Industrial Pharmacy I (4)

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Solutions as a dosage form
Excipients

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Solutions: formulation additives

- All formulation additives **MUST be** compatible with other excipients and have a low toxicity
- **Buffers**
  - Enable the solution to resist any change in pH
  - The choice of suitable buffer depends on the pH and buffering capacity required
  - Buffering systems are based on carbonates, citrates, gluconates, lactates, phosphates or tartrates
  - 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 to avoid irritation

Solutions: formulation additives

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
- The most widely used isotonicity modifiers are sodium chloride 0.9% w/v and dextrose 5% w/v
- Isotonicity adjustments is made after the addition of all other ingredients, because each ingredient will contribute to the overall osmotic pressure of a solution

Viscosity enhancement

- To help solution to remain in place on the skin or in the eyes for some time that is long enough for the drug to give its effect; e.g. carboxymethylcellulose (CMC)

Solutions: formulation additives

Preservatives

- Chemical compounds that are added to formulations to protect them from microbial contamination: benzoic acid, sorbic acid, parabens: esters of para-hydroxybenzoic acid: methylparaben, ethylparaben, propylparaben and butylparaben
- The effect of preservative is dependant on concentration, therefore dilution may lower concentration of the preservative below its effective concentration

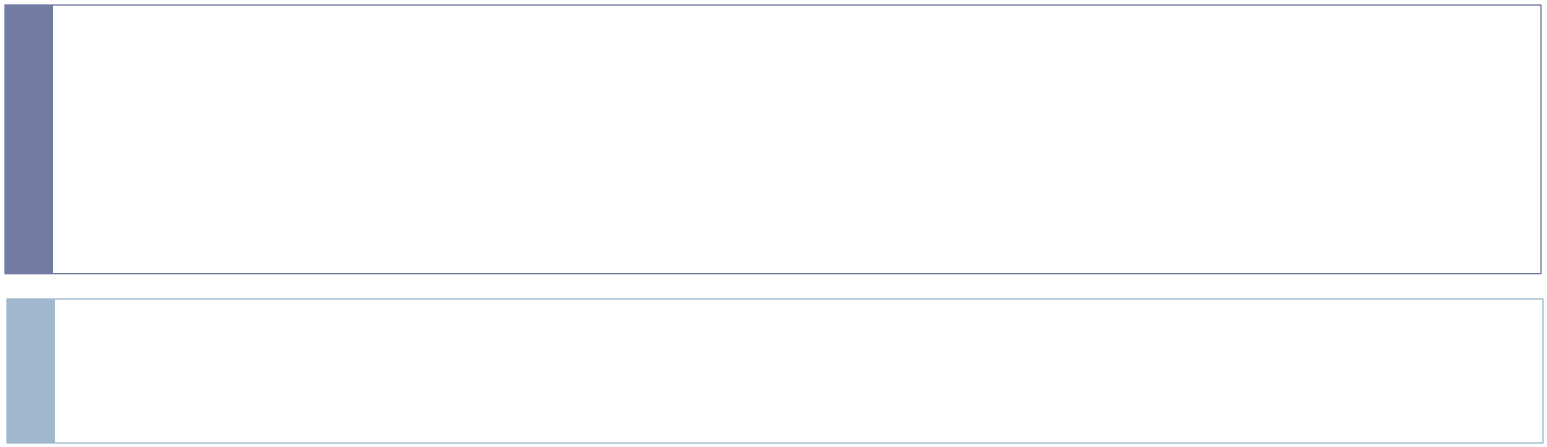
Reducing agents and antioxidants

- The decomposition of pharmaceutical products by oxidation can be controlled by the addition of reducing agents such as sodium metabisulphite, or antioxidants such as ascorbic acid, butylated hydroxyanisole BHA or butylated hydroxytoluene BHT.

Solutions: formulation additives

- **Sweetening agents**
  - They are used to help mask the taste of the drug in a solution; examples: sucrose, sorbitol, mannitol, aspartame (L-aspartic acid-L-phenylalanine methyl ester) and saccharine.
- **Flavors**
  - The simple use of sweetening agents may not be sufficient, therefore synthetic flavors or natural products such as orange oil and anise oil, may be included.
- **Colors**
  - They are added to improve the attractiveness of the product. They are usually associated with the flavor: for example a red colorant is used with raspberry flavor.
  - Another reason for using colors is to enable easy product identification, particularly of poisonous materials.

Oral Solutions



Oral solutions

- Liquid pharmaceuticals for oral administration are usually formulated such that the patient receives the usual dose of the medication in a conveniently administered volume, as 5 mL (one teaspoonful), 10 mL, or 15 mL (one tablespoonful). On the other hand, many solutions for children are given by drop with a calibrated dropper.
- Most solutions intended for oral administration contain **sweeteners**, **flavorants** and **colorants** to make the medication more attractive and palatable.
- When needed, they may also contain **stabilisers** to maintain the chemical and physical stability of the medicinal agents and **preservatives** to prevent the growth of microorganisms in solution.

Syrups

- Syrups are concentrated aqueous preparations of a sugar or sugar substitute with or without flavoring agents and medicinal substances.
- Syrups containing only sugar: **nonmedicated syrups**, e.g simple syrup.
- Syrups containing sugar and flavoring agents: **flavored syrups**, e.g orange syrup, cherry syrup, cocoa syrup.
- These syrups are intended to serve as **pleasant-tasting vehicles** for **water-soluble drugs that are stable in aqueous solution**.
- The most frequently found types of medications administered as **medicated syrups** are **antitussive agents and antihistamines**.

Compounding of Syrups

- **Sucrose** (table sugar) is the sugar most frequently employed in syrups. It may be replaced in whole or in part by other sugars or substances such as sorbitol, glycerin, and propylene glycol.
- **Artificial sweeteners**, like **aspartame** and **saccharine**, are also used as alternatives of sucrose. When using artificial sweetener a **viscosity enhancer such as cellulose derivatives is added**. The viscosity resulting from the use of these cellulose derivatives is much like that of a sucrose syrup.

Advantages of syrup's high viscosity

- **Masking bad taste:** When the syrup is swallowed, and because of its thickness, only a portion of dissolved drug actually makes contact with the taste buds, the remainder of the drug being carried past them and down the throat in the viscous syrup.
- **Relieve throat irritation:** In the case of antitussive syrups, the thick, sweet syrup has a soothing effect on the irritated tissues of the throat as it passes over them.

Compounding of Syrups

- **Most syrups contain a high proportion of sucrose, usually 60 to 80%: this is resulted in** desirable sweetness, viscosity and resistance against microbial growth because of the unavailability of the water required for the growth of microorganisms.
- **According to USP:** simple syrup is prepared by dissolving 85 g of sucrose in enough purified water to make 100 mL of syrup. Syrup has a specific gravity of about 1.313, which means that each 100 mL of syrup weighs 131.3 g. Because 85 g of sucrose is present, then the weight of the purified water is 46.3 g. Thus, 46.3 g, or mL, of purified water is used to dissolve 85 g of sucrose. The solubility of sucrose in water is 1 g in 0.5 mL of water; therefore, to dissolve 85 g of sucrose, about 42.5 mL of water would be required. Thus, only a very slight excess of water (about 3.8 mL per 100 mL of syrup) is employed in the preparation of syrup.

Compounding of Syrups

- The official syrup is both stable and resistant to crystallization and microbial growth.
- If the syrup were completely saturated with sucrose, in cool storage some sucrose might crystallize from solution. The syrup would then be very much unsaturated and probably suitable for microbial growth.

Preparation of syrups

- Syrups are most frequently prepared by one of three general methods, depending on the physical and chemical characteristics of the ingredients. Broadly stated, these methods are

۱. solution of the ingredients with the aid of heat,

۲. solution of the ingredients by agitation without the use of heat, or the simple admixture of liquid components,

۳. addition of sucrose to a prepared medicated liquid or to a flavored liquid, and

- Sometimes a syrup is prepared by more than one of these methods.

Solution with the aid of heat

- This method is used when it is desired to prepare the syrup as quickly as possible and when the syrup's components are not damaged or volatilized by heat.
- In this method the sugar is generally added to the purified water, and heat is applied until the sugar is dissolved. Then other heat-stable components are added to the hot syrup, the mixture is allowed to cool, and its volume is adjusted to the proper level by addition of purified water.
- Caution must be exercised against becoming impatient and using excessive heat. Sucrose, a disaccharide, may be hydrolyzed into monosaccharides, dextrose (glucose), and fructose (levulose), and the combination of the two monosaccharide products is **invert sugar (invert syrup)**. When heat is applied in the preparation of a sucrose syrup, some inversion of the sucrose is almost certain. The speed of inversion is greatly increased by the presence of acids.

Solution with the aid of heat

- Invert sugar is sweeter than sucrose, and darker because of the effect of heat on the fructose portion of the invert sugar.
- When the syrup is greatly overheated, it becomes amber colored as the sucrose caramelizes. Syrups so decomposed are more susceptible to microbial growth than the stable, undecomposed syrups.
- Because of the prospect of decomposition by heat, syrups cannot be sterilized by autoclaving.

Solution by agitation without the use of heat

- This method is used to **avoid heat-induced inversion of sucrose**.
- This process is **more time consuming than use of heat**, but the product has maximum stability.
- When solid substances are added directly to a syrup, they dissolve slowly because the viscous nature of the syrup does not permit the solid substance to distribute readily throughout the syrup to the available solvent and also because a limited amount of available water is present in concentrated syrups. Therefore, when solid agents are to be added to a syrup, it is best to dissolve them in a minimal amount of purified water and incorporate the resulting solution into the syrup.

Elixirs

- Elixirs are clear, **sweetened hydroalcoholic solutions** intended for oral use and are usually flavored to enhance their palatability.
- Non-medicated elixirs are employed as vehicles, and medicated elixirs are used for the therapeutic effect of the medicinal substances they contain.
- **Compared with syrups**, elixirs are usually **less sweet and less viscous** because they contain a lower proportion of sugar and consequently are **less effective than syrups in masking the taste** of medicinal substances. However, because of their hydroalcoholic character, elixirs are **better** able than aqueous syrups to maintain both water-soluble and **alcohol-soluble components in solution**.
- The proportion of alcohol in elixirs varies widely, since the individual components of the elixirs have different water and alcohol solubility characteristics. Each elixir requires a specific blend of alcohol and water to maintain all of the components in solution. In addition to alcohol and water, other solvents, such as glycerin and propylene glycol, are frequently employed in elixirs as co-solvents.

Elixirs

- Although many elixirs are sweetened with sucrose or with a sucrose syrup, some use sorbitol, glycerin, and/or artificial sweeteners.
- **Elixirs having a high alcoholic content usually use an artificial sweetener**, such as saccharin, which is required only in small amounts, rather than sucrose, which is only slightly soluble in alcohol and requires greater quantities for equivalent sweetness.
- All elixirs contain **flavorings** to increase their palatability, and most elixirs have **coloring agents** to enhance their appearance. Elixirs containing **more than 10 to 12% of alcohol** are usually **self-preserving** and do not require the addition of an antimicrobial agent.
- Because of their usual content of volatile oils and alcohol, elixirs should be **stored in tight, light-resistant** containers and **protected from excessive heat**.

Preparation of Elixirs

- Elixirs are usually prepared by **simple solution with agitation** and/or by **admixture of** two or more **liquid** ingredients.
- Alcohol-soluble and water-soluble components are generally dissolved separately in alcohol and in purified water, respectively.
- Then **the aqueous solution is added to the alcoholic solution,** rather than the reverse, **to maintain the highest possible alcoholic strength** at all times so that minimal separation of the alcohol-soluble components occurs.
- When the two solutions are completely mixed, the mixture is made to volume with the specified solvent or vehicle.
- Frequently the **final mixture will be cloudy**, because of separation of **some of the flavoring oils** by the reduced alcoholic concentration. To **solve this problem, talc** (magnesium silicate) is added, to **absorb** the excessive amounts of oils, **followed by filtration**.

Examples on official elixirs

- **Phenobarbital (sedative and hypnotic) Elixir:** contains phenobarbital 20 mg/5 mL,14% alcohol, glycerin is often added to enhance the solubility of phenobarbital.

- **Digoxin (cardiotonic glycoside) Elixir:** 50 µg/5 mL,10% alcohol.

- **Diphenhydramine HCl (antihistamine) Elixir** : contains diphenhydramine HCl , 12.5 mg/5 mL, 5.6% alcohol

Dry mixtures for solution

- A number of medicinal agents, particularly **certain antibiotics**, have **insufficient stability in aqueous solution**. Thus, manufacturers of these products provide them in dry powder or granule form for **reconstitution** with a prescribed amount of purified water immediately before dispensing to the patient.
- The **dry powder mixture contains all of the formulative components**, including drug, flavorant, colorant, buffers, and others, **except for the solvent**.
- Once reconstituted by the pharmacist, the solution remains stable when stored in the refrigerator for the labeled period, usually 7 to 14 days, depending on the preparation. This is a sufficient period for the patient to complete the regimen usually prescribed.
- Example: Penicillin V Potassium for Oral Solution, an antibiotic

Aromatic Waters

- Aromatic waters are clear, aqueous solutions saturated with volatile oils or other aromatic or volatile substances.
- Aromatic waters are prepared from a number of volatile substances, including orange flower oil. peppermint oil, rose oil, anise oil, spearmint oil, wintergreen oil, camphor, and chloroform. Naturally, the odors and tastes of aromatic waters are of the volatile substances from which they are prepared.
- Most of the aromatic substances in the preparation of aromatic waters **have very low solubility in water**, and even though a water may be saturated, its **concentration** of aromatic material is still rather **small**.
- Aromatic waters may be **used for perfuming and/or flavoring**.
- Aromatic waters are **no longer in widespread use**.

Spirits

- Spirits are **alcoholic solutions of volatile substances**. Generally, the **alcoholic concentration** of spirits is rather high, usually **over 60%.**
- Because of the greater solubility of aromatic or volatile substances in alcohol than in water, **spirits can contain a greater concentration of these materials than the corresponding aromatic waters**.
- **When mixed with water** or with an aqueous preparation, the **volatile substances** present in spirits generally **separate** from solution and **form a milky preparation.**
- Spirits may be used pharmaceutically as **flavoring agents** and **medicinally for the therapeutic value of the aromatic solute**.
- The spirits most recently official in the USP–NF are aromatic ammonia spirit, camphor spirit, orange spirit, and peppermint spirit.

Oral rehydration solutions

- Rapid fluid loss associated with diarrhea can lead to dehydration and ultimately death in some patients, particularly infants. **More than 5 million children younger than 4 years die of diarrhea each year** worldwide.
- The loss of fluid during diarrhea is accompanied by depletion of sodium, potassium, and bicarbonate ions. This fluid loss can lead to a progressive loss of blood volume culminating in hypovolemic shock.
- Diarrhea is a normal physiologic body response to get rid of a toxic substance, such as rotavirus or *Escherichia coli*.
- Oral rehydration solutions are usually effective in treatment of patients with mild volume depletion, 5 to 10% of body weight. These are available OTC and their use has diminished the incidence of complications associated with parenterally administered electrolyte solutions.

Oral rehydration solutions

- Therapy with these solutions is based on the observation that **glucose is actively absorbed from the small intestine**, even during diarrhea. This active transport of glucose is coupled with sodium absorption. Sodium absorption promotes anion absorption, which in turn promotes water absorption.
- A liter of typical oral rehydration solution contains 45 mEq **Na^+**, 20 mEq **K^+**, 35 mEq **Cl^-**, 30 mEq **citrate**, and 25 g **dextrose**.
- These formulations are available in liquid or powder packet form for reconstitution. The success of the commercial solutions is based on the accuracy of the formulation. If prepared incorrectly, homemade preparations can cause hypernatremia or worsen the diarrhea.

Oral colonic lavage solutions

- Traditionally, preparation of the bowel for procedures such as a colonoscopy consisted of administration of a clear liquid diet for 24 to 48 hours preceding the procedure, administration of an oral laxative such as magnesium citrate or bisacodyl the night before, and a cleansing enema administered 2 to 4 hours prior to the procedure.
- Another procedure has been devised, which requires less time and dietary restriction and obviates cleansing enemas. This method entails oral administration of a balanced solution of electrolytes with polyethylene glycol (PEG-3350). The **PEG acts as an osmotic agent** in the gastrointestinal tract, and **the balanced electrolyte concentration results in virtually no net absorption or secretion of ions**. Thus, a large volume of this solution can be administered without a significant change in water or electrolyte balance.

Oral colonic lavage solutions

- The formulation of this oral colonic lavage solution is as follows:

236.00 g	PEG-3350
22.74 g	Sodium sulfate
Sodium bicarbonate	6.74 g
5.86 g	Sodium chloride
Potassium chloride	2.97 g In 4800 mL

- The patient is instructed to drink 240 mL of solution every 10 minutes until about 4 L is consumed.
- Ideally, the patient should not have taken any food 3 to 4 hours before beginning to take the solution.