

# National University

Technology of Solid Dosage Forms & Disperse Systems

## **Pharmaceutical solutions dosage forms**

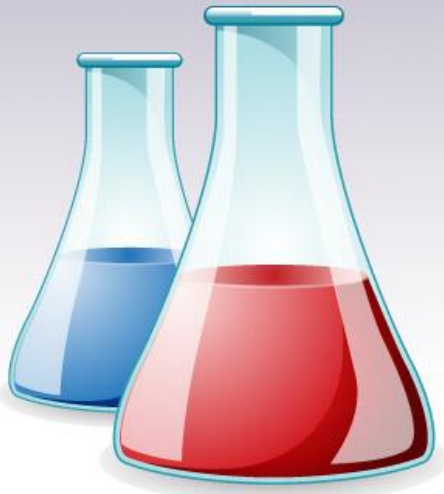
Facilitated by/

Mekaiel Amiel Mekaiel

M.Sc. Pharmaceutical Technology

# General Definition

- Pharmaceutical solutions are defined as liquid preparations in which the therapeutic agent and the various excipients are dissolved in the solvent system.



# Solutions can be formulated for different routes of administration

**Orally:** Syrups, elixirs, drops, ....

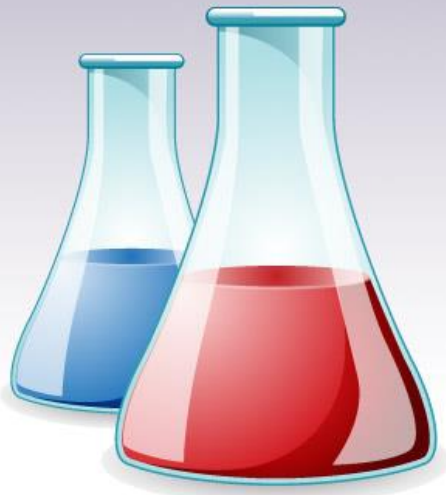
**In mouth and throat:** Mouth washes, gargles, throat sprays, ....



**In body cavities:** Douches, enemas, ear drops, nasal sprays, ....

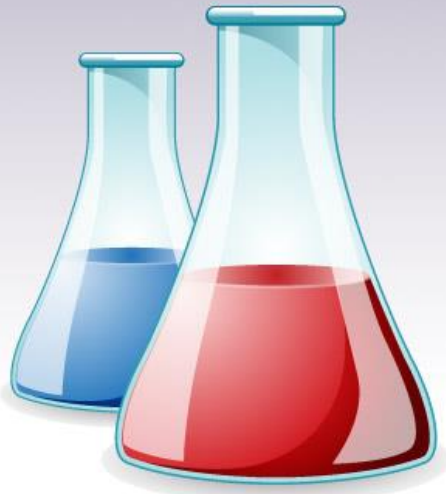
**On body Surfaces:** Collodions, lotions, ....

**Parenterally:**.....



# Advantages of solutions

- (1) Easier to swallow **therefore** easier for:  
children - old age - unconscious people.
- (2) More quickly effective than solid dosage forms.
- (3) Homogenous **therefore** give uniform dose than  
suspension or emulsion which need shake.

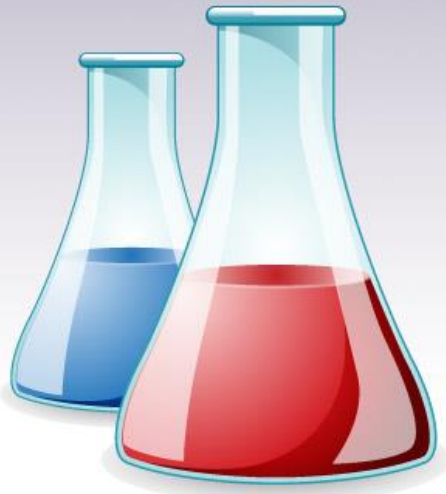


# Disadvantages of Solutions

- (1) Bulky **therefore** difficult to transport and store.
- (2) Unpleasant taste or odours are difficult to mask.
- (3) Needs an accurate spoon to measure the dose.
- (4) Less stable than solid dosage forms.

major signs of instability:

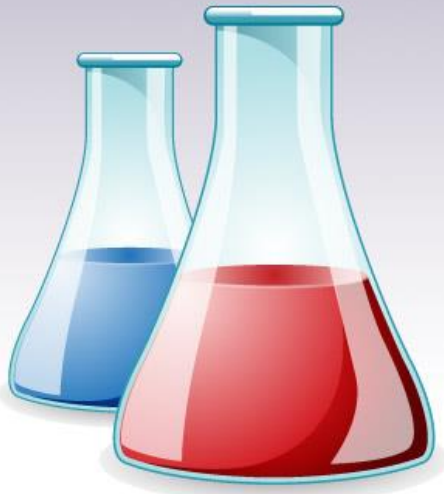
colour change, precipitation, microbial growth,  
chemical gas formation



# Drug solubility

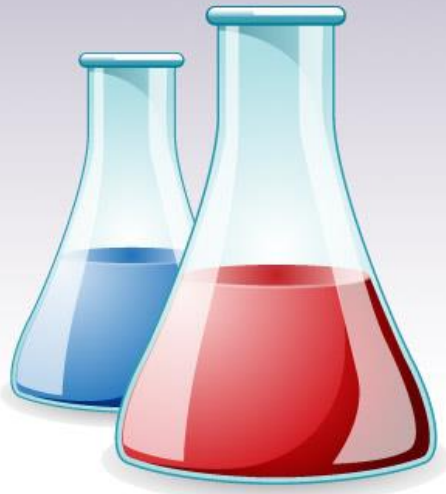
1. High soluble at the selected pH of the formulation.

So, the therapeutic agent is readily incorporated into the vehicle and formulated as an oral solution.



2. Moderate soluble at the selected pH of the formulation.

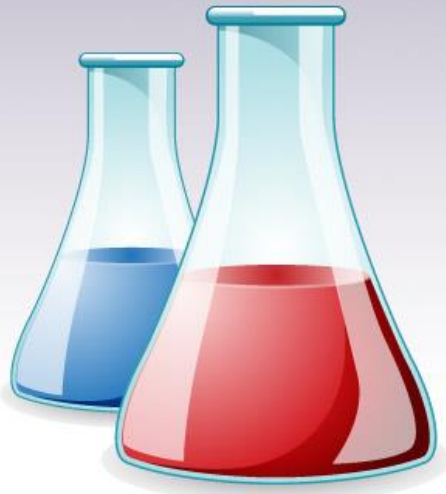
So ,the solubility of the therapeutic agent in the formulation must be enhanced.





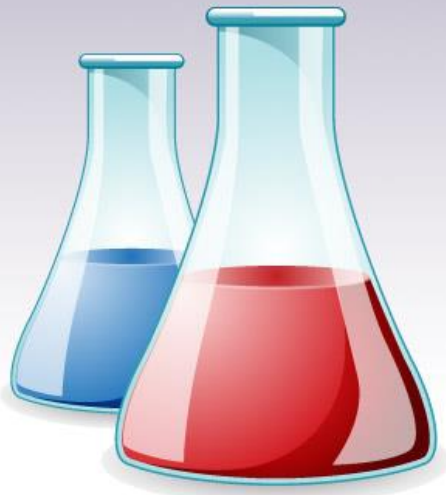
3. low soluble at the selected pH of the formulation.

The drug may therefore be formulated as an alternative-dosage form, e.g. a suspension.

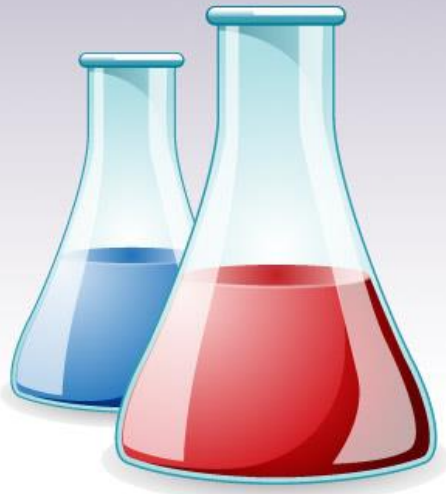


# Factors affecting the solubility of drugs

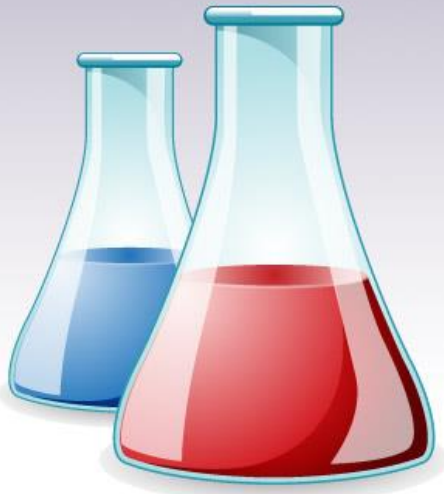
- The solubility properties of drug molecules in a particular solvent system are sometimes difficult to predict and have been reported to be dependent on several physicochemical properties, including:



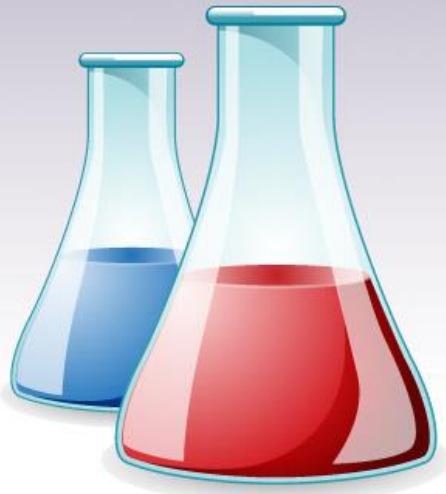
- molecular weight, volume, density, number of rotatable bonds, hydrogen bond donors and hydrogen bond acceptors.



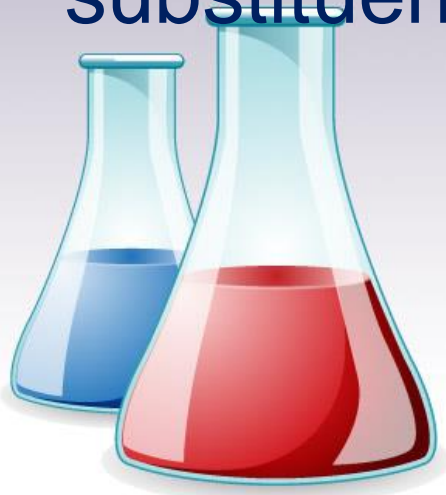
- Furthermore, the properties of the solid state, e.g. crystal habit, crystalline/amorphous properties, will also affect the solubility of the therapeutic agent.



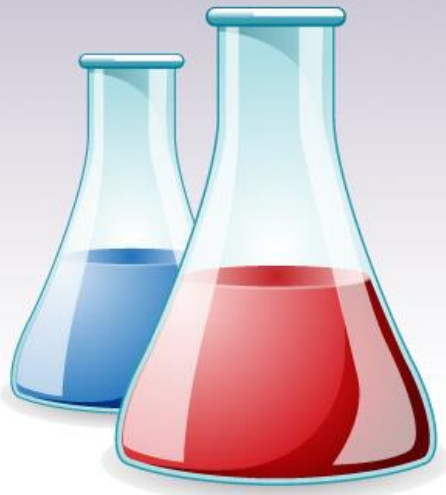
Some empirical relationships between the physicochemical properties and the solubility of therapeutic agents that influence formulation strategies



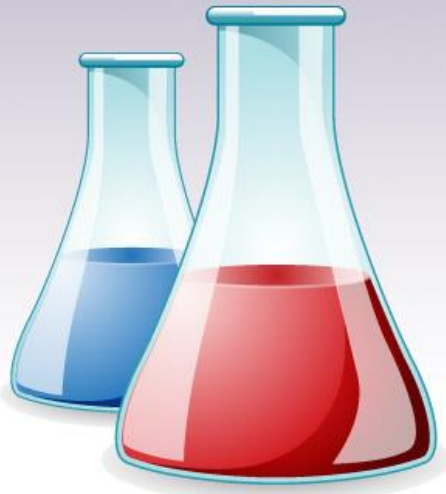
- 1. The solubilities of a chemically related series of therapeutic agent are inversely related to their melting points.
- 2. The solubility of a therapeutic agent is directly affected by both the type of chemical substituent groups and the substituent position.



- 3. The solubilities of therapeutic agents that are either acids or bases (representing the majority of drugs) are pH-dependent.
- The solubility of acids and bases increases as the degree of ionisation increases.



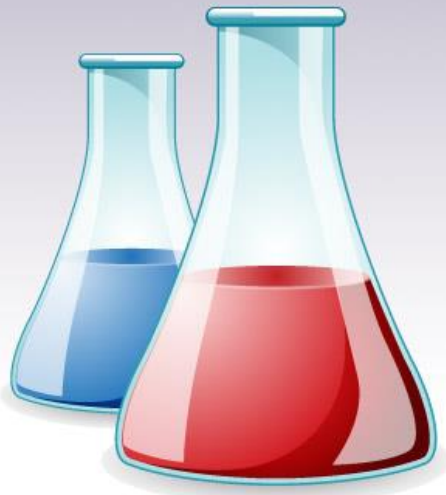
- So, the solubility of acidic compounds increases as the pH of the solution is increased (above the  $pK_a$ ) and the solubility of basic compounds increases as the pH is lowered below the  $pK_a$ .



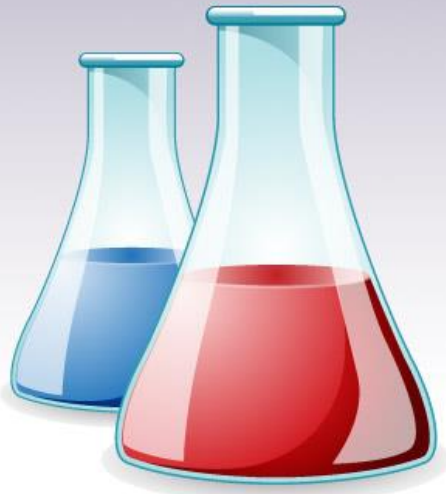


# Formulation methods to enhance/optimize the solubility of therapeutic agents

1. Appropriate selection of drug salt.
2. Optimization of the pH of the formulation.
3. Use of co-solvents.

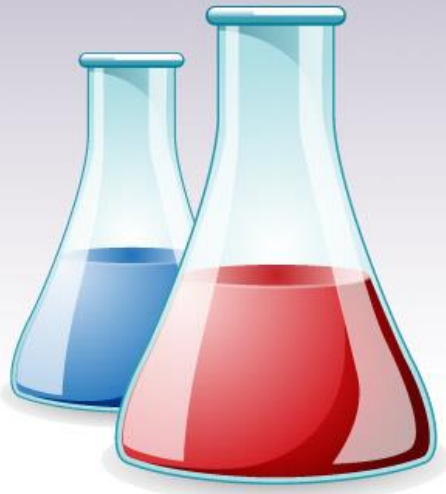


# Excipients used in pharmaceutical solutions for oral administration

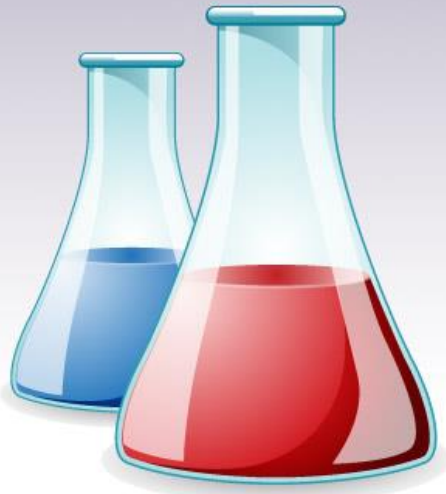


# Excipients

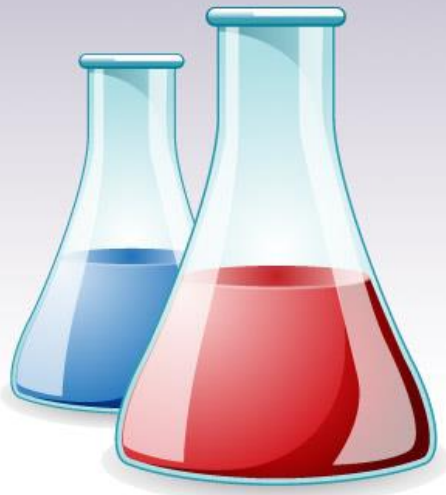
- Are physiologically inert compounds that are included in the formulation to facilitate the administration of the dosage form, e.g. pourability, palatability, to protect the formulation from issues regarding physical and chemical stability and to enhance the solubility of the therapeutic agent.



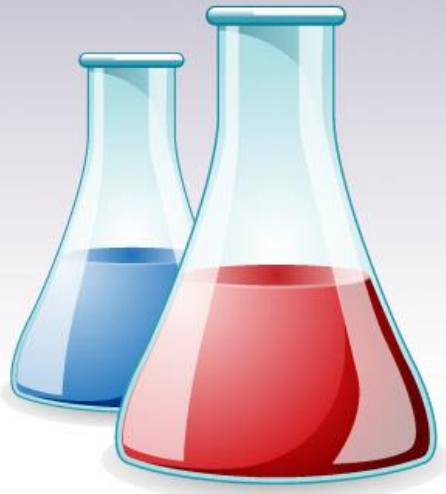
- The vehicle: usually purified water.
- Co-solvents: e.g. propylene glycol, glycerin, alcohol.
- Agents specifically to enhance the solubility of the therapeutic agent in the vehicle, e.g. surface-active agents.



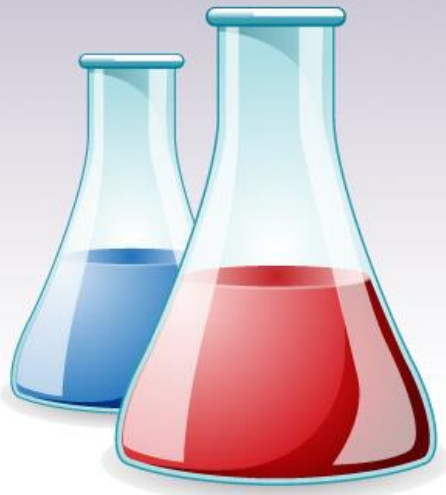
- Preservatives: e.g. parahydroxybenzoate esters (methylhydroxybenzoate and propylhydroxybenzoate), boric acid and borate salts, sorbic acid and sorbate salts, phenolics.
- Sweeteners: e.g. glucose, saccharin, aspartame.



- Rheology (viscosity) modifiers: e.g. hydrophilic polymers (cellulose derivatives, alginic acid, polyvinylpyrrolidone)
- Antioxidants: e.g. sodium formaldehyde sulfoxylate, butylated hydroxyanisole, butylated hydroxytoluene

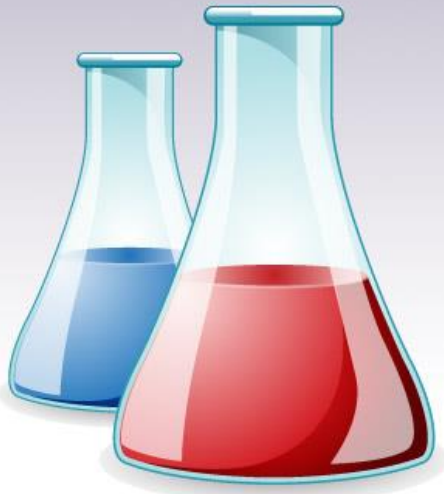


- Buffers to regulate the pH of the formulation, e.g. citrate buffer.
- Colours.
- Flavours.



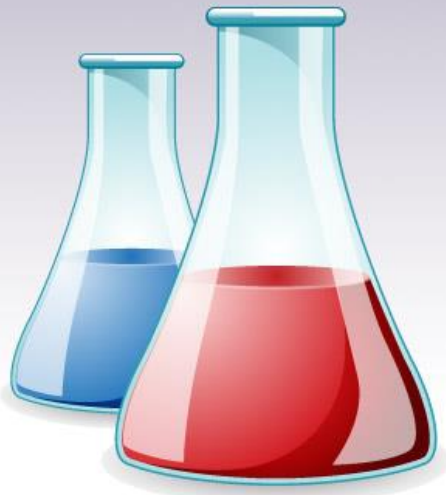
# The vehicle

- The preferred and most commonly used vehicle in solutions for oral administration is Purified Water USP, due to :
  - 1) low cost.
  - 2) low toxicity.





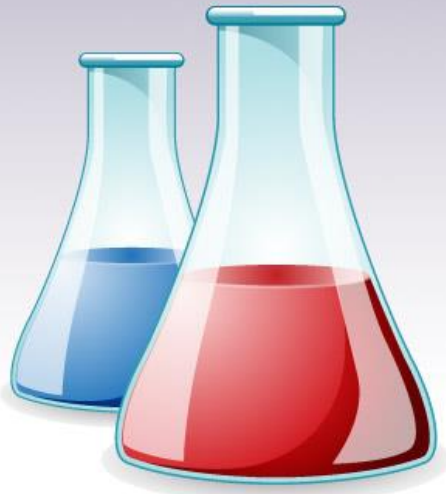
- Classification of solutions according to the vehicle:
- 1. Aqueous solutions.
- 2. Non aqueous solutions.( Give example for them)



# WATER

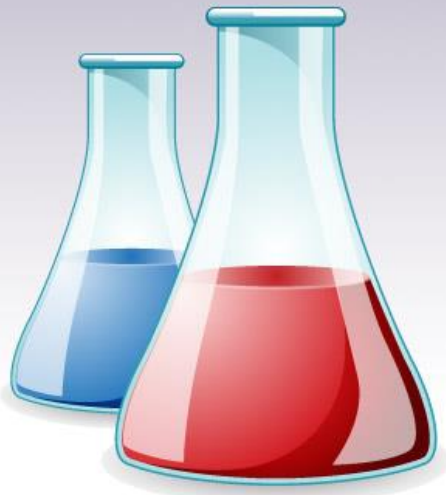
Water is used both as vehicle and as a solvent for the desired flavoring or medicinal ingredients.

Advantages: Tasteless, odourless, lack of pharmacological activity, neutral and very cheap



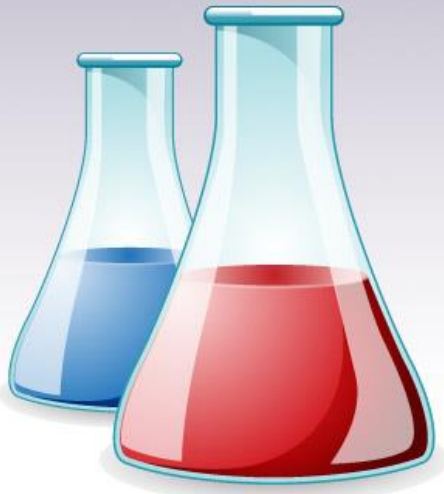
# Tap Water

- It is not permitted to use tap water for the dispensing of pharmaceutical dosage forms due to its possible bacterial contamination and the presence of dissolved salts that destroy the active ingredients or enhance their decomposition.



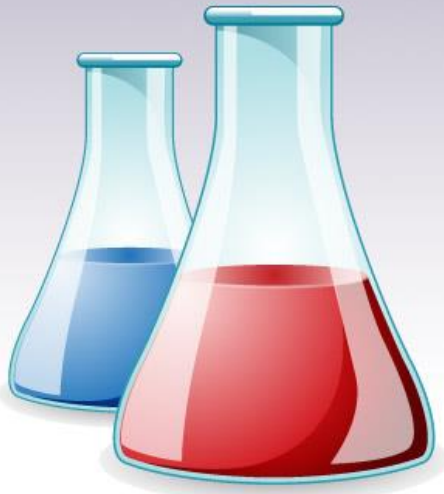
# Freshly Boiled and Cooled Water

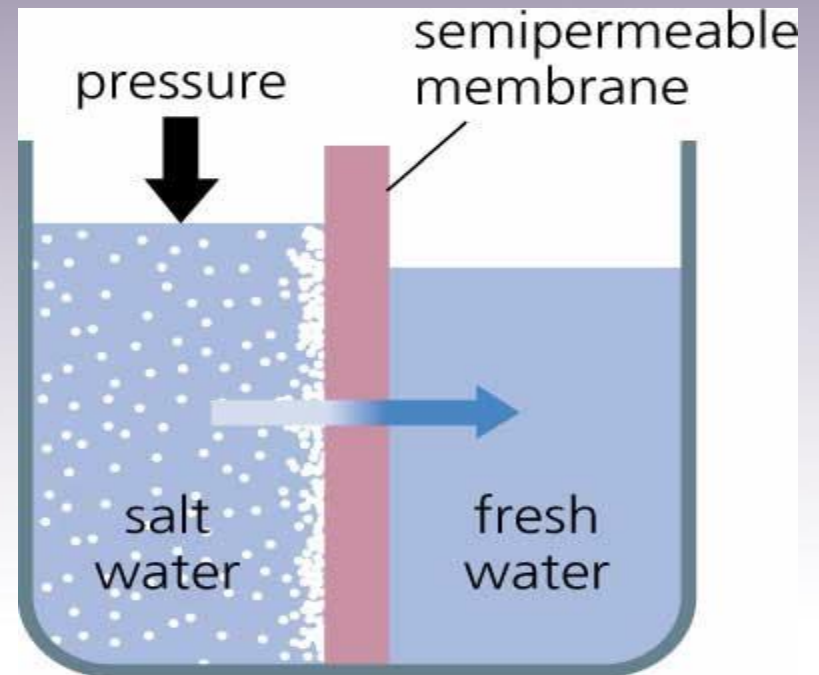
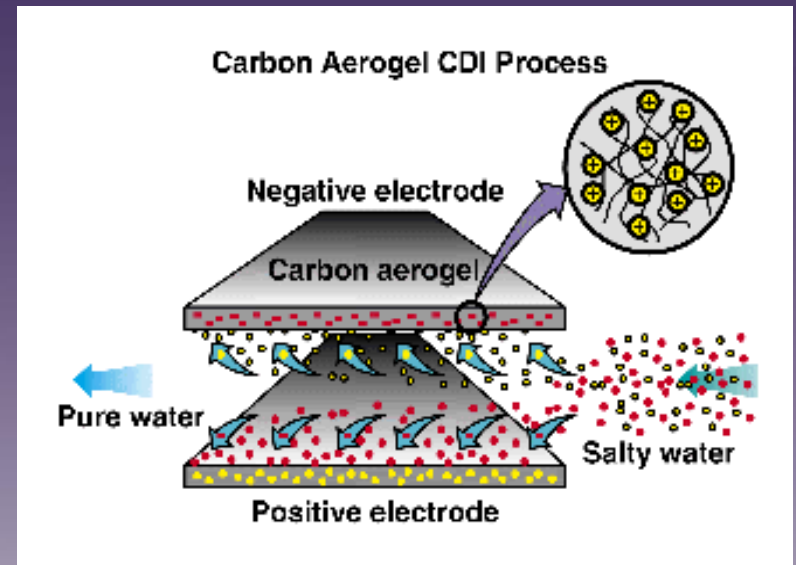
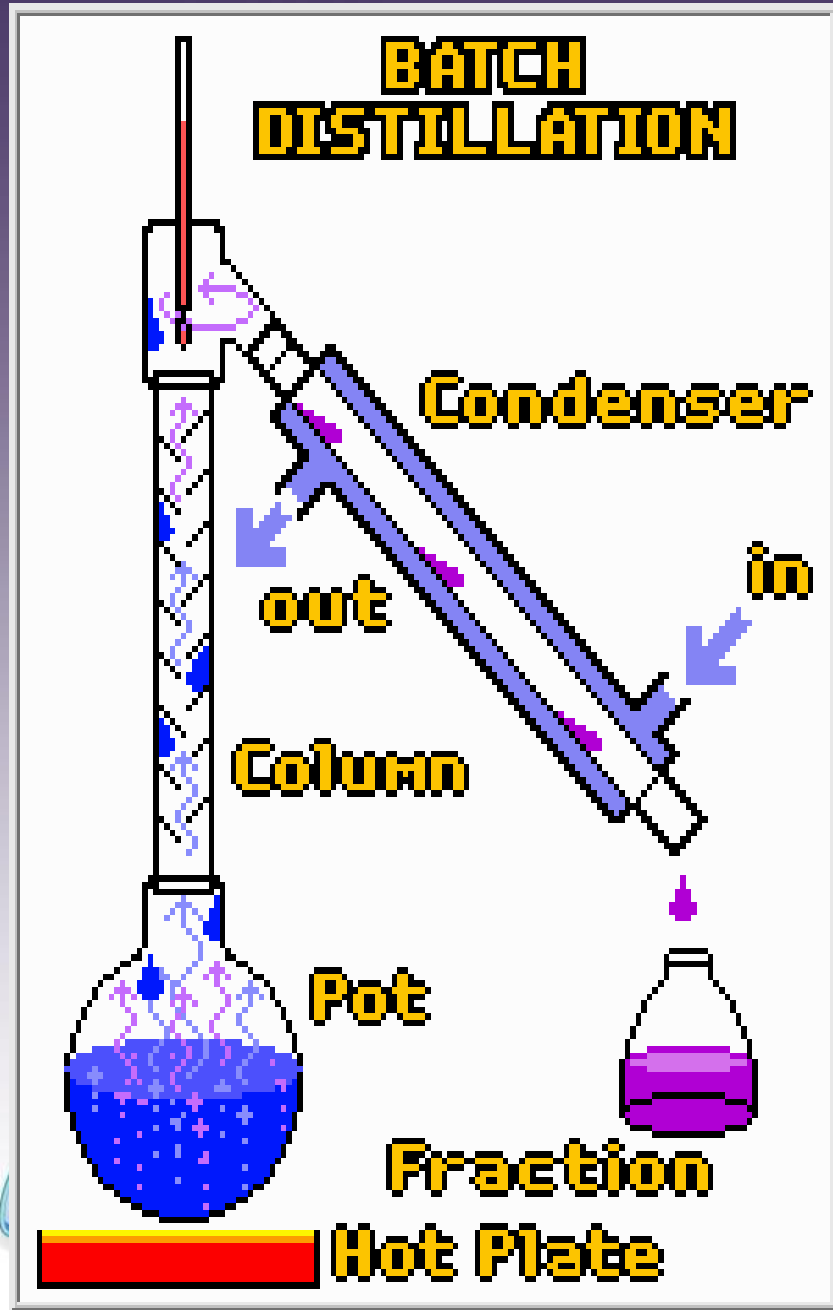
- Boiling is seldom used to destroy vegetative bacteria. But, on storage for long time spores may yield vegetative microorganism.



# Purified Water

- 📄 Must be used for most pharmaceutical operations and in all the tests and assays.
- 📄 Such water is prepared by distillation, deionization or reverse osmosis.

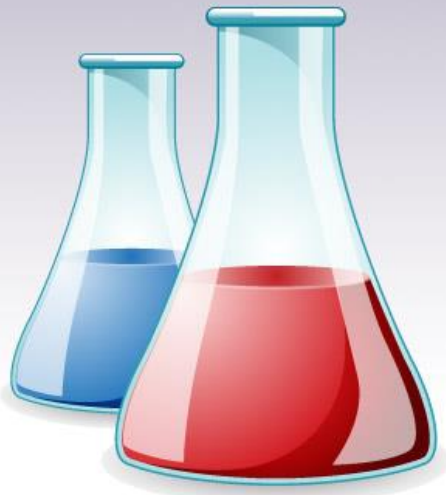




☞ "Hard" waters are those that contain the Ca and Mg cations.

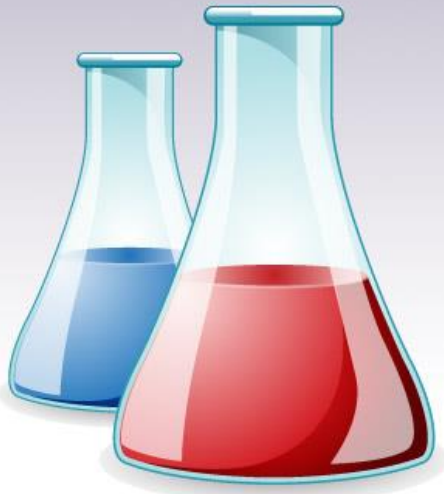
☞ "Alkaline" waters are those that contain bicarbonates as the major impurity.

☞ Ultraviolet energy, heat or filtration (Millipore filtration) can be used to remove or kill the microorganisms present in the water.



# Water for injection

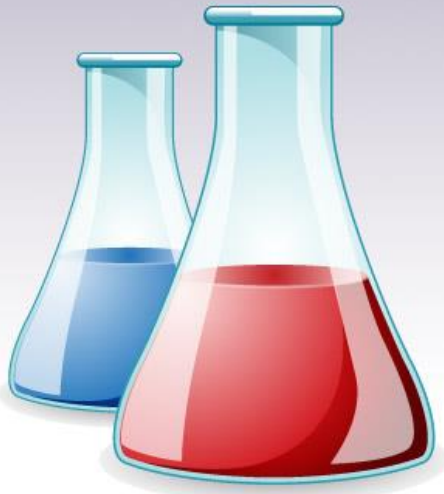
- ☞ Must be used for the formulation of parental solutions.
- ☞ It is obtained by sterilizing pyrogen-free distilled water.





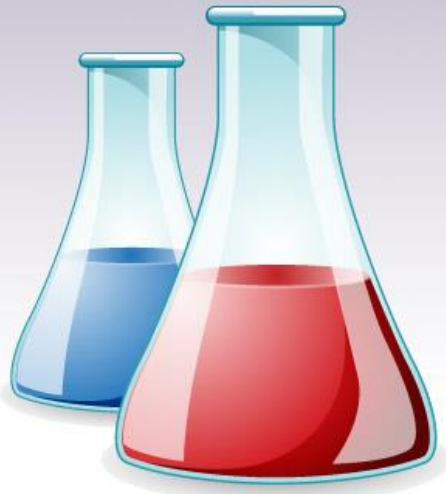
# Co-solvents

- They are employed to increase the solubility of the therapeutic agent within the formulation.



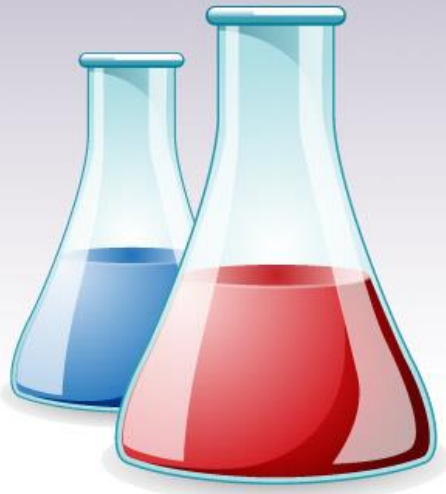
# 1. Glycerol

- Glycerol (also termed glycerin) is an odorless, sweet liquid that is miscible with water and whose co-solvency properties are due to the presence of three hydroxyl groups (termed a triol). It has similar co-solvency properties to ethanol.



## 2. Alcohol USP

- Alcohol USP contains between 94.9 and 96.0% v/v ethyl alcohol (ethanol) and is commonly used as a co-solvent, both as a single co-solvent and with other co-solvents, e.g. glycerol.

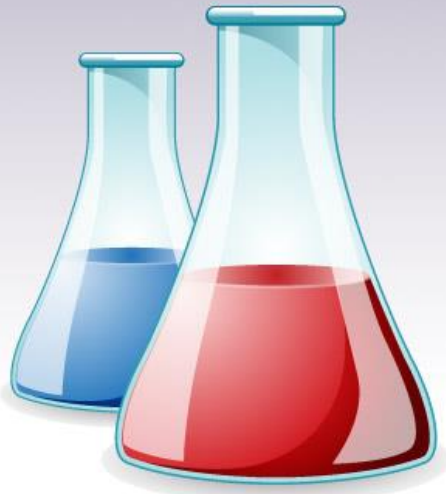


- The known pharmacological and toxicological effects of this co-solvent have compromised the use of alcohol in pharmaceutical preparations.
- As a result there are both labelling requirements for preparations that contain alcohol and upper limits with respect to the concentration of alcohol that may be used in formulations.



# 3. Propylene Glycol USP

- Propylene Glycol USP is an odourless, colourless, viscous liquid diol that contains two hydroxyl groups . It is used in pharmaceutical preparations as a co-solvent, generally as a replacement for glycerin.

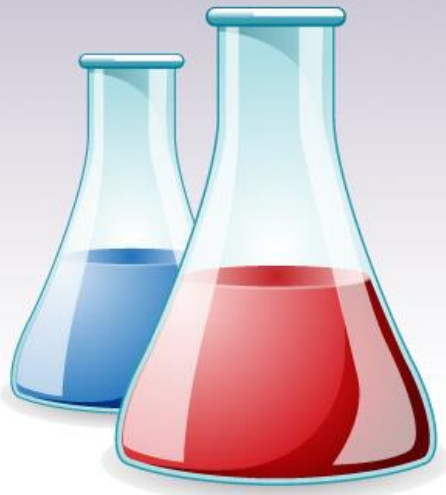


## 4. Poly(ethylene glycol) (PEG)

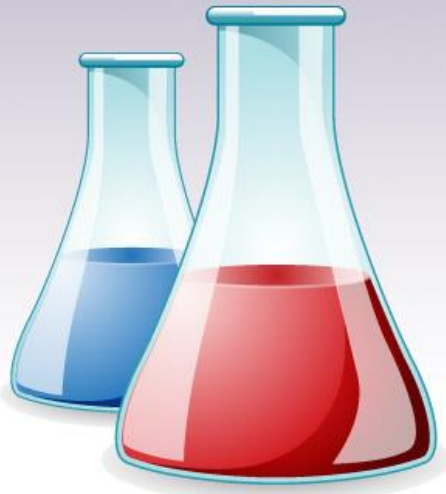
- PEG is a polymer composed of repeating units of the monomer ethylene oxide.
- The physical state of the polymer is dependent on the number of repeat units ( $n$ ) and hence on the molecular weight. Lower-molecular-weight grades (PEG 200, PEG 400) are preferred as co-solvents in pharmaceutical solutions.



# Miscellaneous agents used to enhance the solubility of therapeutic agents



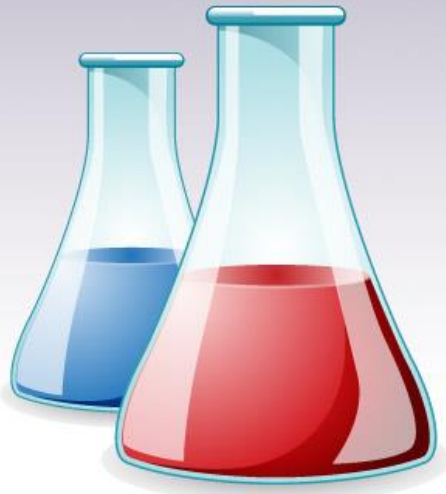
- In addition to the use of co-solvents, other pharmaceutical strategies are available to increase the solubility of therapeutic agents in the vehicle.
- These strategies include the use of surface-active agents and complexation.



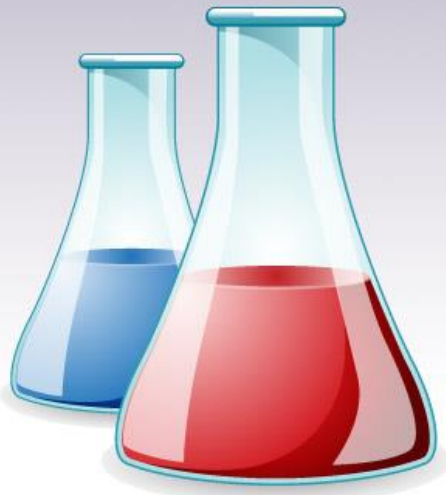


# 1. *Surface-active agents*

- Surface-active agents are chemicals that possess both hydrophilic (water-liking) and hydrophobic (water-disliking) regions.

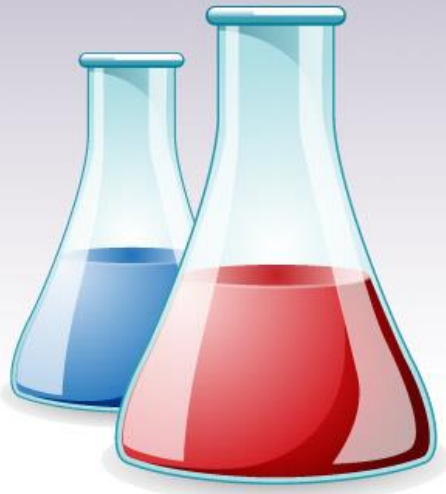


- surface-active agents for the solubilisation of poorly soluble drugs occurs exclusively in the presence of micelles and hence at concentrations of surface-active agents in excess of the CMC.

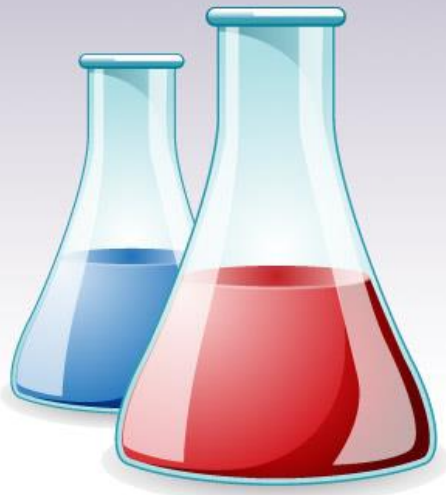


## 2. Complexation

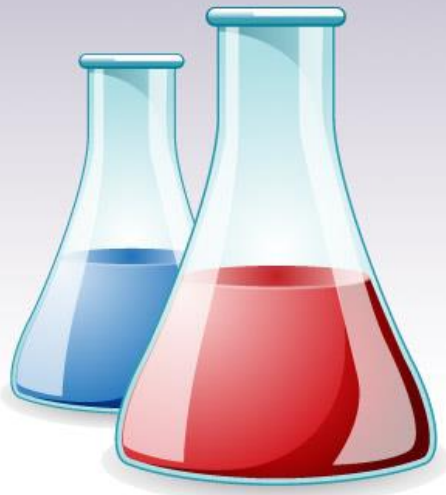
- Complexation refers to the interaction of a poorly soluble therapeutic agent with an organic molecule, e.g. surface-active agents, hydrophilic polymers to generate a soluble intermolecular complex.



- The high molecular weight of the drug–polymer complex would prevent drug absorption across biological membranes.
- So, the ability of the complex to dissociate following administration is very important.

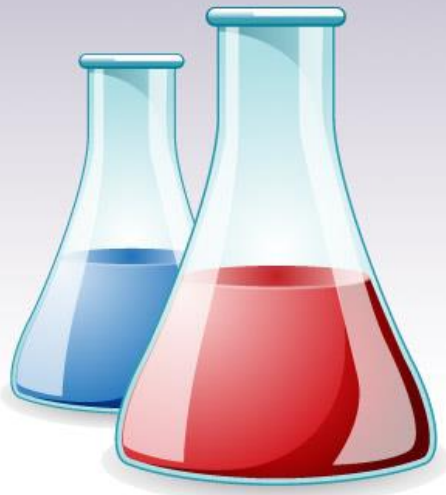


# Other Common excipients in pharmaceutical solutions

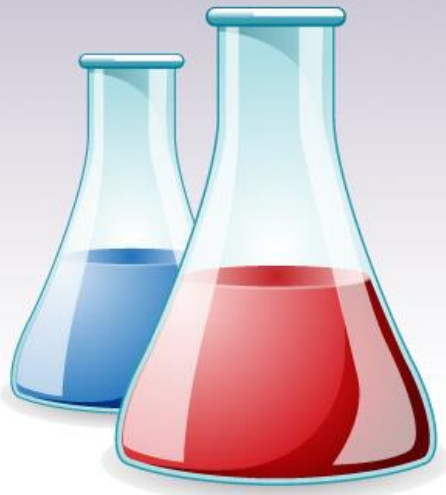


# 1. Buffers

- 1. to maintain the solubility of the therapeutic agent in the formulated product.
- 2. to enhance the stability of products in which the chemical stability of the active agent is pH-dependent.

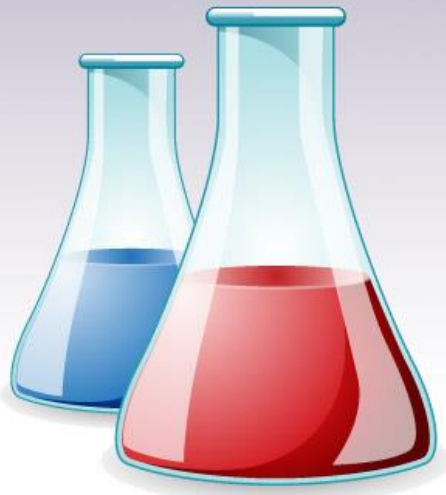


- The concentration of buffer salts employed in the formulation should be selected to offer sufficient control of the pH of the formulation but yet should be overcome by biological fluids following administration, especially for parenteral formulations to ensure that there is no irritation or damage following injection.



## 2. Sweetening agents

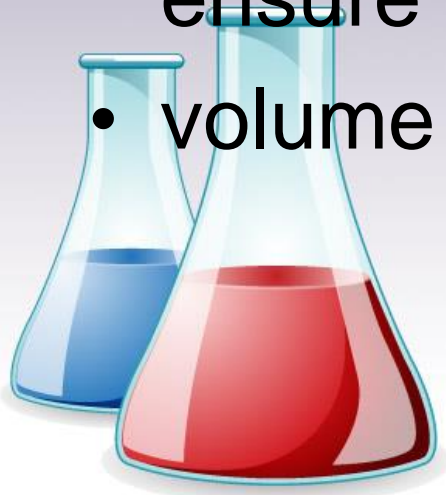
- Are employed in liquid formulations designed for oral administration specifically to increase the palatability of the therapeutic agent.



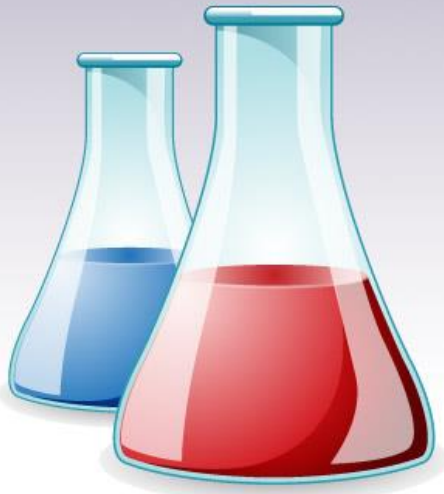


# 3. Viscosity-enhancing agents

- The administration of oral solutions is usually performed using a syringe, a small-metered cup or a traditional 5-ml spoon. The viscosity of the formulation must be sufficiently controlled in order to ensure the accurate measurement of the
- volume to be dispensed.

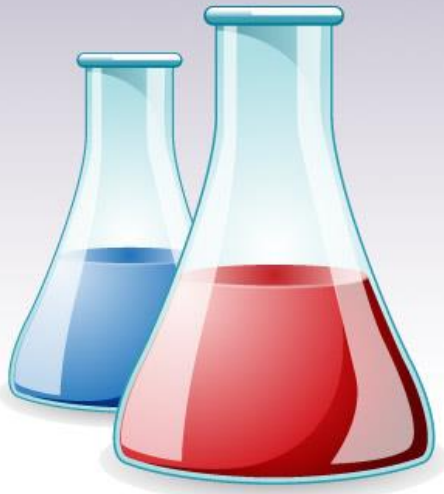


Furthermore, increasing the viscosity of some formulations may increase the palatability.



# 4. Anti-oxidants

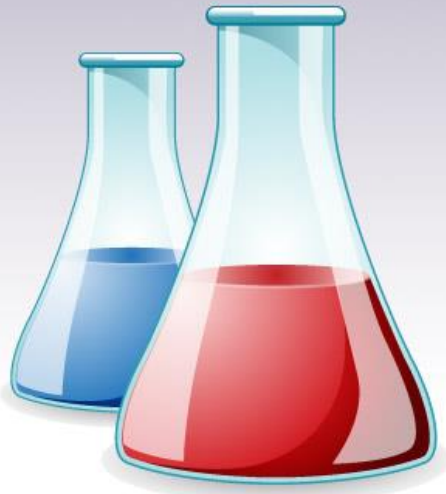
- Typically antioxidants are molecules that are redox systems which exhibit higher oxidative potential than the therapeutic agent or, alternatively, are compounds that inhibit free radical-induced drug decomposition.



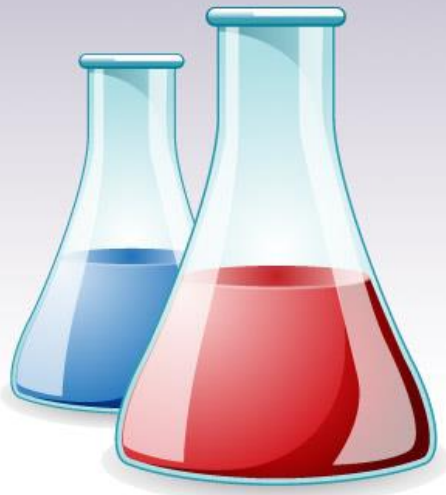
# 5. Preservatives

Preservatives should possess a broad spectrum of antimicrobial activity encompassing Gram-positive and Gram-negative bacteria and fungi:

- be chemically and physically stable over the shelf-life of the product
- have low toxicity.

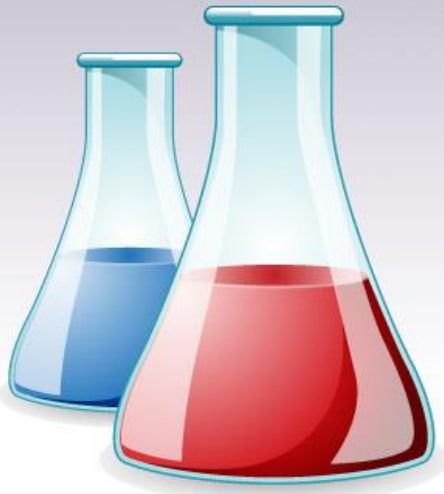


# 6. Flavours and colourants (For students)



# Pharmaceutical solutions

- 1. Aqueous solutions
- 2. Sweet &/ or viscid solutions
- 3. Non-aqueous solutions



# Pharmaceutical Solutions

## Aqueous

1. Douches
2. Enemas
3. Gargles
4. Mouthwashes
5. Nasal washes
6. Juices
7. Sprays
8. Otic solutions
9. Inhalations



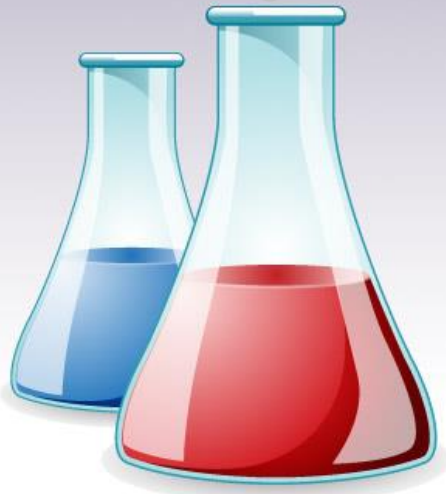
## Sweet &/or Viscid

1. Syrups
2. Honeys
3. Mucilages
4. Jellies

## Nonaqueous

1. Elixirs
2. Spirits
3. Collodions
4. Glycerins
5. Liniments
6. Oleo Vitamin

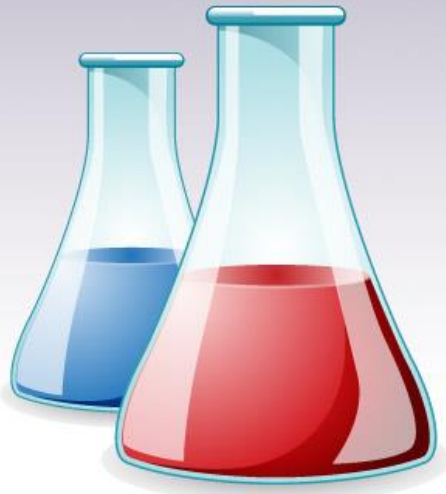
# **Sweet &/or Viscid Pharmaceutical Solutions**



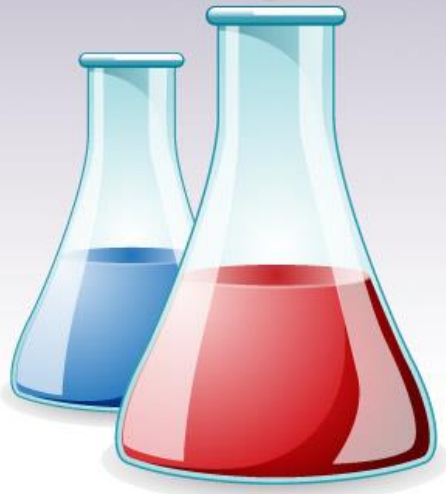


# Jellys

- Preparations having a jelly-like consistency. They are prepared also from gums.
- Are used as lubricants for surgical gloves and catheters
- Lidocaine HCl Jelly USP is used as a topical anaesthetic.



# **Non-Aqueous Pharmaceutical Solutions**



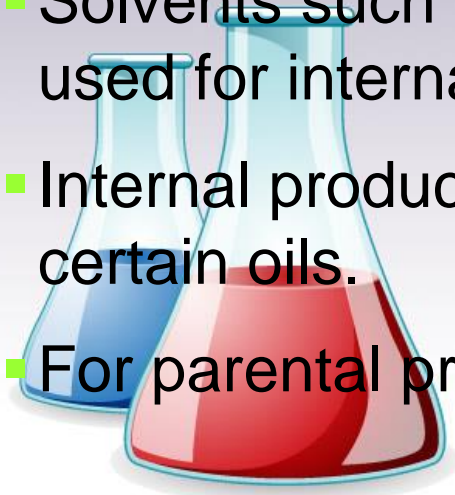
# Advantages

- If the drug is not completely soluble or unstable in aqueous medium it may be necessary to use an alternative non-aqueous solvent.
- Oily solutions of drugs are often used for depot therapy e.g. in muscles

## It is essential to test:

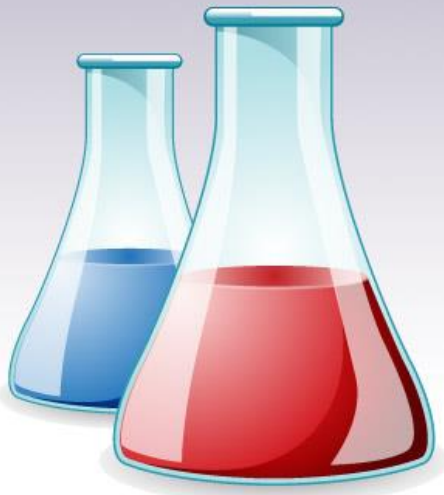
toxicity – irritancy – flammability – cost – stability and compatibility of solvents to avoid problems

- Solvents such as acetone, benzene and petroleum ether are not used for internal products.
- Internal products may contain ethanol, glycerol, propylene glycol certain oils.
- For parental products the choice is very limited



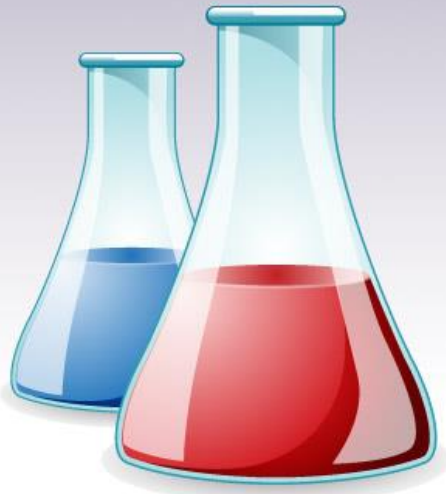
# Douches

- ★ Douche is an aqueous solution, which is directed against a part or into a cavity of the body.
- ★ It functions as a cleansing or antiseptic agent.



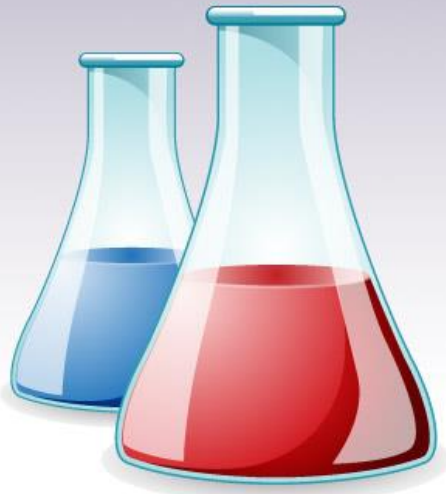
★ Eye douches are used to remove foreign particles and discharges from the eyes.

★ Pharyngeal douches are used to prepare the interior of the throat for an operation and to cleanse it in supportive conditions.

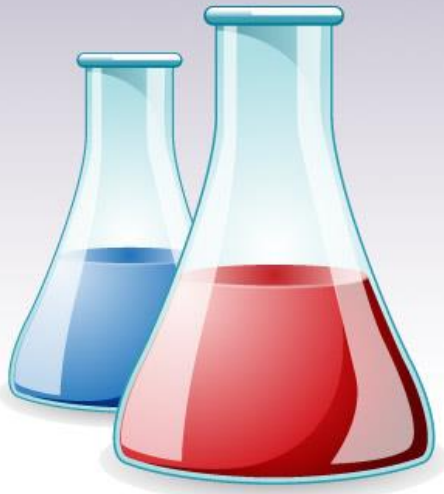


★ Similarly, there are nasal and vaginal douches.

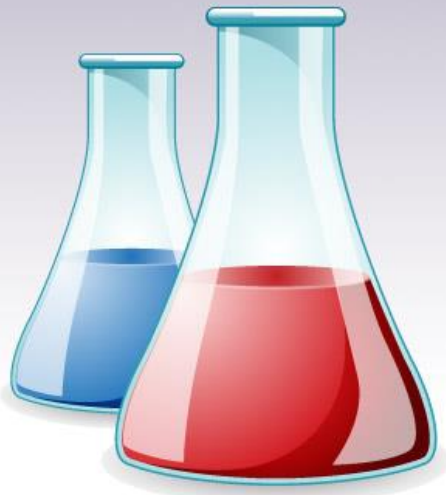
★ Douches most frequently dispensed in the form of a powder with directions for dissolving in a specified quantity of water.



# Oral solutions

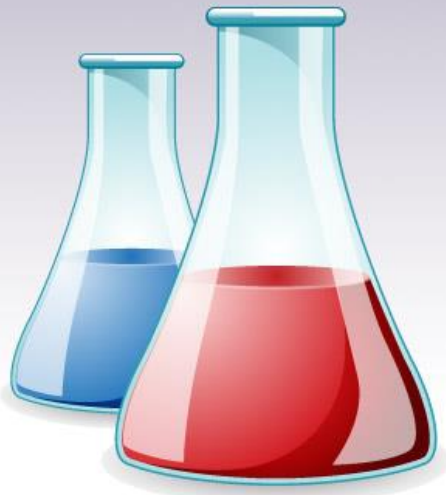


- Oral solutions are clear Liquid preparations for oral use containing one or more active ingredients dissolved in a suitable vehicle.





# Syrups



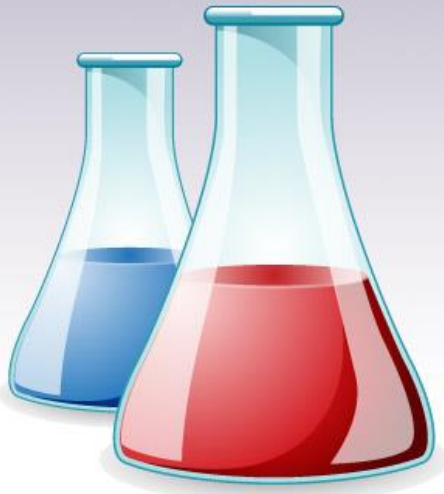
It is a concentrated aqueous solution of a sugar, usually sucrose.(Know about the percent! )

Flavored syrups are a convenient form of

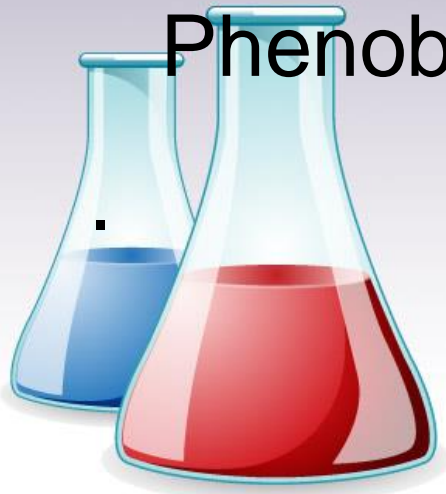
masking disagreeable tastes.



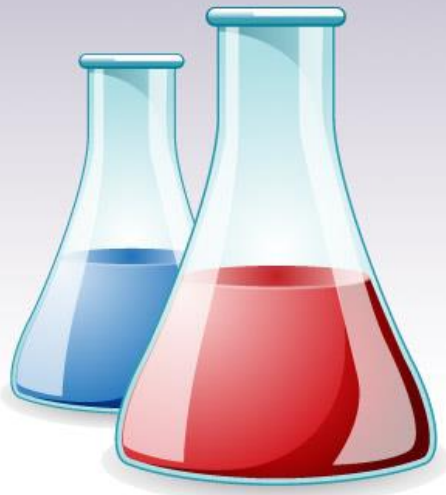
# Elixirs



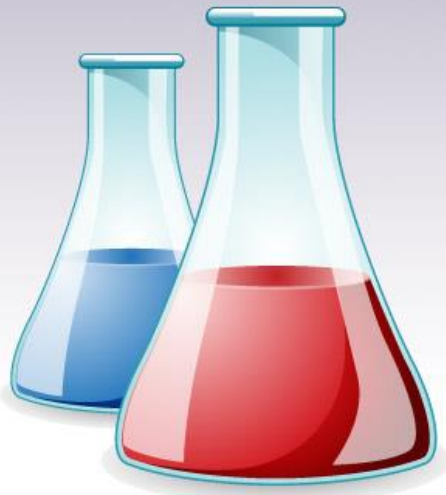
- Are clear, pleasantly flavored, sweetened hydroalcoholic liquids intended for oral use.
- They are used as flavors and vehicles e.g. Dexamethasone Elixir USP and Phenobarbital Elixir USP.



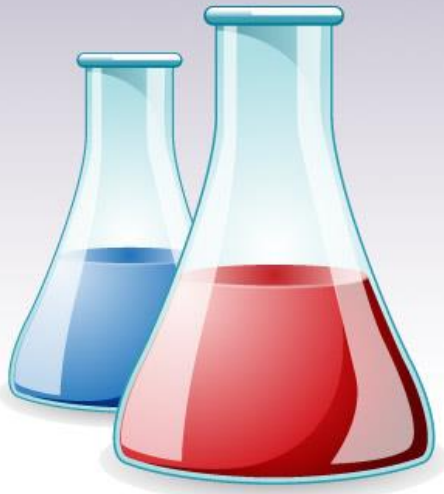
- The main ingredients in elixirs are ethanol and water but glycerin, sorbitol, propylene glycol, flavoring agents, preservatives, and syrups are often used in the preparation of the final product.



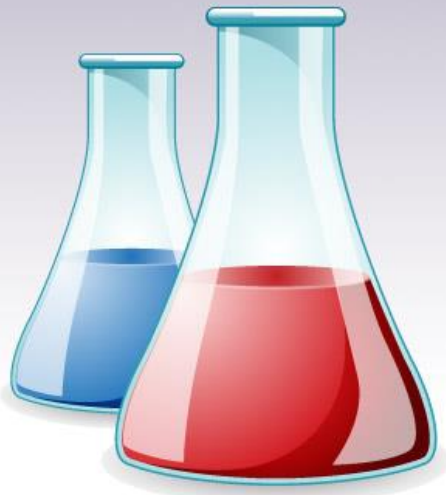
- Elixirs contain ethyl alcohol, however, the alcoholic content will vary greatly, from elixir containing only a small quantity to those that contain a considerable portion as a necessary aid to solubility .



# Linctuses

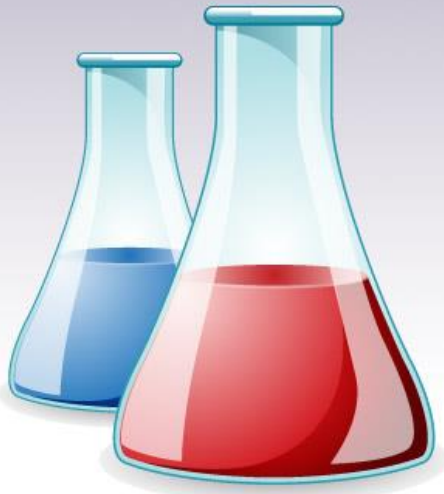


- Linctuses are viscous, liquid oral preparations that are usually prescribed for the relief of cough.
- They usually contain a high proportion of syrup and glycerol which have a demulcent effect on the membranes of the throat.

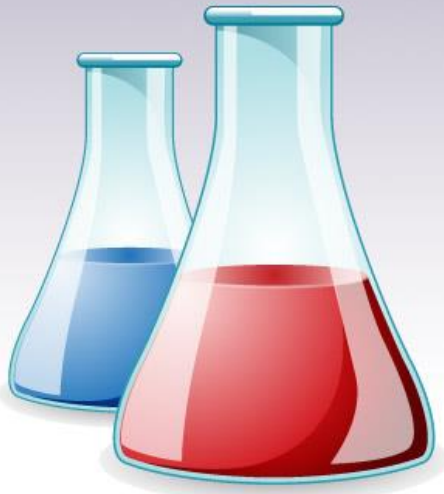




- The dose volume is small (5ml) and, to prolong the demulcent action, they should be taken undiluted.



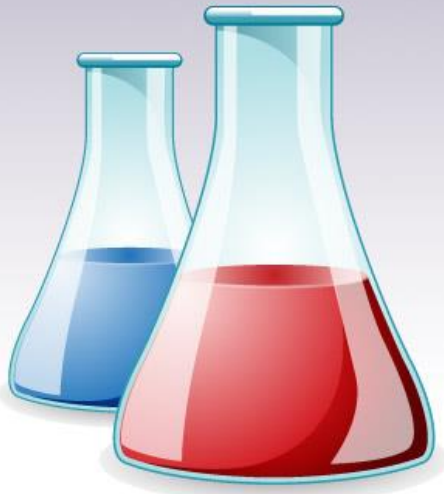
# Oral drops



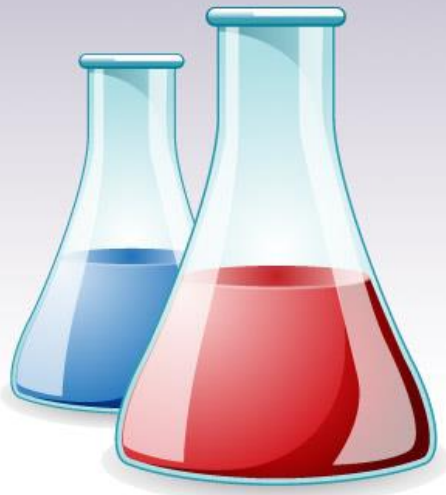
- Oral drops are Liquid preparations for oral use that are intended to be administered in small volumes with the aid of a suitable measuring device. They may be solutions, suspensions or emulsions.



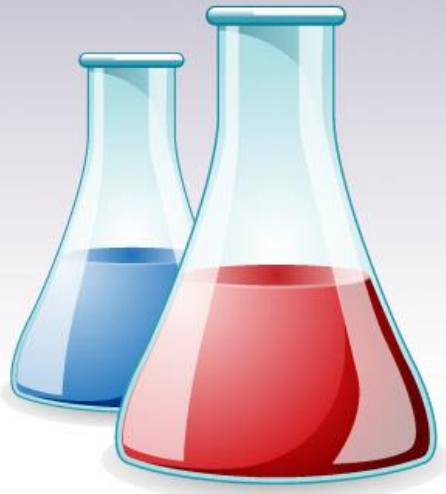
# Gargles



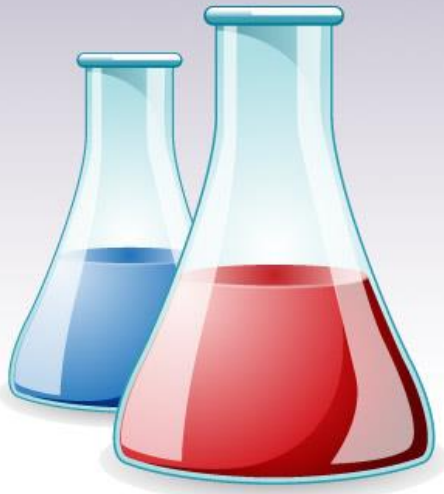
- They are aqueous solutions used in the prevention or treatment of throat infections.



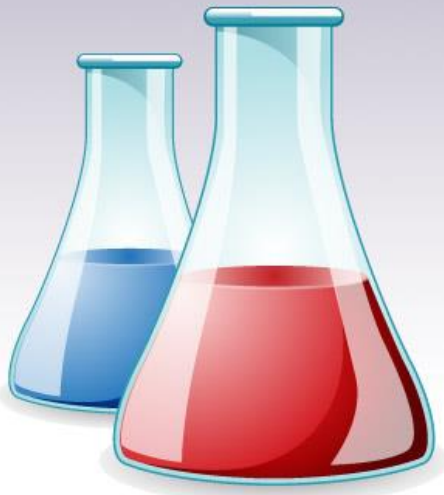
- Usually they are prepared in a concentrated solution with directions for the patient to dilute with warm water before use



# Mouthwashes

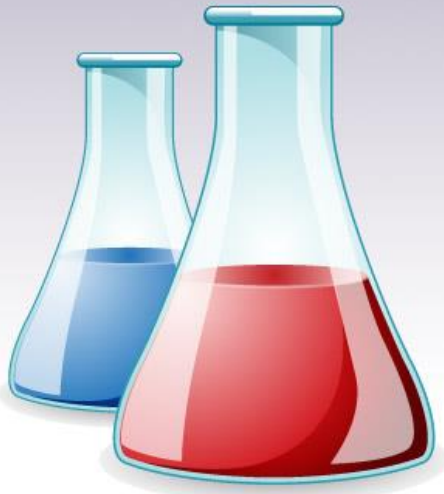


- These are similar to gargles but are used for oral hygiene and to treat infections of the mouth.

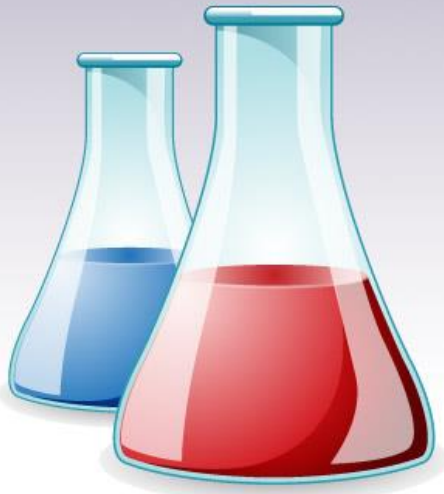




# Liniments

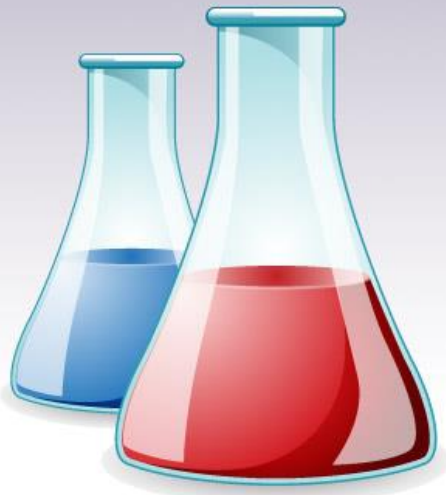


Liniments are fluid, semi-fluid or, occasionally, semi-solid preparations intended for application to the skin.

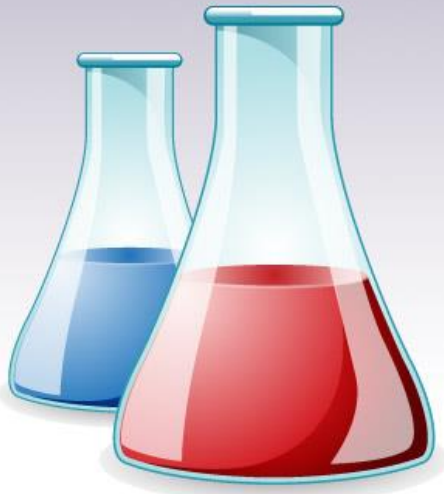


They may be alcoholic or oily solutions or emulsions.

- Most are massaged into the skin (e.g. counter-irritant).
- Liniments should not be applied to broken skin.



# Collodion



- **Collodion** is a flammable, syrupy solution of pyroxylin (a.k.a. "nitrocellulose", "cellulose nitrate", "flash paper", and "gun cotton") in ether and alcohol.



- There are two basic types:

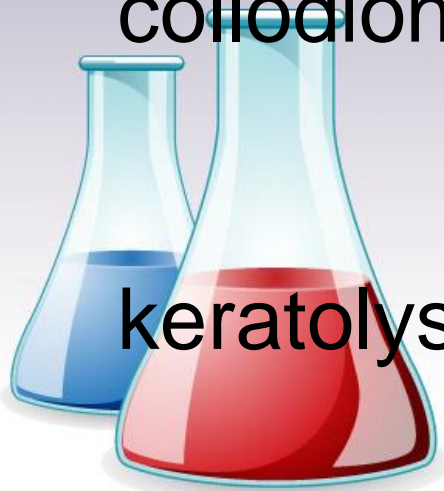
1. The flexible type: It is often used as a surgical dressing or to hold dressings in place. When painted on the skin, collodion dries to form a flexible [nitrocellulose](#) film. While it is initially colorless, it discolors over time.

2. Non-flexible collodion: It is often used in theatrical make-up.



- Compound Wart Remover consists of acetic acid and salicylic acid in an acetone

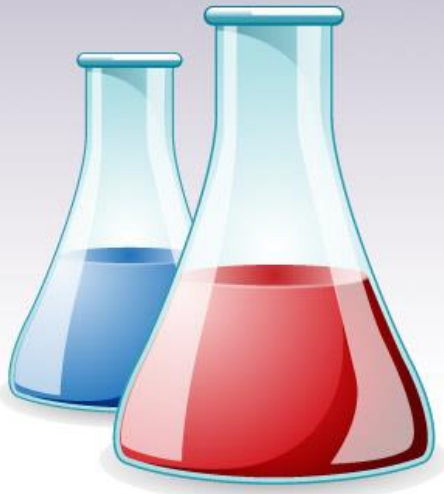
collodion base used in Treatment of warts by



keratolysis.



# Paints





- Paints are liquids for application to the skin or mucous membranes.

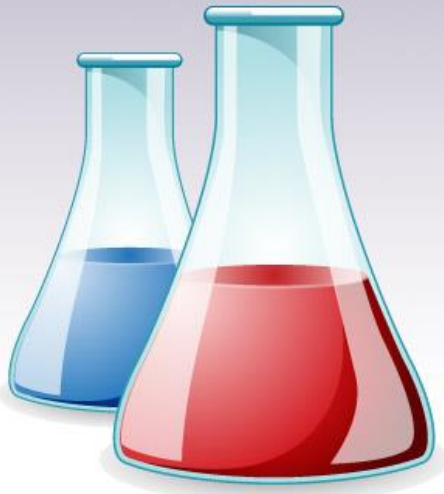
- Skin paints contain volatile solvent that evaporates quickly to leave a dry resinous film of medicament.



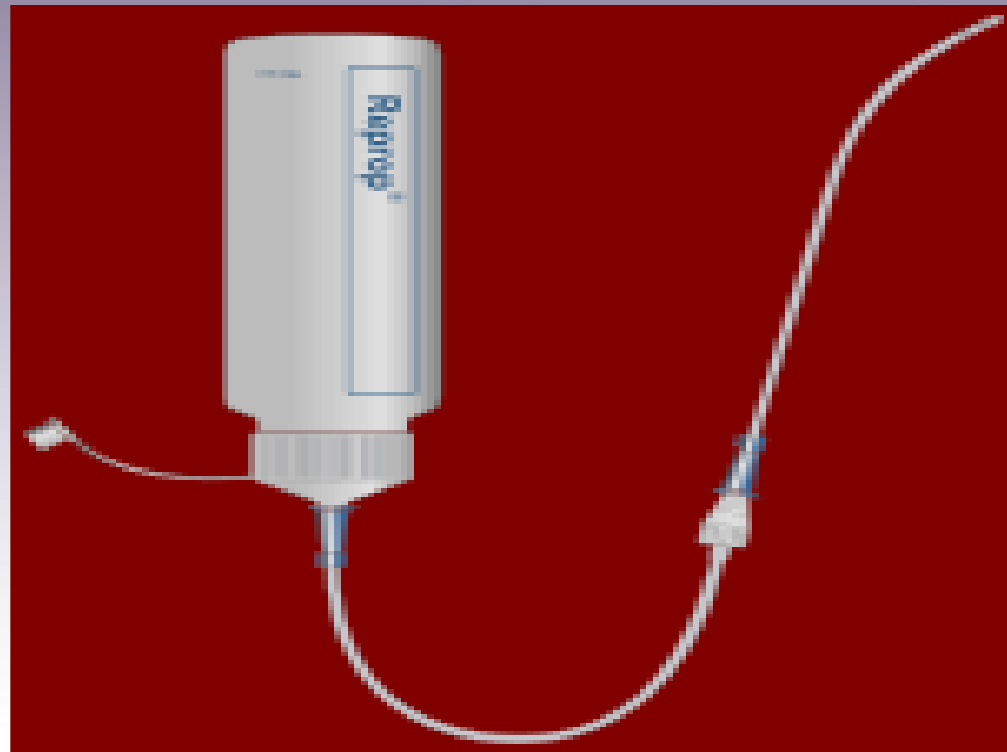
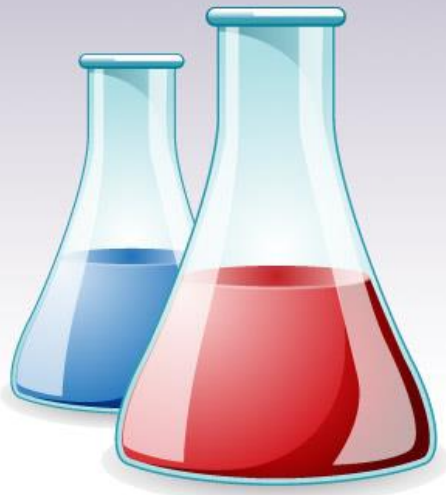
- Throat paints are more viscous due to a high content of glycerol, designed to prolong contact of the medicament with the affected site.



# Enema

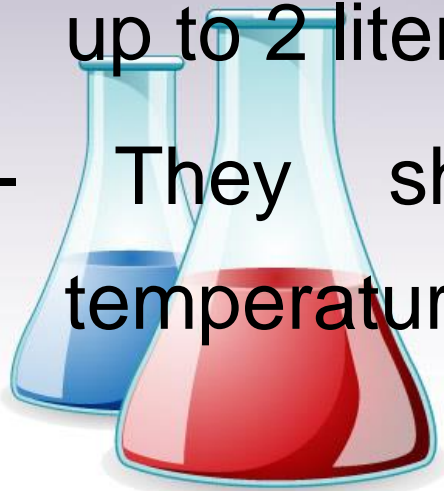


- An **enema** is the procedure of introducing liquids into the rectum and colon via the anus.



## Types of enema:

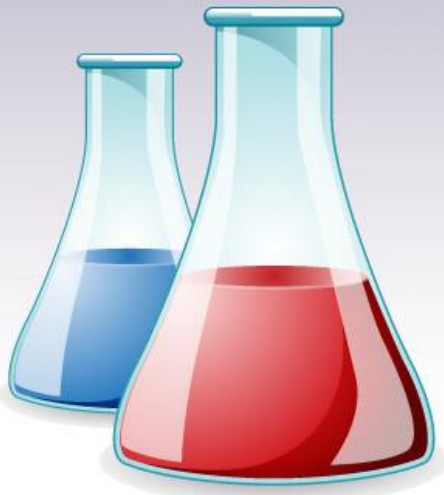
- 1- Evacuant enema: used as a bowel stimulant to treat constipation. E.g. soft soap enema &  $Mgso_4$  enema
- The volume of evacuant enemas may reach up to 2 liters.
- They should be warmed to body temperature before administration.



## 2- Retention enema:

- Their volume does not exceed 100 ml.
- No warming needed.
- May exert:

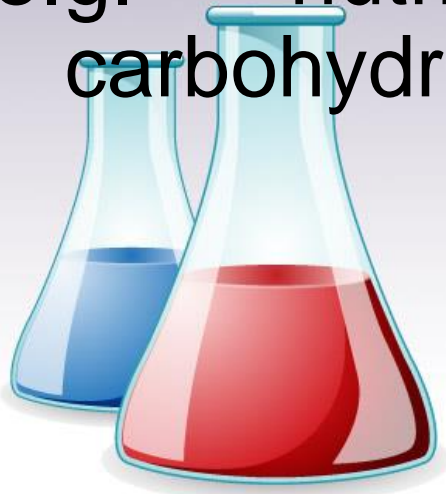
*A- Local effect:* e.g. a barium enema is used as a contrast substance in the radiological imaging of the bowel.



## *B- Systemic effect:*

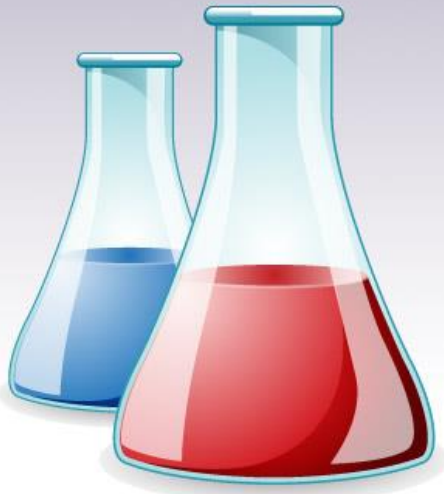
e.g. the administration of substances into the bloodstream. This may be done in situations where it is impossible to deliver a medication by mouth, such as emesis

e.g. nutrient enema which contains carbohydrates, vitamins & minerals.



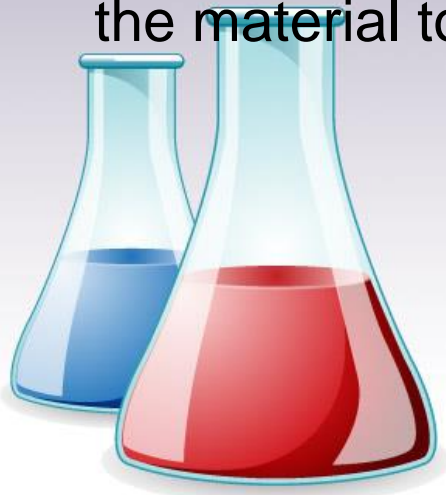
# Parenteral solutions

## 1. Injections





- **An injection** is an infusion method of putting liquid into the body, usually with a hollow needle and a syringe which is pierced through the skin to a sufficient depth for the material to be forced into the body.



There are several methods of injection, including:

1-An intravenous injection:

It is a liquid administered directly into the bloodstream via

a vein.



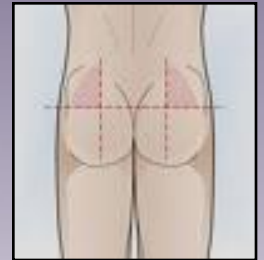
It is advantageous when a rapid onset



- **2- Intramuscular injection:**

- It is the injection of a substance directly into a muscle.

- Many vaccines are administered intramuscularly.



- Depending on the chemical properties of the drug, the medication may either be absorbed fairly quickly or more gradually



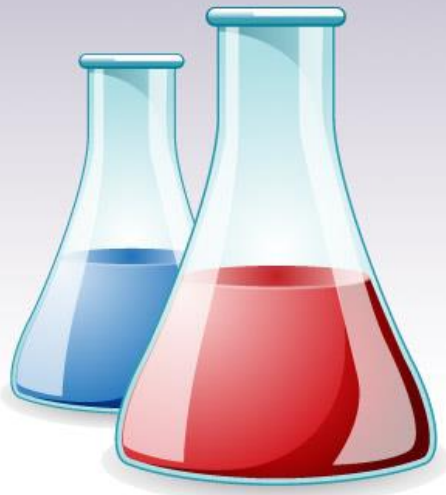
- **3- Subcutaneous injection:**

- **Subcutaneous** injections are given by injecting a fluid into the subcutis, the layer of skin directly below the dermis and epidermis.

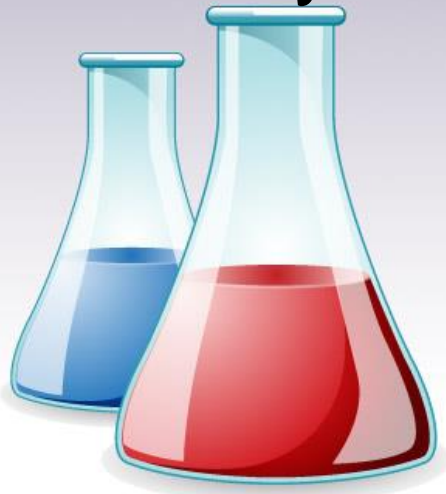
- Subcutaneous injections are highly effective in administering vaccines and such medications as insulin.



# Infusions

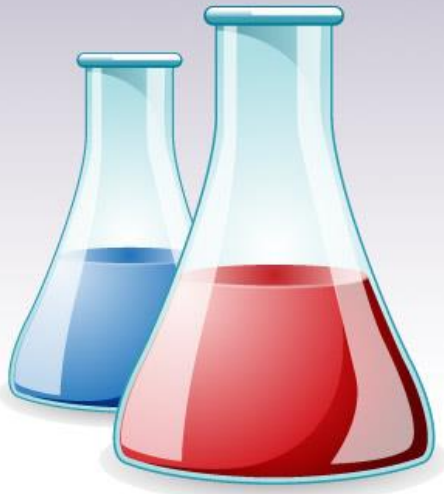


- For large volumes e.g. 500 ml and more.
- Only i.v. route can bear these volumes.

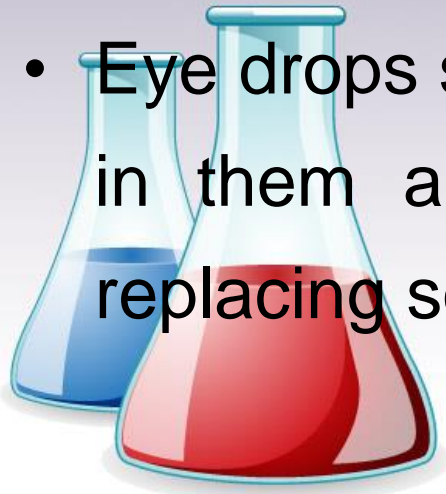


# Ophthalmic dosage forms

Eye drops



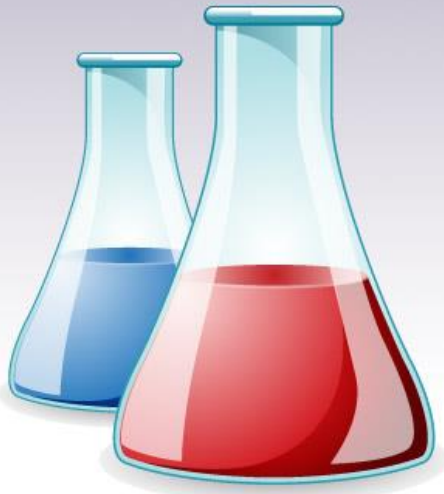
- **Eye drops** are sterile saline-containing drops used as a vehicle to administer medication in the eye.
- Depending on the condition being treated, they may contain steroids, antihistamines or topical anesthetics ,...etc.
- Eye drops sometimes do not have medications in them and are only lubricating and tear-replacing solutions.





# Otic dosage forms

Ear drops



- Ear drops are solutions, (could be suspensions or emulsions) of drugs that are instilled into the ear with a dropper.

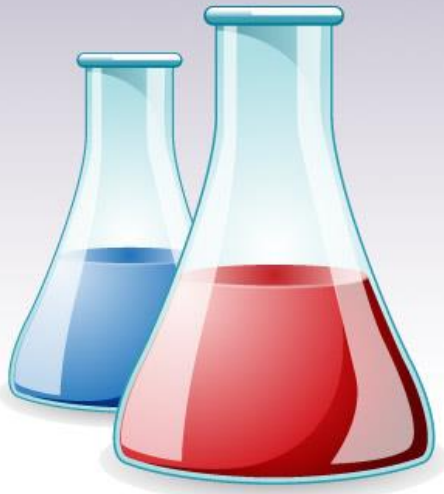


- It is used to treat or prevent ear infections, especially infections of the outer ear and ear

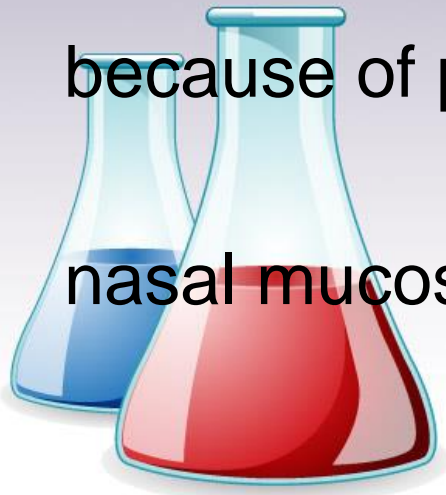


# Nasal dosage forms

Nasal drops and sprays



- Drugs in solution may be instilled into the nose from a dropper or from a plastic squeeze bottle.
- The use of oily nasal drops should be avoided because of possible damage to the cilia of the nasal mucosa.

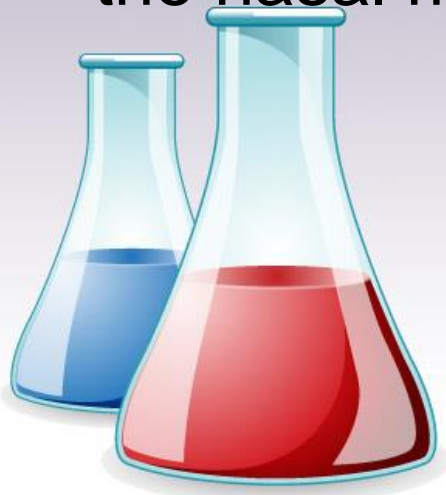


The drug may have a local effect, e.g.

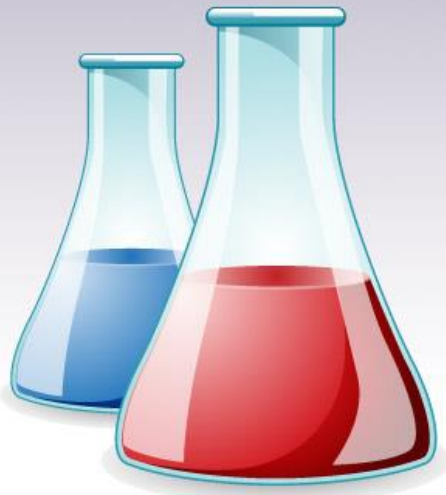
antihistamine, decongestant.

Alternatively the drug may be absorbed through

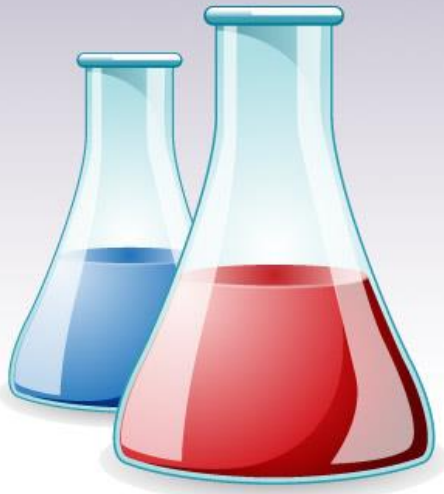
the nasal mucosa to exert a systemic effect.



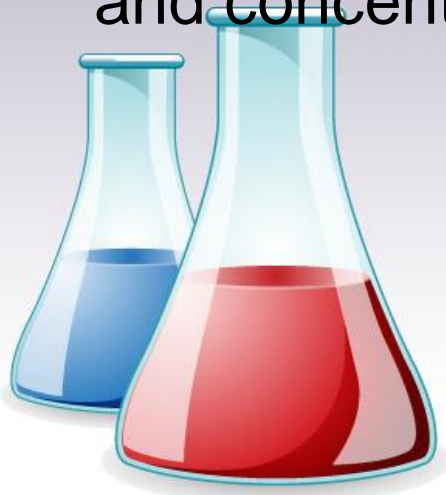
# Intermediate products used in compounding



# Extracts

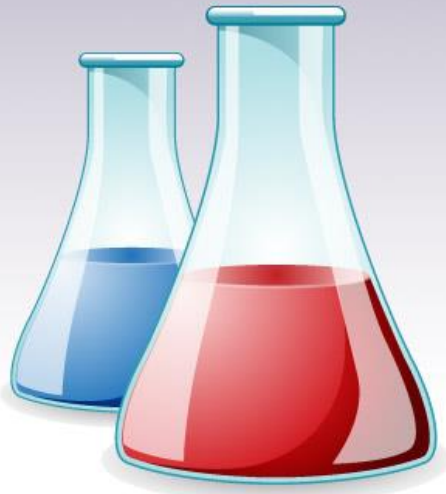


- These are concentrated preparations containing the active principals of vegetable or animal drugs which have been extracted with suitable solvents and concentrated to form liquid, soft or dry extract.

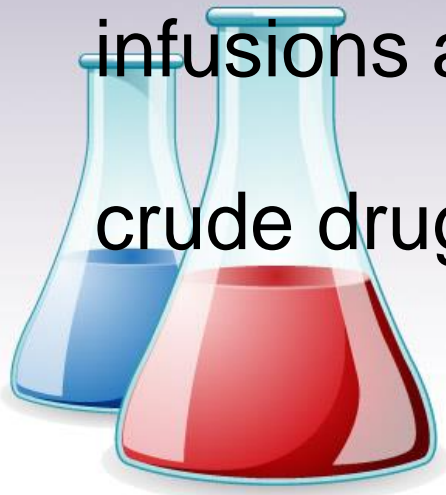




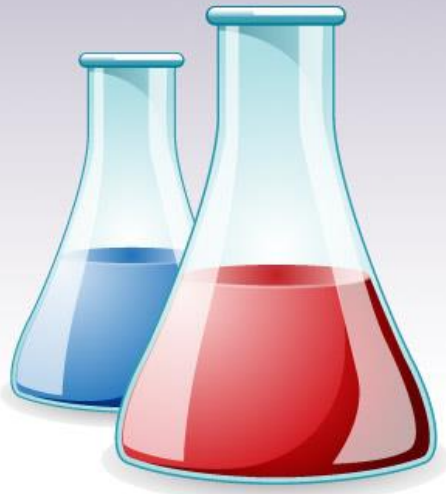
# Infusions



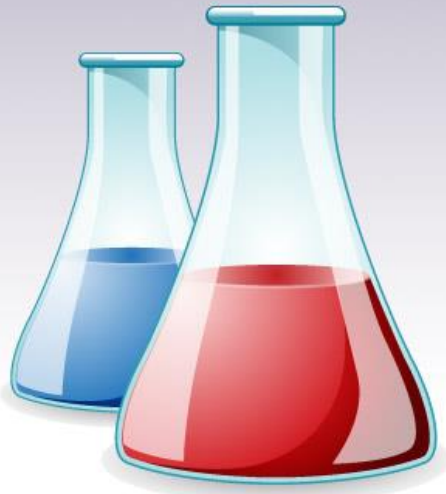
- These are dilute solutions containing the readily soluble constituents of crude drugs and prepared by diluting 1 part of concentrated infusion with 10 parts of water. Concentrated infusions are prepared by cold extraction of crude drugs with 25% ethanol.



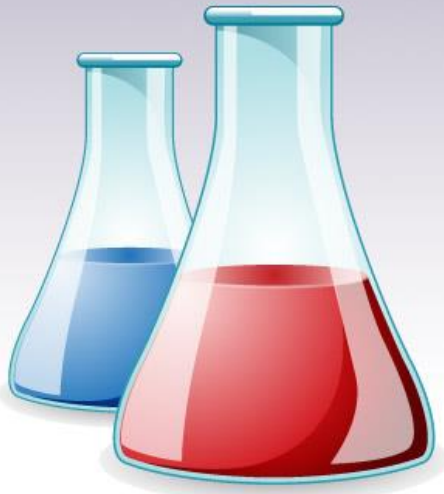
# Tinctures



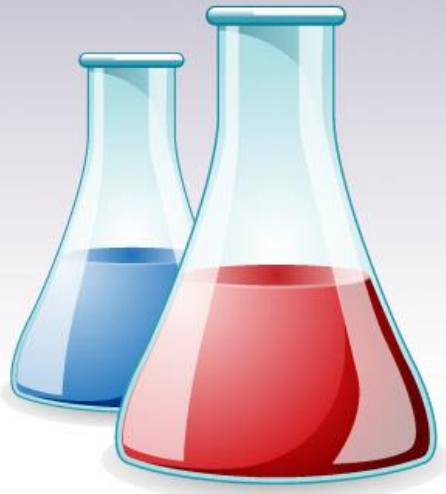
- These are alcoholic preparations containing the active principals of vegetable drugs. They are relatively weak compared to extracts.



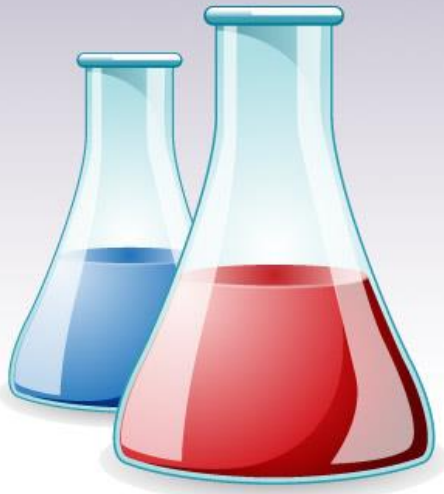
# Glycerins



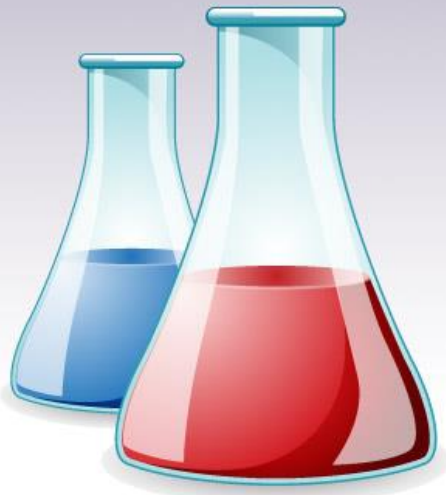
- These are solutions of medicaments in glycerol with or without the addition of water.



# Oxymels

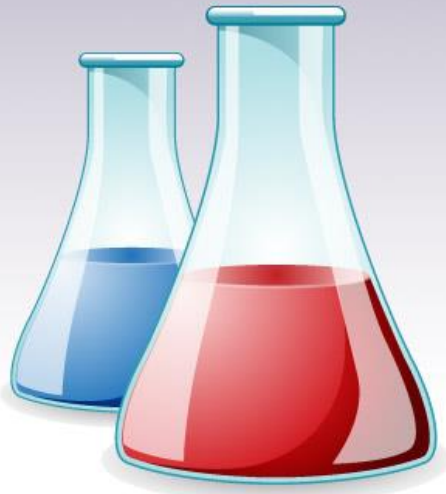


- These are preparations in which the vehicle is a mixture of acetic acid and honey.





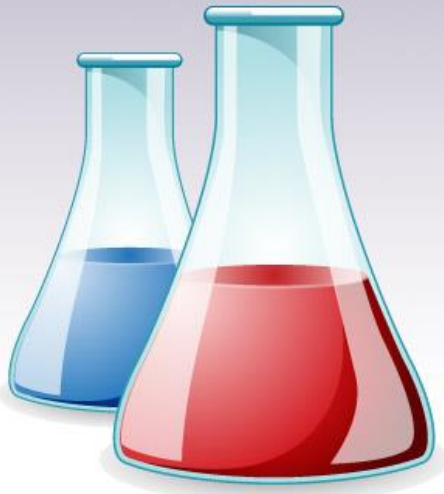
# Aromatic waters



- These are aqueous solutions, usually saturated of volatile oils or other volatile substances. Used as flavoring agents.



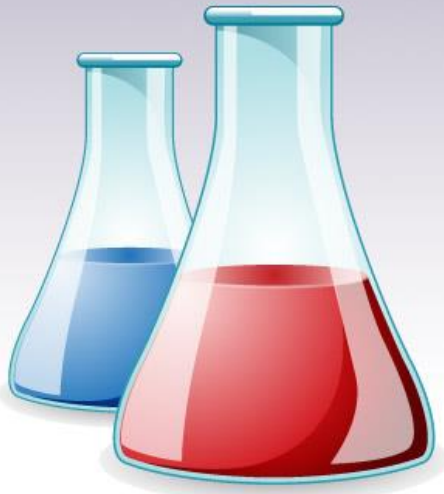
# Spirits



- They are alcoholic or aqueous alcoholic solutions of volatile substances used as flavouring agents.

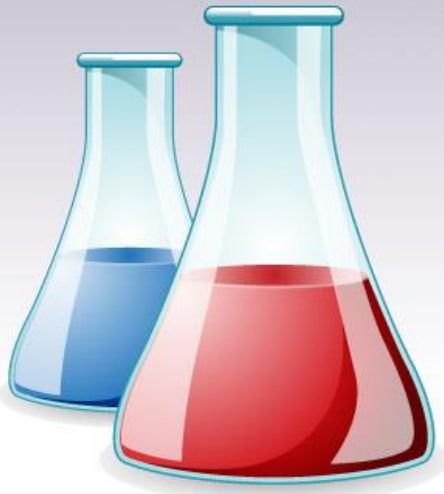


# Mucilages

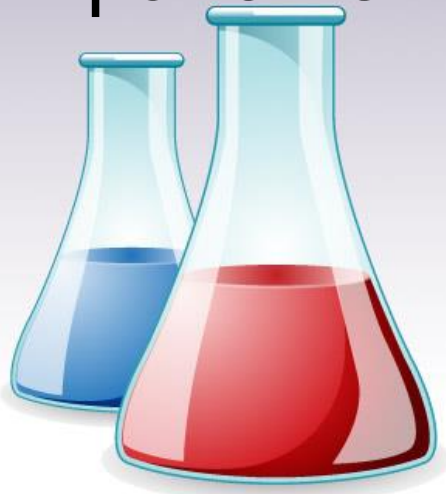


# Mucilages

- The official mucilages are thick viscid, adhesive liquids, produced by dispersing gum (acacia or tragacanth) in water.

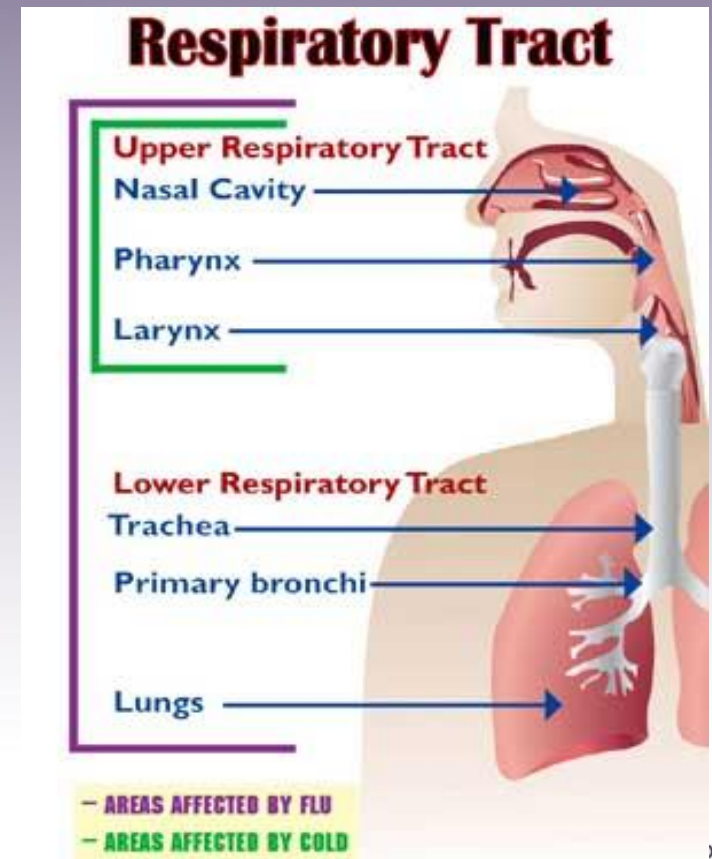
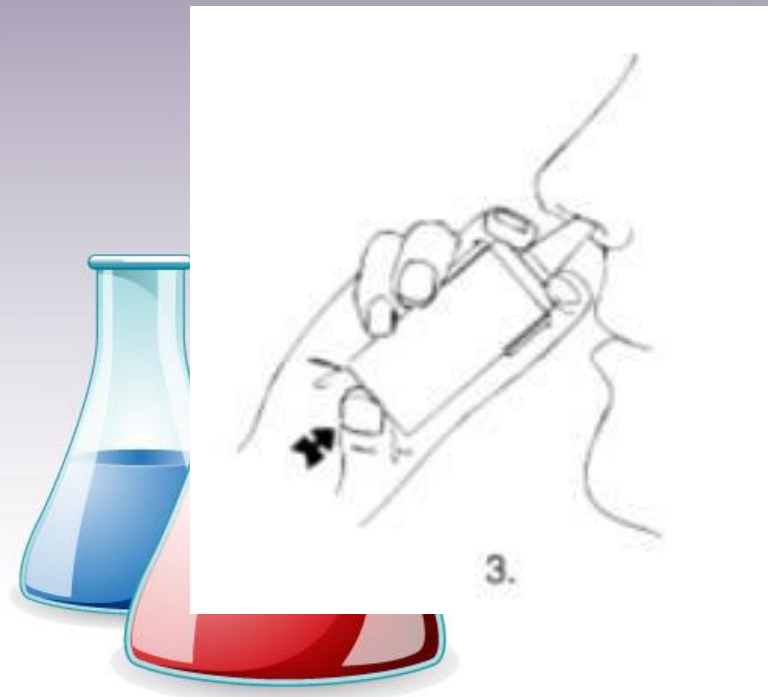


- Mucilages are used as suspending agents for insoluble substances in liquids; their colloidal character and viscosity prevent immediate sedimentation.
- Synthetic agents e.g. carboxymethylcellulose (CMC) or polyvinyl alcohol are nonglycogenetic and may be used for diabetic patients.



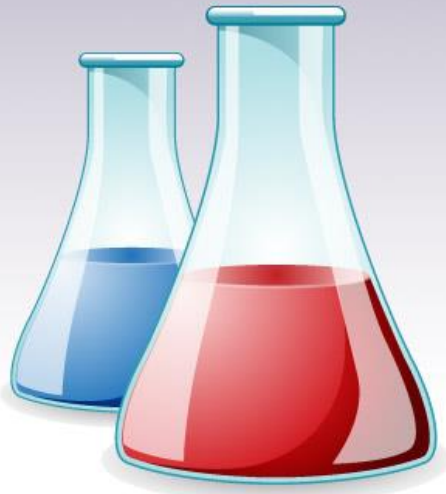
# Sprays

★ Sprays are solutions of drugs in aqueous vehicles and are applied to the mucous membrane of the nose and throat by means of an atomizer nebulizer.





- The spray device should produce relatively **coarse droplets** if the action of the drug is to be restricted to the **upper respiratory tract**. Fine droplets tend to penetrate further into the respiratory tract than is desirable.



THANK YOU

