Pharmaceutics II

صيدلانيات 2
الفصل الثاني
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Solutions

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Introduction

- A solution, is a homogeneous, molecular, mixture of two or more components.
- The simplest solution consists of two components, a solute dissolved in a solvent.
- The solute and the solvent could be in the solid, liquid or gaseous states of matter.
- Most commonly, pharmaceutical solutions are preparations in which the solid solutes, i.e. drug and excipients, are dissolved in a liquid solvent system.

Introduction

- **Water** is the most common solvent, although organic solvents are used in combination with water or on their own.
- All the components of a solution are dispersed as molecules or ions, and the solution is optically clear.

Solubility

- 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 entails breaking the solute–solute forces and the solvent–solvent forces to achieve the solute–solvent attraction.
- 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.
- When a solvent at a given temperature has dissolved all of the solute possible, it is said to be saturated.

Solubility

- Dipolar molecules tend to align themselves with other dipolar molecules so that the negative pole of one molecule points toward the positive pole of the other.
- Large groups of molecules may be associated through dipole–dipole or van der Waals forces.
- Other attractions also occur between polar and nonpolar molecules and ions. These include ion–dipole forces and hydrogen bonding.
- Hydrogen bonds also exist between some alcohol molecules, esters, carboxylic acids, aldehydes, and polypeptides.

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.

The solvent system

1. Aqueous solvents:

Water is the most commonly used solvent

due to its many advantages, such as its lack of toxicity and low cost.

Tap water???!!

Table 24.1 Different types of water, as defined by the *European Pharmacopoeia*

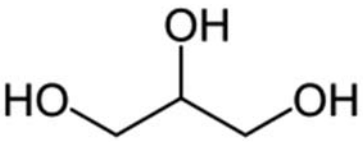
Type of water	Use
Purified Water	Used for the preparation of medicines that do not have to be sterile and apyrogenic.
Highly Purified Water	Used for the preparation of medicines where water of high biological quality is needed, except where Water for Injections is required.
Water for Injections	Used for medicines for parenteral administration. Must be pyrogen-free.
Sterilized Water for Injections	Used for medicines for parenteral administration. Water has been sterilized by heat and is suitably packaged.

- The main methods used in the preparation of purified water are:
- Distillation,
- Ion exchange,
- and reverse osmosis

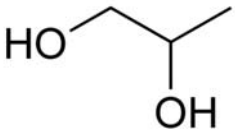
Cont.

- Water does not dissolve many drug compounds to a sufficient degree to enable the preparation of a pharmaceutical solution.
- **Co-solvents:** Other water-miscible liquids with greater drug solubility to enhance drug solubility (glycerol, propylene glycol, ethanol and poly(ethylene glycol).
- Their uses are limited primarily by their toxicity.

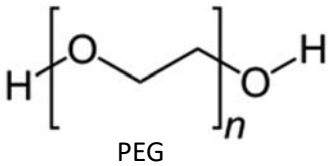
Co-solvents



Glycerol



propylene glycol



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The solvent system

2. Non aqueous solvents:

- Drug is insufficiently soluble or stable in aqueous systems,
- *For specific properties, such as sustained drug absorption*.
- Limited to certain delivery routes, such as intramuscular and topical, due to their unpalatability, toxicity, irritancy or immiscibility with physiological fluids.

Table 24.2 Examples of nonaqueous solvents used in pharmaceutical solutions

Solvent	Use
Alcohols, including polyhydric ones (i.e. those containing more than one hydroxyl group per molecule)	*Ethanol* is the most common organic solvent used in pharmaceutical solutions. It is often used as a cosolvent in oral, topical and parenteral solutions. *Propylene glycol* ($CH_3CH(OH)CH_2OH$) contains two hydroxyl groups per molecule. It is often used as a cosolvent in oral, topical, parenteral and otic solutions. *Glycerol* contains three hydroxyl groups per molecule. It is widely used as a solvent or cosolvent with water in oral and parenteral solutions. *Low molecular weight polyethylene glycols* with the general formula $HOCH_2(CH_2CH_2O)nCH_2OH$. These are used as solvents or cosolvents with water or ethanol. Used in parenteral solutions.
Fixed vegetable oils	Fixed oils are expressed from the seeds, fruit or pit/stone/kernel of various plants. They are nonvolatile oils and are mainly triglycerides of fatty acids. Examples include olive oil, corn oil, sesame oil, arachis oil, almond oil, poppy seed oil, soya oil, cottonseed oil and castor oil. Historically, they have been used for intramuscular administration. They are used to a lesser extent now because of their irritancy and the possibility of allergic reactions to certain oils. They are being replaced by synthetic alternatives such as ethyl oleate.
Esters, such as ethyl oleate, benzyl benzoate and ethyl ethanoate	These are used as a vehicle in certain intramuscular injections.
Dimethyl sulfoxide	Used as a carrier for idoxuridine for topical application to the skin.
Glycofurol	Used as a cosolvent in parenteral solutions for intramuscular or intravenous injections.
Ethyl ether	Used as a cosolvent with ethanol in collodions.

Table 24.3 Traditional terms for different pharmaceutical solutions

Traditional term	Description
Aromatic waters	Saturated aqueous solutions of volatile oils or other aromatic or volatile substances.
Elixirs	Many oral solutions that contain alcohol as a cosolvent have traditionally been designated as elixirs. However, many other oral solutions containing significant amounts of alcohol are not designated as elixirs.
Spirits	Alcoholic or hydroalcoholic solutions of volatile substances. Some spirits are used as flavouring agents, others are medicinal.
Syrups	Oral aqueous solutions containing high concentrations of sucrose or other sugars. 'Syrup BP' is a solution of sucrose (66.7%) in purified water; it promotes dental decay and is unsuitable for diabetic patients. 'Sugar-free' syrups are obtained by replacing sucrose with hydrogenated glucose, mannitol, sorbitol, xylitol, etc.
Tinctures	Alcoholic or hydroalcoholic solutions prepared from vegetable materials or chemical substances. Because of the variability in the vegetable materials, drug concentration can vary.

The drug

- The drug could be a small molecule like aspirin, or a large bio-therapeutic molecule, such as insulin or an antibody.
- The drug is present as molecules or ions throughout the solvent.
- The drug concentration in a pharmaceutical solution should be below its saturation solubility in order to avoid the possibility of drug precipitating out of the solvent.

The excipients

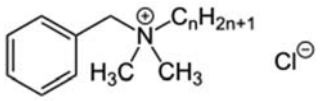
- Substances other than the drug or prodrug which are included in pharmaceutical solutions
- **Uses:**

1. To enhance product stability, bioavailability or
2. Patient acceptability
3. Aid product manufacture and/or identification.

The excipients

Requirements:

1. Non-toxic,
2. Non-sensitizing,
3. Non-irritating
4. Compatible with all the other components of the formulation.
5. Many excipients are acceptable by certain, but not all routes.



n = 8, 10, 12, 14, 16, 18
benzalkonium chloride

Ex. benzalkonium chloride is used in oral, but not nebulizer solutions, as it causes bronchoconstriction.

Table 24.5 Excipients used in pharmaceutical solutions

Excipients	Examples of excipients
Cosolvents	Ethanol, glycerol, propylene glycol. The concentration of ethanol should be limited as it exerts a pharmacological action following oral administration.
Flavouring agents	Used to mask the taste of drugs, many of which have a very unpleasant taste. Synthetic or naturally occurring flavourings such as vanilla, raspberry, orange oil, and lemon oil are used for oral solutions. Menthol is used in both oral and nasal solutions. Certain flavours appeal to certain patient populations and certain parts of the world; this must be borne in mind by the formulator. For example, fruit and bubble gum flavours are acceptable to children, whilst mint flavour is not.
Colouring agents	A colouring agent should correlate with the flavouring agent, e.g. green with mint flavour, red with cherry flavour. As for flavours, colour preference differs between cultures.
Sweeteners	Sucrose, sorbitol, mannitol, saccharin sodium, xylitol and high-fructose corn syrup are used to improve the palatability of oral solutions. Sweetened, but sugar-free, preparations containing aspartame are suitable for diabetic patients and are not cariogenic.
Antimicrobial preservatives	Used to preserve multidose preparations. Examples include benzalkonium chloride, benzyl alcohol, chlorobutanol, thimerosal and combinations of parabens (methyl, propyl, butyl).
Antioxidants	Sodium metabisulfite, sodium sulfite, sodium bisulfate, ascorbic acid, used to stabilize solutions.
Chelating agents	Disodium edetate, used to increase solution stability.
pH adjusters	Acids, e.g. citric acid, buffers. Alkalis, e.g. sodium hydroxide, buffers.
Isotonicity adjusters	Sodium chloride, potassium chloride, mannitol, dextrose, glycerol.
Viscosity enhancers	Hypromellose, hydroxyethylcellulose, poly(vinyl alcohol), povidone, dextran, carbomer 940.

Table 24.4 Requirements of pharmaceutical solutions with respect to their route of administration

Route of administration	Requirements of the solution
Oral	
Oral solutions are swallowed, in which case the drug may exert a local effect on the gastrointestinal tract or be absorbed into the blood and exert a systemic action.	Liquid oral solutions are aqueous formulations. To be acceptable to patients, these must be palatable. Flavouring, colouring and sweetening agents are therefore added to enhance their appearance and taste. Solution pH is usually 7.0, although a pH range of 2–9 can be tolerated. For convenience, the dose is usually in multiples of 5 mL, and the patient is given a 5 mL spoon with the solution. When smaller volumes are required, oral syringes are used. Viscosity should be appropriate for palatability and pourability. Solutions have a higher viscosity than water.
Oral cavity	
Mouthwashes and gargles are used to treat local infection and inflammation in the oral cavity. Gingival solutions are applied to the gingivae. These are not intended to be swallowed and the drug exerts a local effect in the mouth.	Solutions are aqueous formulations. They must be palatable and acceptable to patients. Flavouring, colouring and sweetening agents are often added. As far as possible, the pH should be around neutral.
Topical skin/nail/hair	
Solutions are applied to the skin for local and/or systemic effect. Solutions are also applied to the nails or hair for local effect.	The vehicle may be aqueous or nonaqueous, and different types of formulations are available. An *application* frequently contains parasiticides. A *lotion* is aqueous-based, and is intended for application without friction. A *liniment* is an alcoholic or oily solution (or emulsion) designed to be rubbed into the skin. *Paints* and *tinctures* are concentrated aqueous or alcoholic antimicrobial solutions. A *collodion* is a solution of a polymer, usually pyroxylin, in a volatile organic solvent system (a mixture of ethanol and ether). Following application to the skin, the solvents evaporate, leaving a polymeric film on the skin. *Nail solutions* are applied to the nail to treat nail diseases. All preparations must be acceptable to the patient. Formulations which are easy to transfer from the container and will spread easily and smoothly are preferred. The formulation must adhere to site of application, without being tacky or difficult to remove.

Table 24.4 Requirements of pharmaceutical solutions with respect to their route of administration—con'd

Route of administration	Requirements of the solution
Otic (ear, aural)	
Solutions are instilled in the outer ear to exert a local effect. They are used to remove ear wax or to deliver anti-infective, anti-inflammatory and analgesic drugs.	May be aqueous or nonaqueous solutions. Water, glycerol, propylene glycol and oils may be used as solvents. Nonaqueous vehicles are predominantly used when ear wax removal is desired as ear wax can dissolve in them. As the residence time in the ear is longer for viscous solutions, the viscosity of aqueous solutions is increased by the use of polymers. Propylene glycol and glycerol solutions are naturally viscous and these increase the residence time. Solutions do not need to be isotonic as they are external preparations.
Ocular	
Eye drops are used to treat local disorders of the eye, e.g. infection. Ocular solutions may also be used to treat intraocular disorders, such as glaucoma. *Eye lotions* are solutions for rinsing or bathing the eye, or for impregnating eye dressings.	Most ocular solutions are aqueous. They must be manufactured sterile as the product is to come in contact with tissues that are very sensitive to contamination. Once opened, a multidose ocular product should remain free from viable microorganisms during its period of use and must contain antimicrobial preservatives. Ideally the solution pH should be close to the physiological pH of tears (pH 7.4) or slightly more alkaline to reduce pH-induced lacrimation, irritation and discomfort. Physiological pH may not, however, be the optimum pH for drug solubility, absorption and stability, or for the function of other components of the solution; thus ocular solutions do not always have a pH of approximately 7.4. Fortunately, the eye can tolerate solutions with pH as low as 3.5 and as high as 9. Ideally, ocular solutions must be isotonic with the tears to minimize irritation and discomfort. Some deviation from isotonicity can be tolerated without marked discomfort when small volumes of solutions are administered, as the latter are rapidly diluted with tears. When large volumes are used (e.g. to wash the eyes), the solution must be approximately isotonic. Most products have a viscosity of 15 mPa s to 25 mPa s (for comparison, the viscosity of water is 1 mPa s). An increase in viscosity prolongs the solution's residence in the eye.

Nasal	
Nose drops and nasal sprays, used for local, e.g. decongestant, effect, or for systemic drug delivery.	*Nasal solutions* are aqueous formulations. Solution pH is in the normal pH range of nasal fluids (pH 5.5–6.5). Solutions are usually isotonic to nasal fluids. Solution viscosity is similar to that of nasal mucus (which is higher than that of water). Flavouring or sweetening agents are sometimes used to mask taste, as a small proportion of nasal solution may be swallowed following nasal administration. Multidose solutions require preservatives.
Pulmonary	
Inhaled solutions are administered by pressurized metered-dose inhalers or by nebulizers for local or systemic effect.	Solutions of drug and excipients dissolved in liquefied propellants, such as trifluoromonofluoroethane, are used in pressurized metered-dose inhalers. Solutions used in nebulizers are aqueous formulations. As relatively large volumes may be administered by nebulizers, the solutions must be isotonic and have a pH not lower than 3 and not higher than 10. Multidose preparations containing preservatives are available, although generally, sterile, single-unit doses without a preservative are used.
Rectal	
Solution enemas are usually administered for local or systemic drug action.	*Enemas* can be aqueous or oily solutions. *Micro enemas* have a volume of 1 mL to 20 mL, whereas macro enemas have volumes of 50 mL or more. *Macro enemas* should be warmed to body temperature before administration.

Table 24.4 Requirements of pharmaceutical solutions with respect to their route of administration—con'd

Route of administration	Requirements of the solution
Vaginal	
Vaginal solutions are administered for local effect, for irrigation or for diagnostic purposes.	*Vaginal solutions* are aqueous. Excipients to adjust the pH may be included.
Parenteral	
'Parenteral' refers to the injectable routes of administration. Drugs are most commonly injected into the veins (intravenous), into the muscles (intramuscular) and into (intradermal) and under (subcutaneous) the skin, although they can also be injected into arteries, joints, joint fluid areas, the spinal column, spinal fluid and the heart.	*Parenteral solutions* must be sterile and pyrogen-free. Preservatives, such as benzyl alcohol, are included under certain conditions such as in multidose products. Intravenous – the solution must be aqueous, as oil droplets can occlude the pulmonary microcirculation. Intramuscular and subcutaneous – the solution can be aqueous or nonaqueous. Ideally, a parenteral aqueous solution should have a pH close to physiological pH (which is 7.4) to avoid pain, phlebitis and tissue necrosis. A pH of 7.4 may not, however, be the optimum pH for drug solubility and product stability, and as a reasonably wide pH range can be tolerated, the pH of most licensed parenteral solutions is between 3 and 9. A wide pH range is tolerated as the administered solution is diluted on administration, most notably with the intravenous route. Parenteral solutions must be isotonic when large volumes are administered by intravenous infusion. When smaller volumes are used, a wider range of tonicity can be tolerated as dilution with body fluids occurs.

Preparation of solutions

- Most solutions are prepared by simple mixing of the solutes with the solvent.
- The amounts of solute to be dissolved are usually well below the capacity of the volume of solvent employed.
- The strengths of pharmaceutical preparations are usually expressed in terms of percent strength

Preparation of solutions

- Some chemical agents in a given solvent require an extended time to dissolve. To hasten dissolution, a pharmacist may employ one of several techniques, such as applying heat, reducing the particle size of the solute, using a solubilizing agent, and/or subjecting the ingredients to vigorous agitation.

Advantages of pharmaceutical solutions

1. The drug is already dissolved in the solvent system, hence drug action can be rapid, allowing their use in emergencies, e.g. adrenaline solution, as an injection
2. The drug in a solution is already in a molecular form and available for absorption
3. Solutions provide dose uniformity, and specific volumes that can be measured accurately
4. Oral solutions are easily swallowed and are beneficial for patients or whom swallowing may be difficult, e.g. children and older people
5. Solutions are easier to manufacture compared to other dosage forms.

Disadvantages of solutions

1. Stability
2. Solubility
3. Liquids are bulky and less easy for the patient to carry,
4. Liquids are also more expensive to transport, which increases the medicine's cost.
5. The packaging of pharmaceutical solutions requires materials of higher quality

Solution stability

- A pharmaceutical solution must be stable for the duration of its shelf -life (period of storage and use).
- It must retain the same physical, chemical, microbiological, therapeutic and toxicological properties
- Many drug molecules undergo chemical reactions, such as, hydrolysis, oxidation, decarboxylation, epimerization, dehydration, with hydrolysis, oxidation and reduction
- Chemical reactions occur more readily at high temperature, at certain pHs, in the presence of UV light and of substances which can act as a catalyst, and in solutions.

Solution stability

- Pharmaceutical solutions are formulated at the pH favoring drug stability, and include excipients to enhance product stability.
- To reduce photo-oxidation, solutions are packaged in containers that do not allow light transmission.
- To reduce oxidation, antioxidants and/ or metal chelators (as heavy metal ions catalyse oxidation) are used.
- To inhibit microbial growth during use, preservatives are used in multidose products.
- All the excipients used within a solution must be of suitable quality, non-toxic, compatible with the drug and with one another, and active at the solution pH.

Enhancement of drug solubility

1. pH adjustment:

Most drugs are either weak acids or weak bases.

In solution, an equilibrium exists between the undissociated drug molecules and their ions. The equilibrium may be represented as:

Weak acid: $HA \leftrightarrow H^+ + A^-$

Weak base: $B + H^+ \leftrightarrow BH^+$

Cont.

- Weakly acidic drugs are ionized when the pH of the solvent is increased. Conversely, lowering pH favors ionization of weakly basic drugs.
- The pH can be adjusted using acids or alkali, or using buffers such as citrate, acetate, phosphate and carbonate buffers.
- Extremes of pH should be avoided however, so that the solution is physiologically acceptable;
- In addition, the chosen pH should not adversely affect the stability of the drug and excipients.
- Bioavailability of the drug should also not be compromised by a change in pH, unionized drug molecules being absorbed to a greater extent through biological membranes than their ionized counterparts.

Enhancement of drug solubility

2. Co-solvents:

- Co-solvents are used to increase the water solubility of drugs which do not contain ionizable group(s) and whose solubility can thus not be increased by pH adjustment.
- Non-polar drugs are poorly soluble in water – a polar solvent. To increase the solubility of such drugs in water, a third component such as a water-miscible organic liquid with a low polarity should be added.
- Only a few are used as co-solvents in pharmaceutical solutions.
- Examples include glycerol, propylene glycol, ethanol and the low molecular weight poly(ethylene glycol).
- The concentration of the co-solvent is however limited by its physiological acceptability.

Enhancement of drug solubility

3. Complexation with cyclodextrins:

- Cyclodextrins (CDs) are non-reducing cyclic glucose based oligosaccharides.
- The three most important CDs are alpha, beta and gamma cyclodextrins.
- The interior cavity of cyclodextrins is apolar, while their exterior is hydrophilic.

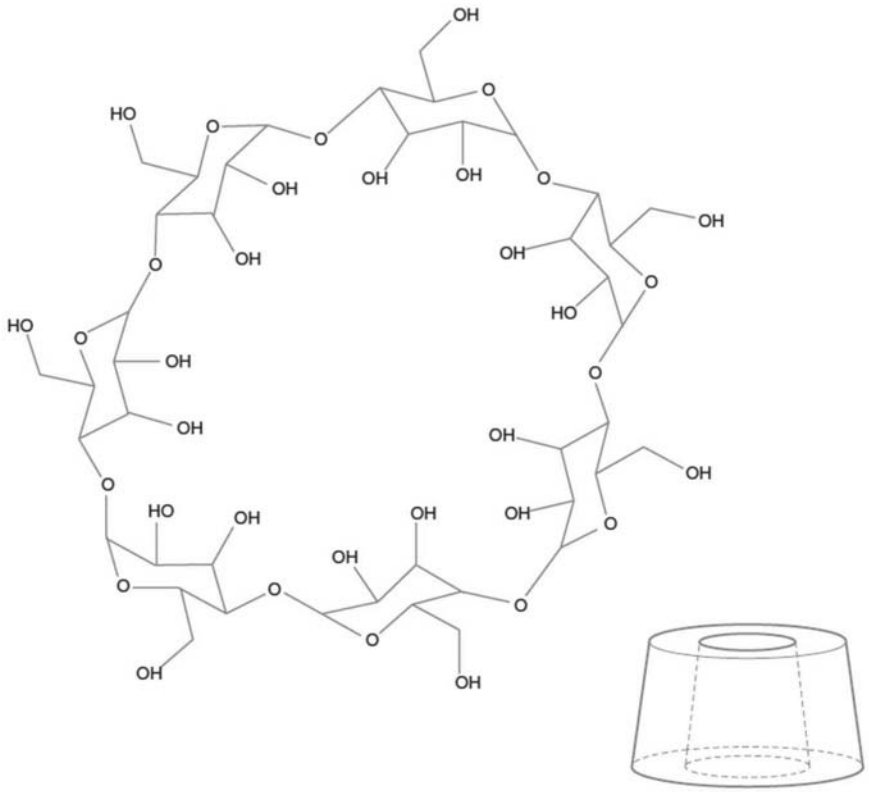


Figure 24.1 • The structure of a cyclodextrin molecule. The sketch shows both the chemical structure and the three-dimensional physical structure. The inside surface of the structure is hydrophobic and the exterior is hydrophilic.

Cont.

- The hydrophilic exterior results in CDs being soluble in water.
- the less polar interior can accommodate non-polar drug molecules via non-covalent interactions, thereby allowing the nonpolar drug to be ‘hidden’, enabling it to be molecularly dispersed in water. Thus, drug inclusion within CDs effectively increases their aqueous solubility.

Enhancement of drug solubility

4. Surfactants and micelles

- surfactants (surface active agents) and amphiphiles which have two distinct regions in their chemical structure: hydrophilic and the other hydrophobic.
- such molecules tend to accumulate at the boundary between two phases, such as water-air or water-oil interfaces.
- They reduce the surface tension of liquids, and self assemble to form micelles once the critical micellar concentration (CMC) is reached.

Cont.

- Poorly water-soluble drugs can be solubilized in micelles to enhance their aqueous solubility.
- The location of the solubilisate (the drug which is solubilized within the micelles) depends on its nature: non-polar solubilisates being located within the micelles' hydrophobic interior cores,
- Solubilisates containing polar groups are oriented with the polar group at the micellar surface, while slightly polar solubilisate partition between the micelle surface and the core.

Cont.

- The aqueous solubility of a wide range of drugs has been increased by surfactants, especially for oral and parenteral administrations.
- For example, solubilization of steroids with polysorbates has allowed their formulation in aqueous ophthalmic preparations, while solubilization of the water-insoluble vitamins A, D, E and K has enabled the preparation of aqueous injections.
- The surfactant chosen for a particular drug must solubilize the drug and be compatible with it, and all the other components of the solution.