Pharmaceutical Solutions and Other Liquid Dosage Forms

Pharmaceutical solutions:

are liquid preparations that contain one or more chemical substances dissolved in a suitable solvent or mixture of mutually miscible solvents.

Classification

1- According to its use as oral, otic, ophthalmic, or topical,etc.

2- According to their composition , classified as ,

- “ syrups” are aqueous solutions containing a sugar.
- “ elixirs” are sweetened hydro alcoholic (combinations of water and ethanol) solutions.
- “spirits” are aromatic materials if the solvent is alcoholic.
- “ aromatic waters” if the solvent is aqueous.

- Solutions prepared by extracting active constituents from crude drugs are termed “tinctures” or “Fluid extracts”, depending on their method of preparation and concentration.

- Tinctures may also be solutions of chemical substances dissolved in alcohol or in a hydro alcoholic solvent.

- Certain solutions prepared to be sterile and pyrogen free and intended for parenteral administration are classified as “ injections”.

Advantages of solutions as an oral dosage form:

- 1. Liquids are easier to swallow, so they are preferred for pediatric and geriatric use.
- 2. Drugs administered in the form of a solution are immediately available for absorption.
- 3. Solutions are homogenous systems i.e the drug is uniformly distributed throughout the preparation.
- 4. Irritation is reduced by administration of a solution of a drug due to the immediate dilution by the gastric contents.

Disadvantages of solutions as an oral dosage form:

- 1. Liquids are bulky to transport and store.
- 2. Poor stability of ingredients in aqueous solutions.
- 3. Solutions often provide suitable media for the growth of m.o. and may therefore require the incorporation of a preservative.
- 4. The taste of a drug, is always more pronounced when in solution. Solutions can, however, easily be sweetened and flavored to make them more palatable.
- 5. Accurate dosage usually depends on the ability of the patient to use a spoon or, a volumetric dropper.

Solutions can be classified according to the type of solvent in which the active ingredients are dissolved into:

- A. Aqueous Solutions
- B. Non- Aqueous Solutions.

A. Aqueous Solutions:

Water is the most widely used solvent for use as a vehicle for pharmaceutical products due to:

1. Lack of toxicity.
2. Physiological compatibility.
3. Ability to dissolve a wide range of materials.

- Naturally occurring water containing varying amounts of dissolved inorganic salts, Na, K, ca, Mg and iron, Cl^-, SO_4^{--} and CO_3^{--}, along with dissolved and undissolved organic matter and microorganisms.

Drinking water

must meet the regulations with respect to bacteriologic purity.

Acceptable drinking water should be

- Clear,
- Colorless
- Odorless and
- Neutral or only slightly acid or alkaline,

The deviation from neutral being due to the nature of the dissolved solids and gases (carbon dioxide contributing to the acidity and ammonia to the alkalinity of water).

∵ Drinking tap water is unacceptable for the manufacture of aqueous pharmaceutical preparations because of the possible chemical incompatibilities between dissolved solids and the medicinal agents being added.

Signs of such incompatibilities are

- Precipitation
- Discoloration
- and occasionally effervescence.

∴Purified water, is used in preparation of aqueous dosage forms except those for parenteral administration (injections) which need highly pure, sterile and pyrogen free water.

Purified water, is obtained by

A. Distillation.

B. Ion exchange.

C. Reverse osmosis.

It contains fewer solid impurities than ordinary drinking water reaching only 1% as much dissolved solids as tap water.

A. Distillation Method:

Stills in various sizes and styles with capacities ranging from about 0.5 to 100 gallons of distillate per hour are used.

The first portion of aqueous distillate (about the first 10-20%) must be discarded, Why?

Since it contains many foreign volatile substances usually found in drinking water.

Also, the last portion of water (about 10% of the original volume of water) remaining in the distillation apparatus must be discarded Why?

Distillation to dryness results in decomposition of the remaining solid impurities to volatile substances that contaminates the previously collected portion of distillate.

B. Ion Exchange Method:

Advantages over distillation is that

- no heat is required,
- simple equipment,
- ease of operation
- and minimal maintenance of the equipment.

The ion exchange equipment passes water through a column of cation and anion exchangers consisting of water – insoluble synthetic polymerized resins of high molecular weight.

The resins are mainly of two types:

a. The cation, or acid exchangers, which permit the exchange of the cations in water with hydrogen ion-from the resin.

b. The anion, or base exchangers, which permit the removal of anions from water.

These two processes are successively employed to remove both cations and anions from water.

The processes are indicated as follows:

With M^+ indicating the metal cation (as Na^+)

and the X^- indicating the anion (as cl^-).

- **Cation exchange:**

H–resin + M+ + X- + H2O →M-resin + H+ + X- + H2O

(Pure)

- **Anion exchange:**

Resin-NH2 + H+ + X- + H2O →Resin-NH2 + HX + H2O

(Pure)

- Water purified is referred to as demineralized or deionized water.

C. Reverse Osmosis:

- A pressurized stream of water is passed parallel to the inner side of a filter membrane core.
- A portion of the feed water, permeates the membrane as filtrate, while the rest of water exits the system without being filtered.
- The filtered portion is called the "permeate" because it has permeated the membrane.
- The water that has passed through the system is called the "concentrate" because it contains the concentrated contaminants rejected by the membrane.

What is the difference between osmosis and reverse osmosis?

- In osmosis, the flow through a semipermeable membrane is from a less concentrated solution to a more concentrated solution, while in reverse osmosis, the flow is from the more concentrated to the less concentrated solution, thus the term reverse osmosis.

Approaches to the improvement of aqueous solubility:

- Complete solution of all ingredients in water is sometimes difficult.

- It is important that the concentration of any material does not come close to its limit of solubility to prevent precipitation if the product is cooled or if any evaporation of the vehicle take place.

- In these cases one or more of the following methods may be used in order to improve aqueous solubility.

1. Cosolvency:

- The solubility of a weak electrolyte or non-polar compound in water ↑ by the addition of a water-miscible solvent in which the compound is also soluble.

- Vehicles used in combination to increase the solubility are called "co solvents".

- The choice of suitable cosolvents is limited because of possible toxicity and irritancy, particularly for oral or parenteral use.

Suitable blends should possess values of dielectric constant between 25 and 80.

e.g.a water / ethanol blend, other suitable solvents including sorbitol, glycerol, propylene glycol and syrup.

- A blend of propylene glycol and water is used to improve the solubility of co-trimoxazole,

- paracetamol is formulated as an elixir by the use of alcohol, propylene glycol and syrup.

2. pH control:

- The solubility of a weak base can be ↑ by ↓ the pH of its solution whereas solubility of a weak acid is ↑ by a pH ↑ .
- The chosen pH must not conflict with other product requirements.
- The pH of optimum solubility Mostly is not the pH of optimum stability.

- The pH of parenteral and ophthalmic solutions, must be controlled as extremes application to mucous membranes can cause pain and irritation.

specially subcutaneous and intramuscular injections.

pH changes may affect :

- The bioavailability of drugs
- and the preservative activity by altering the degrees of its ionization.

Maximum solubility may best be achieved by a balance between pH control and concentration of cosolvent.

The inclusion of cosolvents such as alcohol or propylene glycol will ↓ the dielectric constant of the vehicle and ∴ ↑ the solubility of unionized form of the drug.

This ↓ of the polarity of the solvent system will also ↓ the degree of dissociation of the drug and hence its pka will be ↑.

This will ↑ the concentration of the unionized (less soluble) species, i.e. an ↑ in the pH of the system is necessary to maintain solubility.

3. Solubilization:

The solubility of a drug in water can be improved by the addition of a surface active agent.

This phenomenon is micellar solubilization.

A large excess of surfactant is undesirable because of

- Cost
- Possible toxic effects
- Its effect on products aeration during manufacture.
- It may also reduce the bioavailability of a drug due to its strong adsorption within the micelle,

An insufficient amount of surfactants,may not solubilize all of the drug or may lead to precipitation on storage or on dilution of the product.

Hydrophilic surfactants with HLB values above 15 will be of particular value as solubilizing agents.

The material chosen must be:

- Non-toxic and non-irritant bearing in mind its intended route of administration.
- It must also be miscible with the solvent system,
- Compatible with other ingredients,
- Free from disagreeable odor and taste
- and non-volatile.

Examples

The solubilization of fat-soluble vitamins using polysorbates, enabling their inclusion with water-soluble vitamins in the same formulation.

The solubilization of iodine to produce iodophores is achieved by the use of macrogol ethers,

The advantages over simple iodine solutions are:

- Improved chemical stability,
- Reduced loss of active agent due to sublimation,
- Less corrosion of surgical instruments
- and in some cases, enhanced activity.

The solubility of phenolic compounds such as cresol and chloroxylenol which are soluble in water up to 2% and 0.03% respectively can be↑ by solubilization with soaps

e.g. Lysol contains 50% cresol in an aqueous system by the use of potassium soaps of oleic , linoleic and linolenic acids.

It may be also possible to combine solubilization and cosolvency in one formulation.

A 5% chloroxylenol solution can be formulated by the inclusion of potassium ricinoleate, as well as ethanol and terpineol as cosolvents.

Glycerol has also been used with polysorbate 80 to improve the solubility of vitamin A.

4. Complexation:

- Is to interact a poorly soluble drug with a soluble material to form a soluble intermolecular complex.

- ∵ most complexes are macromolecular

  ∴they tend to be inactive, being unable to cross lipid membranes. therefore, complex formation should be easily reversible so that the free drug is released during or before contact with biological fluids.

- The term "hydrotropy", which has been defined as the increase in aqueous solubility of a material by the inclusion of additives.

- Many complexes are not water-soluble and may, in fact, be better suited for the prolonged release of the drug.

- E.g. the complexation of iodine with 10-15 % solution of polyvinylpyrrolidone to improve the aqueous solubility of the active agent.

- The interaction of salicylates or benzoates with xanthines such as theophylline or caffeine for.

5. Chemical modification:

Chemical modification of a drug in order to produce a water soluble derivative.

Examples

- The synthesis of the sodium phosphate salts of hydrocortisone, prednisolone and betamethasone.

- The water soluble chloramphenicol sodium succinate has no antibacterial activity but is suitable for parenteral administration as a solution to obtain high blood levels after which it is converted back to the active base.

6. Particle size control:

- The size and shape of very small particles, if less than 1μm diameter, can affect their solubility.

- As particle size decreases, solubility will increase.

(B) Non-Aqueous Solutions:

To ensure complete solution of the ingredients at all storage temperatures if the drug is unstable in aqueous systems, by using an alternative solvent.

The advantages.

using the intramuscular injection of solutions of drugs in oils as depot therapy.

Choosing a suitable solvent :

Its toxicity,
Irritancy
Sensitizing potential
Flammability,
Cost,
Stability
Compatibility with other excipients

Non-aqueous solvents in pharmaceutical preparations can be classified as:

(I) Fixed oils of vegetable origin:

non-volatile oils which consist mainly of fatty acid esters of glycerol.

example, Almond oil which consists of glycerides mainly of oleic acid, used as a solvent for oily phenol injection BP,

water being unsuitable Why?

because of the caustic nature of aqueous phenol solutions,

Olive oil, sesame oil, maize oil, cotton seed oil, Soya oil and castor oil, are all suitable for parenteral use.

- Some fixed oils are tasteless and a dourless to be suitable for oral use as solvents for such materials as vitamins (A) and (D).

- Fractionated coconut oil is used as the solvent for phenoxymethyl penicillin which would otherwise hydrolyse rapidly if present in an aqueous system.

- Oils tend to be unpleasant to use externally, unless presented as an emulsion. Arachis oil is one of the few examples and is used as the solvent in Methyl Salicylate liniment B.P.

(II) Alcohols

- It is used as primary solvent for many organic compounds.
- Together with water, it forms a hydroalcoholic mixture that dissolves both alcohol-soluble and water- soluble substances, a feature useful in the extraction of active constituents from crude drugs.
- Alcohol is a solvent and excipient because of its miscibility with water and its ability to dissolve many water- insoluble ingredients, including drug substances, flavorants and antimicrobial preservatives.
- It is used as an antimicrobial preservative alone or with parabens, benzoates, and other agents.

- For the undesired pharmacologic and toxic effects of alcohol when ingested by children. The (FDA) recommended alcohol content limit of 0.5% for OTC oral products for children under 6 years of age, 5 % for children 6 to 12 years of age and 10% for children over 12 years of age.

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- The strength of diluted alcohol prepared by mixing equal volumes of alcohol and purified water is not exactly half that of the more concentrated alcohol but slightly greater. Why?

The final volume of mixture is not the sum of the individual volumes of the two components but about 3 % less than what expected as liquids contract upon mixing.

- Rubbing alcohol contains about 70% ethyl alcohol by volume.
- The remainder consisting of water, denaturants, with or without color additives, perfume oils and stabilizers.
- The use of this denaturant mixture makes the separation of ethyl alcohol virtually impossible with ordinary distillation apparatus.
- This denaturant mixture is composed of 8 parts by volume of acetone, 1.5 parts by volume of methyl isobutylketone, and 100 parts by volume of ethyl alcohol.
- The product is volatile and flammable and should be stored in tight containers.

- It is employed as:

1- Rubefacient and soothing externally,

2- Germicide for instruments

3- Skin cleanser prior to injection.

4- Vehicle for topical preparations

Isopropyl rubbing alcohol is about 70% by volume isopropyl alcohol,

- The remainder consisting of water with or without color additives, stabilizers and perfume oils.
- It is used externally as a:

1- Rubefacient and soothing rub

2- Vehicle for topical products.

(III) Polyhydric alcohols:

- Alcohols containing two hydroxyl groups per molecule are known as glycols but due to their toxicity are rarely used internally.

- One important exception is propylene glycol which is used in conjunction with water or glycerol as cosolvent.

CH3.CH (OH)-CH2-OH

- The lower molecular weight polyethylene glycols (PEG) or macrogols can be used as cosolvents with alcohol or water but their main use is in the formulation of water-miscible ointment bases.

OH CH2 (CH2CH2O)nCH2OH

Glycerol

- an alcohol possessing three hydroxyl groups per molecule, is also widely used particularly as a cosolvent with water for oral use.

- Glycerin has preservative qualities, it can be used externally at higher concentrations, for example in phenol Ear Drops.

(IV) Dimethyl sulphoxide :

This is a highly polar compound and is thought to aid the penetration of drugs through the skin.

(V) Ethyl ether:

This material is widely used for the extraction of crude drugs. It is, however, used as a cosolvent with alcohol in some collodions.

(VI) Liquid paraffin:

The oily nature makes it unpleasant to use externally, although it is often used as a solvent for the topical application of drugs in emulsion formulations.

Internally, it is indigestible and absorbed only to a limited extent, it is an example of emollient cathartic when given internally in the form of emulsion.

(VII) Miscellaneous solvents:

- Isopropyl myristate and isopropyl palmitate are used as solvents for external use in cosmetics as:

- Their low viscosity
- lack of greasiness make them pleasant to use.

- Xylene is present in some ear drops to dissolve ear wax.

- It may be possible to improve the solubility of a drug in a particular vehicle by the addition of a cosolvent.

example

- ✓ Nitrocellulose is poorly soluble in both alcohol and ether but soluble in mixture of both.
- ✓ The formulation of Digoxin injection is best achieved by the inclusion of both ethyl alcohol and propylene glycol.

Formulation additives in solutions:

- (I) Buffers
- (II) Flavors and perfumes
- (III) Colors
- (IV) Preservatives

(I) Buffers:

- when dissolved in a solvent, enables it to resist any change in pH when an acid or an alkali is to be added.
- The choice of suitable buffer depends on the pH and buffering capacity required.
- It must be compatible with other excipients and have low toxicity.
- Most pharmaceutically acceptable buffering systems are based on carbonates, citrates, gluconates, lactates, phosphates or tartarates. Borates can be used for external application but not to mucous membranes or to abraded skin.

- As the pH of most body fluids is 7.4

✓ products such as injections, eye drops and nasal drops should be buffered at this value.

- Many body fluids themselves, have a buffering capacity

✓ when formulating low volume intravenous injections or eye drops a wider pH range can be tolerated.

∴There must be a compromise between a pH which is physiologically acceptable and a pH of maximum stability and solubility and optimum bioavailability.

- **Benzyl penicillin injection**.

The optimum pH range for the stability of penicillin solutions is 6-7.

- Hydrolysis readily occurs in aqueous solutions with the formation of inactive benzyl penicilloic acid

- This is accompanied by ↓ in pH which further catalyses hydrolysis leading to progressively ↑acidity and more rapid hydrolysis until the antibiotic has been destroyed.

- Decomposition can be retarded by buffering the pH of the solution to 6-7 with 45% W/V sodium citrate.

II) Flavors and perfumes:

- Sweetening agents may not be sufficient to render palatable a product.∴ a flavouring agent can be included specially in pediatric formulation.

- Flavouring and perfuming agents are natural or synthetic.

- Natural products include fruit juices, aromatic oils (peppermint and lemon oils), herbs and spices as concentrated extracts, alcoholic or aqueous solutions, syrups or spirits.

Artificial perfumes and flavours are synthetic,

- They tend to be:

- Cheaper
- More readily available,
- Less variable in chemical composition
- More stable

They are usually available as alcoholic or aqueous solutions or as powders.

- Sometimes there is a strong association between the use of a product and its flavour or perfume content.

example, products intended for the relief of indigestion are often mint flavoured as mint has been used for its carminative effect.

- Other materials for the masking of unpleasant tastes include menthol, peppermint oil and chloroform.

In addition to their own particular tastes and odours, they also act as desensitizing agents by the exertion of a mild anaesthetic effect on the sensory taste receptors.

Flavour- enhancing agents such as citric acid and glycine or monosodium glutamate are widely used in solutions

(III) Colours:

- It is useful to include a colour which is associated with the used flavour to improve the attractiveness of the product.
- There is available range of both natural and synthetic colours. The former, which tend to be more widely acceptable than synthetic ones.
- They exhibit problems namely variations in availability and in chemical composition, both of which may cause formulation difficulties.
- Synthetic dyes tend to give brighter colours and are generally more stable than natural materials.

(IV) Preservatives:

- There are two strategies to be adopted in the preparation of microbiologically acceptable pharmaceutical preparations.

- 1- To minimize the access of microorganisms from the sources.

- 2- To formulate the final product with inclusion of preservatives.

Sources of contamination of solutions:

(1) Equipment:

- Should be simple for the purposes required
- With a minimum of junctions, valves and pumps, to allow cleaning in place.

(2) Raw materials:

- Particularly those of natural origin, and water are a rich source of microorganisms.
- Any treatment applied to remove or reduce the microbial load must be such that the materials are not adversely affected.
- A variety of processing procedures are available including ionizing radiations, microwaves, gassing and heat.

(3) Personnel:

- To control contamination, of little importance unless the personnel understand and appreciate the problems and significance of microbial contamination.

- Education in hygiene minimizes the introduction of microorganisms by staff.

- A full range of appropriate clothing must be available to protect the product from body surfaces such as hood, mask, overall protective gloves and boots.

preservatives

- When choosing a suitable preservative, it must be ensured that:

1- Adsorption on to the container from the product does not occur or

2- Its efficiency is not impaired by the pH of the solution or by interactions with other ingredients.

e.g.many of the widely used parahydroxybenzoic acid esters are unable to exert their antimicrobial activity. Why?

As they are adsorbed into the micelles of some non-ionic surfactants.

Some examples of antimicrobial agents:

(1) Phenolics:

- Distillation fractions of coal tar, include cresols, xylenols and phenol.
- all are toxic and caustic to skin and tissues.
- Modification of the phenol molecule by the introduction of cl_2 and cH_3 groups as in chlorocresol and chloroxylenol has the dual effect of eliminating toxic and corrosive properties and at the same time enhancing and prolonging antimicrobial activity.
- Thus, chlorocresol is used as bactericide in injections.

(2) Alcohols, acids and esters:

- Ethyl alcohol, has long been used as preservative.

- Aromatic substitution produce compounds which are less volatile and less rapidly active.

e.g. phenylethanol for eye drops and contact lens solutions,

benzyl alcohol in injections.

- The organic acids, sorbic and benzoic and their esters, because of their low toxicity, are well established as preservatives.

- We must be aware of chemical interactions between the various components of a solution that may alter the stability and/or potency.

- Esters of p-hydroxybenzoic acid (methyl- ethyl- propyl and butyl parabens), used in oral preparations, have a tendency to partition into certain flavoring oils.

- This effect reduce the effective concentration of the preservatives in the aqueous medium of the product below the level needed for preservative action.

(3) Quaternary ammonium compounds:

- These cationic surface active compounds are derivatives of an ammonium halide in which the hydrogen atoms are substituted by at least one lipohilic group (Alkyl group).
- They are mild in use and active at high dilutions as to be non-toxic.
- They are active as cations, ∴ alkaline conditions ↑ activity.
- They interfere with cell permeability such that bacteria, mainly the gram – positive groups, leak their contents and undergo lysis.
- Gram negative bacteria are less susceptible.
- Mixtures with other antimicrobial agents can be used.

(V) Reducing agents and antioxidants:

The decomposition of pharmaceutical products by oxidation can be controlled by the addition of reducing agents or antioxidants.

(VI) Sweetening agents:

- ↓MW carbohydrates particularly sucrose are the most widely used sweetening agents.

- Sucrose is colourless, very soluble in water, stable over a pH range of about 4-8.

- Polyhydric alcohols such as sorbitol, mannitol and to a lesser extent glycerol can be included in preparations for diabetic use.

- Artificial sweeteners can be used both in conjunction with sugars and alcohols to enhance the degree of sweetness or on their own in formulations for patients who must restrict their sugar intake.

- They are more sweeter than sucrose and therefore rarely required at a concentration greater than about 0.2%.

- The most widely used is the sodium or calcium salt of saccharin, exhibiting a high water solubility and are chemically and physically stable over a wide pH range.

(VII) Isotonicity modifiers :

Solutions for injection, for application to mucous membranes and large volume solutions for ophthalmic use must be made iso-osmotic with tissue fluid to avoid pain and irritation.

preparation of solutions:

- chemical agents in solvent require an extended time for dissolving.

- To hasten dissolution we may employ one of several techniques:,

1-applying heat

2- reducing the particle size of the solute,

3- using a solubilizing agent,

4- or subjecting the ingredients to vigorous agitation.

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

- Many medicinal agents are destroyed at ↑temperatures, and the advantage of rapid solution may be completely offset by drug deterioration.

- If volatile solutes are used or if the solvent is volatile (as alcohol), the heat ↑ the loss of these agents and must be avoided.

- Chemical agents, e.g. calcium salts, undergo exothermic reactions as they dissolve and give off heat. ∴ the use of heat discourages the formation of a solution.

- E.g. calcium hydroxide, in the preparation of calcium Hydroxide Topical Solution. It is soluble in water to the extent of 140 mg per 100 ml at 25°C, and 170 mg per 100 ml at 15°C. ∴ the temperature of preparation or storage can affect the concentration of the resultant solution.

- In addition to or instead of ↑ the temperature of the solvent to↑ the rate of solution, we may ↓ the particle size of the solute, by grinding the solid with a mortar and pestle on a small scale or industrial micronizer on a large scale, the ↓ particle size ↑the surface area of the solute.

- For ↓ and ↑ scale manufacture of solutions, the only equipment suitable is mixing vessel, for agitation and a filtration to ensure clarity of the solution.

- Solutes present in ↓ concentrations, are often predissolved in a small volume of the solvent and then added to the bulk.

- Volatile materials such as flavours and perfumes are added at the end of the process and after cooling to ↓ loss by evaporation.

Stability of solutions

- Chemical and physical stability of solutions in their containers is important. A solution must retain its initial clarity, odour, colour, taste and viscosity over its shelf life.

- Clarity can easily be assessed by visual examination or by a measurement of its optical density.

- Colour assessed both visually and spectrophotometrically.

- The stability of flavours and perfumes must be also assessed by chromatographic methods.