Solutions

What is the Solution?

- Solutions are **homogeneous mixtures** of two or more components.
- They contain **one or more solutes** dissolved in **one or more solvents**, usually solids dissolved in liquids.
- The solvent is often aqueous but can be oily, alcoholic or some other solvent.
- There are many types of pharmaceutical solutions.
- Solutions may be used as **oral dosage forms, mouthwashes, gargles, nasal drops and ear drops and externally as lotions, liniments, paints**, etc.
- Solutions may also be used in **injections and ophthalmic preparations**.

Solutions for oral dosage

- Oral solutions are usually formulated so that the patient receives the usual dose of the medication in a conveniently administered volume, **5 mL or a multiple** thereof, given to the patient using a 5 mL medicine spoon.
- Advantages of solutions for oral use over a solid dosage form are that

1. liquids are much easier to swallow than tablets or capsules and the medicament is readily absorbed from the gastrointestinal tract.
2. Ease of taking is especially useful for children, elderly patients or those with chronic conditions such as Parkinson's disease, who may have difficulty swallowing a solid oral dosage form.

Solutions for oral dosage

- An advantage of solutions over suspensions is that

1. the medicament is **dispersed homogeneously** throughout the preparation, **without the need to shake the bottle**.
2. This makes the preparation easier for the patient to use and should ensure consistent dosage.

Solutions for oral dosage

- Disadvantages of solutions are that they are

1. **bulky**, not convenient to carry around
2. **less microbiologically and chemically stable** than their solid counterparts.
3. Oral solutions may have an **unpleasant taste**.
4. **The accuracy of oral dosage** is dependent on the patient measuring the dose carefully.

The different forms of oral solutions

- **Syrups**, which are aqueous solutions that contain sugar. An example is Epilim® syrup (sodium valproate).
- **Elixirs**, which are clear, **flavoured liquids** containing a high proportion of sucrose or a suitable polyhydric alcohol and sometimes ethanol. Examples are phenobarbital elixir and chloral elixir.
- **Linctuses**, which are viscous liquids used in the treatment of **cough**. They usually contain a high proportion of sucrose, other sugars or a suitable polyhydric alcohol or alcohols. Examples are Simple Linctus BP and diamorphine linctus

The different forms of oral solutions

- **Mixtures** is a term often used to describe pharmaceutical oral solutions and suspensions. Examples are chloral hydrate mixture and ammonium and ipecacuanha mixture BP.
- **Oral drops** are oral solutions or suspensions which are administered in small volumes, using a suitable measuring device. A proprietary example is Abidec® vitamin drops.

Solutions for other pharmaceutical uses
1.Mouthwashes and gargles

- Gargles are used to relieve or treat **sore throats** and mouthwashes are used on the **mucous membranes of the oral cavity** to refresh and mechanically clean the mouth.
- Both are concentrated solutions, although gargles tend to contain higher concentrations of active ingredients than mouthwashes.
- Both are usually diluted with warm water before use.
- They may contain antiseptics, analgesics or weak astringents.
- The liquid is usually not intended for swallowing.
- Examples are Phenol Gargle BP and Compound Sodium Chloride Mouthwash BP, chlorhexidine (Corsodyl®) mouthwash and povidone-iodine (Betadine®) mouthwash.

Nasal solutions

- Most nasal preparations are solutions, administered as nose **drops** or **sprays**.
- They are usually formulated to be **isotonic to nasal secretions** (equivalent to 0.9% normal saline) and **buffered** to the normal pH range of nasal fluids (pH5.5–6.5) to prevent damage to ciliary transport in the nose.
- The most frequent use of nose drops is as a **decongestant** for the common cold or to administer **local steroids** for the treatment of allergic rhinitis.
- Examples are normal saline nose drops and ephedrine nose drops,

Nasal solutions

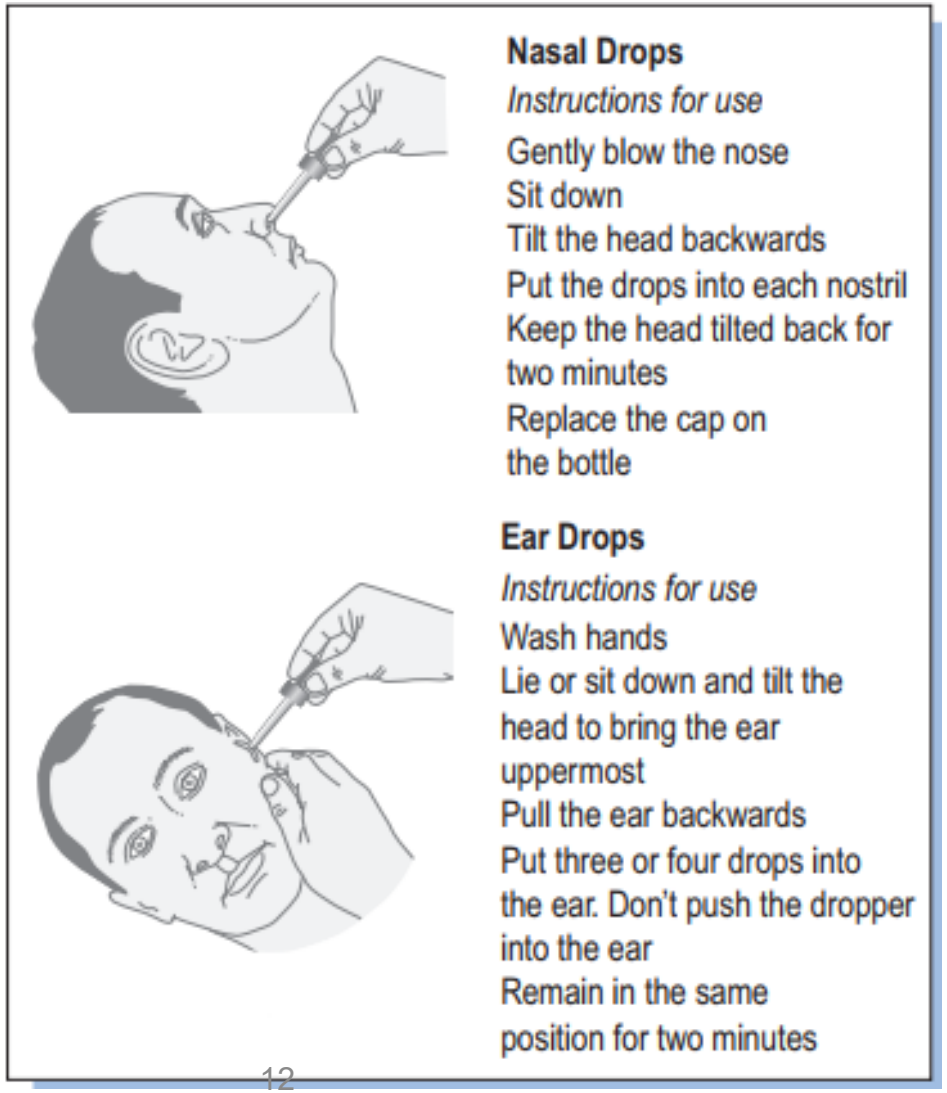
- Overuse of topical decongestants can lead to oedema of the nasal mucosa and they should only be used for short periods of time (about 4 days) to avoid rebound congestion, called rhinitis medicamentosa.
- The nasal route may also be useful for new biologically active peptides and polypeptides.
- The nasal mucosa rapidly absorbs applied medicaments to give a systemic effect. There are some products utilizing nasal delivery currently available on the market, e.g. desmopressin (e.g.Desmospray®, DDAVP®), used in the treatment of pituitary diabetes insipidus.
- Accurate dosage is achieved using **metered spray devices**.

Ear drops

- Ear drops are solutions of one or more active ingredient which exert a **local effect** in the ear, e.g. by **softening earwax** or **treating infection or inflammation.**
- They may also be referred to as otic or aural preparations.
- Propylene glycol, oils, glycerol (to increase viscosity) and water may be used as vehicles.
- Examples are aluminium acetate ear drops, almond oil ear drops and Sodium Bicarbonate Ear Drops BP.

Containers for nasal and aural preparations

- Manufactured nasal solutions may be packed in **flexible plastic bottles** which deliver a fine spray to the nose when squeezed, or in **a plain glass bottle** with a **pump spray or dropper**.
- Manufactured ear drops are usually packed in **small glass or plastic containers with a dropper**.
- Patients should be advised not to share nasal sprays or nose and ear drops in order to minimize contamination and infection.



Enemas

- Enemas are **oily or aqueous** solutions that are administered rectally.
- They are usually anti-inflammatory, purgative, sedative or given to allow X-ray examination of the lower bowel.
- Examples are arachis oil enema and magnesium sulphate enema.
- Retention enemas are administered to give either a local action of the drug, e.g. prednisolone, or for systemic absorption, e.g. diazepam.
- They are used after defecation.
- The patient lies on one side during administration and remains there for 30 min to allow distribution of the medicament.

Enemas

- Microenemas are single-dose, small-volume solutions. Examples are solutions of sodium phosphate, sodium citrate or docusate sodium.
- They are packaged in plastic containers with a nozzle for insertion into the rectum.
- Large-volume (0.5–1 L) enemas should be warmed to body temperature before administration.
- Patients should be advised on how to use the enema if they are self-administering and the time that the product will take to work.
- The label ‘For rectal use only’ should be used.

Expression of concentration

- Strengths of pharmaceutical solutions can be expressed in a number of ways.
- The two most commonly used are in terms of

I. amount of drug contained in 5 mL of vehicle or

II. percentage strength.

Formulation of solutions

- Solutions comprise the **medicinal agent** in a solvent as well as any **additional agents**.
- Additional agents: **colour, flavour, sweetness or stability** to the formulation.
- Most solutions are now manufactured on a large scale although it may be occasionally required to make up a solution extemporaneously.
- When compounding a solution, **information on solubility and stability** of each of the solutes must be taken into account.
- **Chemical and physical interactions** that may take place between constituents must also be taken into account, as these will affect the preparation's stability or potency.

Solubility

- The **saturation** solubility of a chemical in a solvent is the **maximum concentration of a solution**, which may be prepared at a **given temperature.**
- For convenience, this is usually simply called solubility.
- Solubilities for medicinal agents in a given solvent are given in the British Pharmacopoeia (BP) and other reference sources.
- Solubilities are usually stated as the number of parts of solvent (**by volume**) that will dissolve one part (**by weight or volume**) of the substance.
- Most solutions for pharmaceutical use are not saturated with solute.

Solubility

- Potassium chloride is soluble in 2.8–3 parts of water.
- This means that 1 g of potassium chloride will dissolve in 2.8–3 mL of water at a temperature of 20°C (taken as normal room temperature).
- Diazepam is described as being **‘very slightly soluble’** in water (which means 1 in 1000 to 1 in 10 000), ‘**soluble**’ in alcohol (which means 1 in 10 to 1 in 30) and ‘**freely soluble**’ in chloroform (which means 1 in 1 to 1 in 10).
- This means that 1 g of diazepam will dissolve in between 10 and 30 mL of alcohol, but would need 1000–10 000 mL of water to dissolve, at a temperature of 20°C.

Vehicles

- In pharmacy, the **medium which contains the ingredients of a medicine** is called the vehicle.
- In solutions, this is the **solvent**.
- The choice of a vehicle depends on the **intended use** of the preparation and on the **nature** and **physicochemical properties** of the active ingredients.

Water as a vehicle

- Water is the vehicle used for most pharmaceutical preparations.

1. widely available,
2. relatively inexpensive,
3. palatable
4. non-toxic for oral use
5. non-irritant for external use.
6. good solvent for many ionizable drugs.

- Different types of water are available

Potable water

- Potable water is **drinking water**, drawn freshly from a mains supply.
- It should be **palatable** and **safe** for drinking.
- Its chemical composition may include **mineral impurities**, which could react with drugs, e.g. the presence of calcium carbonate in hard water

Purified water

- Purified water is prepared from suitable **potable water by distillation**, by treatment with **ion exchange materials** or by any other suitable treatment method such as **reverse osmosis**.
- Distilled water is purified water that has been prepared by distillation

Water for preparations

- Water for preparations is potable or **freshly boiled and cooled** purified water, which can be used in **oral or external preparations** which are not intended to be sterile.
- The boiling removes dissolved oxygen and carbon dioxide from solution in the water.
- Any stored water, for example drawn from a local storage tank, should not be used because of the risk of contamination with microorganisms

Water for injections

- Water for injections is **pyrogen-free distilled water**, **sterilized** immediately after collection and used for **parenteral products.**

Aromatic waters

- Aromatic waters are near-saturated **aqueous solutions of volatile oils** or other aromatic or volatile substances, and are often used as a vehicle in oral solutions.
- Some have a mild carminative action, e.g. dill.
- Aromatic waters are usually prepared from a concentrated ethanolic solution, in a dilution of 1 part of concentrated water with 39 parts of water.
- **Chloroform water** is used as an antimicrobial preservative and also adds sweetness to preparations

Other vehicles used in pharmaceutical solutions

- **Syrup BP** is a solution of 66.7% sucrose in water. It will promote dental decay and is unsuitable for diabetic patients.
- **Hydrogenated glucose syrup**, mannitol, sorbitol, xylitol, etc. can replace the sucrose to give ‘sugar-free’ solvents
- **Alcohol (ethyl alcohol, ethanol).** This is rarely used for internal preparations but is a useful solvent for external preparations
- **Glycerol (glycerin)** may be used alone as a vehicle in some external preparations. It is viscous and miscible both with water and alcohol. It may be added as a stabilizer and sweetener in internal preparations. In concentrations above 20% v/v, it acts as a preservative

Other vehicles used in pharmaceutical solutions

- **Propylene glycol** is a less viscous liquid and a better solvent than glycerol
- **Oils**. Bland oils such as fractionated coconut oil and arachis oil may be used for fat-soluble compounds, e.g. Calciferol Oral Solution BP. Care is required when using nut oils due to hypersensitivity reactions
- **Acetone** is used as a co-solvent in external preparations
- **Solvent ether** can be used as a co-solvent in external preparations for preoperative skin preparation. The extreme volatility of ether and risk of fire and explosion limit its usefulness.

Factors affecting solubility

1. Compounds that are predominantly non-polar tend to be more soluble in non-polar solvents, such as chloroform or a vegetable oil. **Polar compounds tend to be more soluble in polar solvents**, such as water and ethanol.
2. The **pH** will also affect solubility, as many drugs are weak acids or bases. The ionized form of a compound will be the most water soluble, therefore a weakly basic drug will be most soluble in an aqueous solution that is acidic. Acid or alkali may therefore be added to manipulate solubility.
3. Most compounds are more soluble at **higher temperatures**.
4. **Particle size reduction** will increase the rate of solution.

Increasing the solution of compounds with low solubility

Co-solvency

- The addition of co-solvents, such as ethanol, glycerol, propylene glycol or sorbitol, can increase the solubility of weak electrolytes and non-polar molecules in water.

Solubilization

- Surfactants may be used as solubilizing agents. Above the critical micelle concentration (CMC), they form micelles which are used to help dissolve poorly soluble compounds.
- The dissolved compound may be in the centre of the micelle, adsorbed onto the micelle surface, or sit at some intermediate point, depending on the polarity of the compound. Examples of surfactants used in oral solutions are polysorbates, while soaps are used to solubilize phenolic disinfectants for external use.

Preservation of solutions

- Most water-containing pharmaceutical solutions will support microbial growth unless this is prevented.
- Contamination may come from raw materials.
- Preservatives may be added to the formulation to reduce or prevent microbial growth.
- **Chloroform** is the most widely used in oral extemporaneous preparations, although there are disadvantages to its use, including its high volatility and reported carcinogenicity in animals. Use in the UK is limited to a chloroform content of **0.5%** (w/w or w/v). For oral solutions, chloroform at a strength of 0.25% v/v will usually be incorporated as Chloroform Water BP.

Preservation of solutions

- **Benzoic acid** at a strength of **0.1% w/v** is also suitable for oral administration, as are **ethanol, sorbic acid, the hydroxybenzoate esters and syrup.** Some of the alternative preservatives have pH-dependent activity.
- **Syrups** can be preserved by the maintenance of a high concentration of sucrose as part of the formulation. Concentrations of sucrose greater than **65% w/w** will usually protect an oral liquid from growth of most microorganisms by its osmotic effects.
- Preservatives used in external solutions include **chlorocresol** (0.1% w/v), **chlorbutanol** (0.5% w/v) and the **parahydroxybenzoates** (parabens).

Additional ingredients

- Solutions that are intended for oral use may contain excipients such as **flavouring, sweetening and, sometimes, colouring agents**.
- These are added to improve the **palatability and appearance** of a solution for the patient.
- Stabilizing and viscosity enhancing agents may also be used.

Flavouring agents

- Flavours added to solutions can make a medicine more acceptable to take, especially if the drug has an unpleasant taste.
- Selection of flavours is a complex process in the pharmaceutical industry. **Flavours should be chosen to mask particular taste types**, e.g. a fruit flavour helps to disguise an acid taste.
- The **age of the patient** should be taken into account when selecting a flavour, as children will tend to enjoy fruit or sweet flavours.
- Some flavours are associated with particular uses, e.g. peppermint is associated with antacid preparations.
- The flavour and colour should also complement each other.

Sweetening agents

- Many oral solutions are sweetened with **sugars (**glucose and sucrose).
- **Sucrose** enhances the viscosity of liquids and also gives a pleasant texture in the mouth. Prolonged use of liquid medicines containing sugar will lead to an increased incidence of dental caries, particularly in children.
- Oral solutions without sugar as a sweetening agent use **sorbitol, mannitol, xylitol, saccharin and aspartame** as alternatives.
- Oral liquid preparations that do not contain fructose, glucose or sucrose are labelled '**sugar free**' in the British National Formulary (BNF).

Colouring agents

- Colouring agents are added to pharmaceutical preparations to enhance the **appearance** of a preparation or to increase the **acceptability** of a preparation to the patient.
- Colours are often matched to the flavour of a preparation, e.g. a yellow colour for a banana-flavoured preparation.
- Colour is also useful to give a consistent appearance where there is natural variation between batches.
- Colours can give distinctive appearances to some medicines.

Colouring agents

- Colouring agents should be **non-toxic** and **free of any therapeutic activity** themselves.
- Natural colourants are most likely to meet this criterion and include materials derived from plants and animals, e.g. **carotenoids, chlorophylls, saffron, red beetroot extract, caramel and cochineal**. The disadvantage of Natural colourants is that batches may vary in quality.
- Synthetic organic dyes such as the **azo compounds** are alternatives for colouring pharmaceutical solutions as they give a wide range of bright, stable colours.

Colouring agents

- Colours appear in pharmaceutical formulae **less often now**, especially in children's medicines.
- Coloured dyes in medicines can **lead to confusion** when diagnosing diseases, e.g. a red dye appearing in vomit could be wrongly assumed to be blood.
- In the European Union, colours are selected from a list permitted for medicinal products, with designated 'E' numbers between 100 and 180.

Stabilizers

- **Antioxidants** may be used where ingredients are liable to degradation by oxidation, e.g. in oils.
- Those which are added to oral preparations include **ascorbic acid, citric acid, sodium metabisulphite and sodium sulphite**.
- These are odourless, tasteless and non-toxic.

Viscosity-enhancing agents

- **Syrups** may be added to increase the viscosity of an oral liquid.
- They also improve palatability and ease pourability.

Oral syringes

- Oral syringe should be supplied with the dispensed oral liquid.
- The standard 5 mL or 10 mL capacity oral syringe is marked in 0.2 mL divisions to measure fractional doses.
- An adapter fits into the neck of all common sizes of the medicine bottle.
- Instructions should be supplied with the oral syringe: ‘Shake the bottle and then remove the lid and insert the adapter firmly into the top of the bottle.

Oral syringes

- Push the tip of the oral syringe into the hole in the adapter and turn the bottle upside down. Pull the syringe plunger to draw liquid to the appropriate volume.
- Turn the bottle right way up and carefully remove the syringe, holding the barrel.
- Gently put the tip into the child's mouth to be inside the cheek.
- Slowly and gently push the plunger in and allow the child to swallow the medicine before removing the syringe.

Oral syringes

- Do not squirt the liquid or direct it towards the throat. After completing the process, remove the adapter and replace the cap on the bottle.
- The adapter and syringe should be rinsed and left to dry’.
- Patient information leaflets are available to accompany the oral syringe.

Diluents

- If a prescriber insists that a manufactured solution is diluted, then a **suitable diluent must be selected**.
- An indication of the expiry date for the diluted preparation is also given in references.
- The dilution should be **freshly prepared**.
- A **short shelf-life** for a diluted solution may require patients to return to the pharmacy to collect the balance of their medication.

Examples

- Traditionally used as an **expectorant cough preparation**.
- Ammonium bicarbonate, ipecacuanha and camphor water are mild expectorants.
- Anise water acts as a mild expectorant and a flavouring agent. Liquid liquorice extract is used as a mild expectorant, flavouring and sweetening agent.
- Chloroform water acts as a sweetener and a preservative.
- Ammonium bicarbonate is soluble 1 in 5 of water, so will dissolve to give a solution.

Example 33.3

Prepare 100 mL of Ammonium and Ipecacuanha Mixture BP.

	Master formula	For 100 mL
Ammonium bicarbonate	200 mg	2 g
Liquorice liquid extract	0.5 mL	5 mL
Ipecacuanha tincture	0.3 mL	3 mL
Concentrated camphor water	0.1 mL	1 mL
Concentrated anise water	0.05 mL	0.5 mL
Double strength chloroform water	5 mL	50 mL
Water	to 10 mL	to 100 mL

Examples

- Traditionally used as a cough suppressant.
- Oxymel is a solution of acetic acid, water and purified honey, used as a demulcent and sweetening agent in linctuses.
- Glycerol is also a demulcent and sweetener.
- Compound tartrazine solution is a colouring agent and syrup is a demulcent vehicle.
- Diamorphine is soluble 1 in 1.6 of water and 1 in 12 of alcohol.

Example 33.4

Prepare 200 mL of Diamorphine linctus.

	Master formula	For 200 mL
Diamorphine hydrochloride	3 mg	120 mg
Oxymel	1.25 mL	50 mL
Glycerol	1.25 mL	50 mL
Compound tartrazine solution	0.06 mL	2.4 mL
Syrup	to 5 mL	to 200 mL

Examples

- Traditionally used for short-term use in insomnia.
- Chloral hydrate is soluble 1 in 0.3 of water and has an unpleasant taste.
- Blackcurrant syrup is used as a flavouring agent to mask this.

Example 33.5

Prepare 50 mL of Chloral elixir, paediatric.

	Master formula	For 50 mL
Chloral hydrate	200 mg	2 g
Water	0.1 mL	1 mL
Blackcurrant syrup	1 mL	10 mL
Syrup	to 5 mL	to 50 mL

Examples

- Traditionally used for the alkalinization of urine to relieve discomfort in mild urinary tract infections or cystitis.
- Citric acid and potassium citrate are the active ingredients; both are soluble 1 in 1 of water.
- Lemon spirit, which is lemon oil in alcoholic solution, is a flavouring agent.
- The quillaia tincture is a surfactant used to emulsify any displaced lemon oil.
- Syrup is a sweetening agent.

Example 33.6

Prepare 200 mL of Potassium Citrate Mixture BP.

	Master formula	For 200 mL
Potassium citrate	3 g	60 g
Citric acid monohydrate	500 mg	10 g
Syrup	2.5 mL	50 mL
Quillaia tincture	0.1 mL	2 mL
Lemon spirit	0.05 mL	1 mL
Double strength chloroform water	3 mL	60 mL
Water	to 10 mL	to 200 mL

Examples

- Mechanically cleans and freshens the mouth.
- Concentrated peppermint emulsion is used as a flavouring and the chloroform water is a sweetener and preservative.
- Sodium chloride is soluble 1 in 3 of water and sodium bicarbonate is soluble 1 in 11 of water.

Example 33.7

Prepare 500 mL of Compound Sodium Chloride Mouthwash BP.

	Master formula	For 500 mL
Sodium chloride	1.5 g	7.5 g
Sodium bicarbonate	1 g	5 g
Concentrated peppermint emulsion	2.5 mL	12.5 mL
Double strength chloroform water	50 mL	250 mL
Water	to 100 mL	to 500 mL

Examples

- For the softening and removal of earwax.
- Sodium bicarbonate is soluble 1 in 11 of water.
- Glycerol is a viscous liquid used to thicken the drops.

Example 33.8

Prepare 10 mL of Sodium Bicarbonate Ear Drops BP.

	Master formula	For 10 mL
Sodium bicarbonate	5 g	500 mg
Glycerol	30 mL	3 mL
Water	to 100 mL	to 10 mL