC COMPOUNDS IN WATER AS A DEMONSTRATION OF CHEMICAL STRUCTURE-SOLUBILITY RELATIONSHIP

COMPOUND	FORMULA	MILLILITERS OF WATER REQUIRED TO DISSOLVE 1 G OF COMPOUND
Benzene	C_6H_6	1,430.0
Benzoic acid	C_6H_5COOH	275.0
Benzyl alcohol	$C_6H_5CH_2OH$	25.0
Phenol	C_6H_5OH	15.0
Pyrocatechol	$C_6H_4(OH)_2$	2.3
Pyrogallol	$C_6H_3(OH)_3$	1.7
Carbon tetrachloride	CCl_4	2,000.0
Chloroform	$CHCl_3$	200.0
Methylene chloride	CH_2Cl_2	50.0



Factors Affecting Drug Solubility

Chemical Substituent

Inorganic Molecules

Inorganic Molecules

1. If both the cation and anion of an ionic compound are monovalent, the solute–solute attractive forces are usually easily overcome, and, therefore, these compounds are generally water soluble (e.g., NaCl, LiBr, KI, NH_4NO_3 , and NaNO_2).
2. If only one of the two ions in an ionic compound is monovalent, the solute–solute interactions are also usually easily overcome and the compounds are water soluble (e.g., BaCl_2 , MgI_2 , Na_2SO_4 , and Na_3PO_4).



Factors Affecting Drug Solubility

Chemical Substituent

Inorganic Molecules

3. If both the cation and anion are multivalent, the solute–solute interaction may be too great to be overcome by the solute–solvent interaction, and the compound may have poor water solubility (e.g., CaSO_4 , BaSO_4 , and BiPO_4 ; exceptions: ZnSO_4 , FeSO_4).
4. Common salts of alkali metals (e.g., Na, K, Li, Cs, and Rb) are usually water soluble (exception: Li_2CO_3).
5. Ammonium and quaternary ammonium salts are water soluble.
6. Nitrates, nitrites, acetates, chlorates, and lactates are generally water soluble (exceptions: silver and mercurous acetate).



Factors Affecting Drug Solubility

Chemical Substituent

Inorganic Molecules

7. Sulfates, sulfites, and thiosulfates are generally water soluble (exceptions: calcium and barium salts).
8. Chlorides, bromides, and iodides are water soluble (exceptions: salts of silver and mercurous ions).
9. Hydroxides and oxides of compounds other than alkali metal cations and NH_4^+ ion are generally water insoluble.
10. Sulfides are water insoluble except for their alkali metal salts.
11. Phosphates, carbonates, silicates, borates, and hypochlorites are water insoluble except for their alkali metal salts and ammonium salts.



Factors Affecting Drug Solubility

Chemical Substituent

Organic Molecules

Organic Molecules

1. Molecules having one polar functional group are usually soluble to total chain lengths of five carbons.
2. Molecules having branched chains are more soluble than the corresponding straight-chain compound.
3. Water solubility decreases with an increase in molecular weight.
4. Increased structural similarity between solute and solvent is accompanied by increased solubility.



Factors Affecting Drug Solubility

Melting Point

The solubilities of a chemically related series of therapeutic agent are inversely related to their melting points. Therefore, as the melting point of the therapeutic agent is increased, the solubility would be expected to decrease.



Factors Affecting Drug Solubility

pH

The solubilities of therapeutic agents that are either acids or bases (representing the vast majority of drug substances) are pH-dependent.

The solubility of acids and bases increases as the degree of ionization increases and may be easily calculated using the following equation:

For a weak acid (**HA**):

$$pH = pKa + \log \frac{[A^-]}{[HA]}$$

For a weak Base (**B**):

$$pH = pKa + \log \frac{[B]}{[BH^+]}$$



Factors Affecting Drug Solubility

pH

These equations show the solubility of acidic compounds increases as the pH of the solution is increased (above the pK_a) and the solubility of basic compounds increases as the pH is lowered below the pK_a .

The solubility of zwitterionic (exhibit both acidic and basic properties) therapeutic agents is affected by pH.

At basic pH values the therapeutic agent behaves primarily as an acid whereas at low pH values the molecule behaves as a base.

The pH range at which the therapeutic agent exhibits minimal solubility lies between the pK_a values of the acidic and basic groups.



Solubility Enhancement

Appropriate Selection of Drug Salt

The majority of therapeutic agents are commercially available to the pharmaceutical scientist in a range of salt forms, each form exhibiting a different aqueous solubility.

The differences in solubility may be accredited, at least in part, to the crystal properties of the salt, which, in turn, affect the energy required to dissociate solute–solute bonds.



Solubility Enhancement

Optimisation of the pH of the Formulation

The solubility of an ionized therapeutic agent is a function of both the pK_a of the compound and the pH of the formulation.

Importantly, the acceptable pH range of solutions for oral administration is large, ranging from circa 5 to 8 pH units.

Therefore, a common formulation strategy involves the selection of a pH value for the formulation that optimizes the ionization and hence solubility of the therapeutic agent.

Control of the pH in the formulation is achieved using a buffer that does not adversely affect the solubility of the therapeutic agent.



Solubility Enhancement

Use of Co-solvents

In the formulation of pharmaceutical solutions for oral administration, aqueous solutions are preferred due to the lack of toxicity of water as the vehicle.

However, if the solubility of the therapeutic agent renders this approach inappropriate, the incorporation of co-solvents within the formulation offers a pharmaceutically acceptable approach.

Co-solvents are primarily liquid components that are incorporated into a formulation to enhance the solubility of poorly soluble drugs to the required level.

Commonly employed co-solvents include glycerol, propylene glycol, ethanol and poly(ethylene glycol), details of which are provided in subsequent sections.



Solubility Enhancement

Use of Co-solvents

The solubility of the chosen therapeutic agent in a series of mixed solvents is measured to determine the most suitable solvent system for the given purpose.

The final choice of the co-solvent system for a particular formulation involves consideration of the solubility of the therapeutic agent in the vehicle, the toxicity of the vehicle and the cost of the formulation.



Dissolution

The Process of Dissolution

When a solute dissolves, the substance's intermolecular forces of attraction must be overcome by forces of attraction between the solute and the solvent molecules.

This process involves the breakage of solute–solute and solvent solvent bonds (endothermic processes) and the formation of a bond between the solute and the solvent (exothermic process).

Dissolution occurs whenever the Gibb's free energy (**G**) of the process is negative and involves a balance between the enthalpy of dissolution (**H**) and the associated entropy (**S**) at the temperature of dissolution (**T**), as defined below:

$$\Delta G = \Delta H - T\Delta S$$



Dissolution

Factors Affecting Dissolution

The solubility of a pure chemical substance at a given temperature and pressure is constant; however, its rate of solution, that is, the speed at which it dissolves, depends on temperature, particle size of the substance and the extent of agitation.

Most chemical agents are more soluble at elevated temperatures than at room temperature because an endothermic reaction between the solute and the solvent uses the energy of the heat to enhance dissolution.

The finer the powder, the greater the surface area, which comes in contact with the solvent, and the more rapid the dissolving process.

Also, the greater the agitation, the more unsaturated solvent passes over the drug and the faster the formation of the solution.



References

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