Pharmaceutical solutions

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By the end of this section, you will:

1. Understand concepts of solubility, solution and concentration.
2. Relate this basic understanding to solution formulation.
3. Be familiar with the principles underlying the formation of solutions.
4. Be familiar with the pharmaceutical excipients commonly used in solution formulation and their role.
5. Be familiar with the common limitation faced in in solution formulation.
6. Will be able to overcome solution formulation problems.

Important definitions I

1. A solution*: generally defined as a mixture of two or more components that form a single phase which is homogeneous down to the molecular level.
2. Pharmaceutical solutions: are “liquid preparations that contain one or more chemical substances dissolved in a suitable solvent or mixture of mutually miscible solvents”
3. Solvent: the component that determines the phase of the solution; it usually (but not necessarily) constitutes the largest proportion of the system.
4. Solute: the molecules or ions that are dispersed throughout the solvent, i.e. they are said to be dissolved in the solvent.

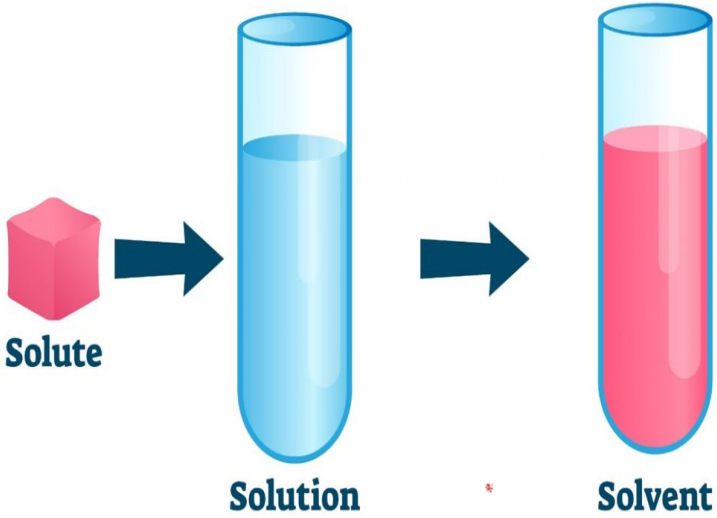
*This definition is general one, it may be applied to all types of solution involving any of the three states of matter (gas, liquid, solid) dissolved in any of the three states of matter, i.e. solid in liquid, liquid in solid, liquid in liquid, solid in vapour, etc.

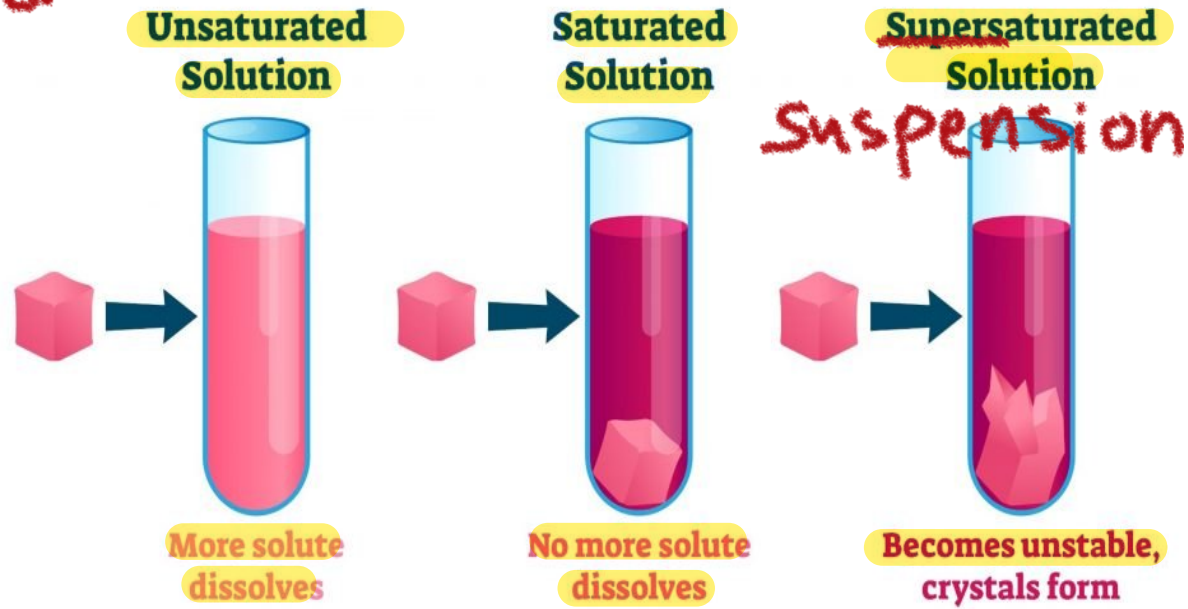
Solubility

- If you continue adding table salt to a glass of water you will reach a stage whereby no more can dissolve. By doing this you have produced a saturated solution.
- Solubility is the concentration of a saturated solution.
- So solubility is a concentration value, BUT a concentration value isn't necessarily the solubility.
- When you add solid above the solubility you end up with a suspension (which will be the focus of the next section of this course).

Solubility

dissolve salt in water





1. all salt miscible in water → solution
2. no more salt can dissolve → saturated solution
3. solid salt above solubility → suspension

Solubility

Solubilities may be expressed by any of the variety of concentration terms (explained in section two of this course) . In general, solubility is expressed in terms of the maximum mass or volume of solute that will dissolve in a given mass or volume of solvent at a particular temperature and pressure at equilibrium.

1. Quantity per quantity → g/g or g/mL or mL/mL
2. Parts → part per million → ppm
3. Molarity → n / V(L)
4. Molality → n / m of solvent (kg)
5. Mole fraction
   ↳ n / total n

- The solubility of a material depends on the solvent and the solute.
- Nonetheless, be aware of another phenomenon called supersaturation.
- Supersaturation is the stage where the concentration of a material in solution is higher than the solubility.
- Such systems are unstable and eventually the excess material will precipitate to form a saturated solution (and a suspension). This point is very important and needs to be considered during pharmaceutical solutions formulation and when assigning the storage conditions.

Concentration exceeds solubility

Important definitions II

1. Dissolution: The transfer of molecules (or ions) from a solid state into solution

2. Solubility: Is the extent to which dissolution of solute in the solvent proceeds under a prescribed set of experimental conditions. OR to

   Amount of a substance that passes into solution after equilibrium is established between the solution and undissolved solute.

   - Saturation:
   - Solution at equilibrium containing excess (undissolved) solute

3. Concentration: is means by which amount of a material in a given quantity of solution is expressed.

So why does solubility matter?

In the body, a pharmaceutical active ingredient must be “in solution” before it can be absorbed by the blood and ultimately carried to the receptor site to render a therapeutic effect.

Critical to solution formulation – you MUST choose a solvent whereby you are at a reasonable distance from the solubility.

The drug will be present in biological fluids at some stage – you need to understand solubility to understand bioavailability. → the amount of drug that enters bloodstream

* An injected drug must NOT precipitate out on injection. *

↳ must be fully dissolved

Disintegration →

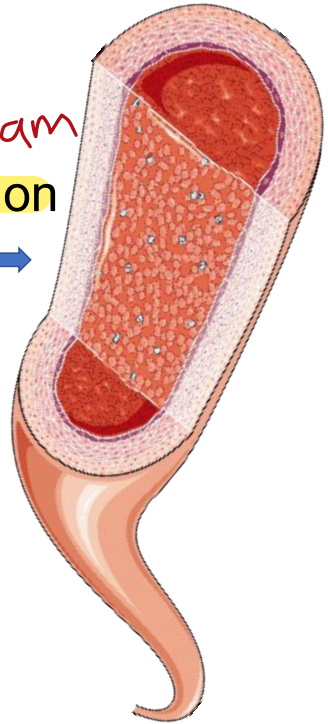
the tablet breaks into smaller pieces after entering the body.

Dissolution →

the drug dissolve in body fluids

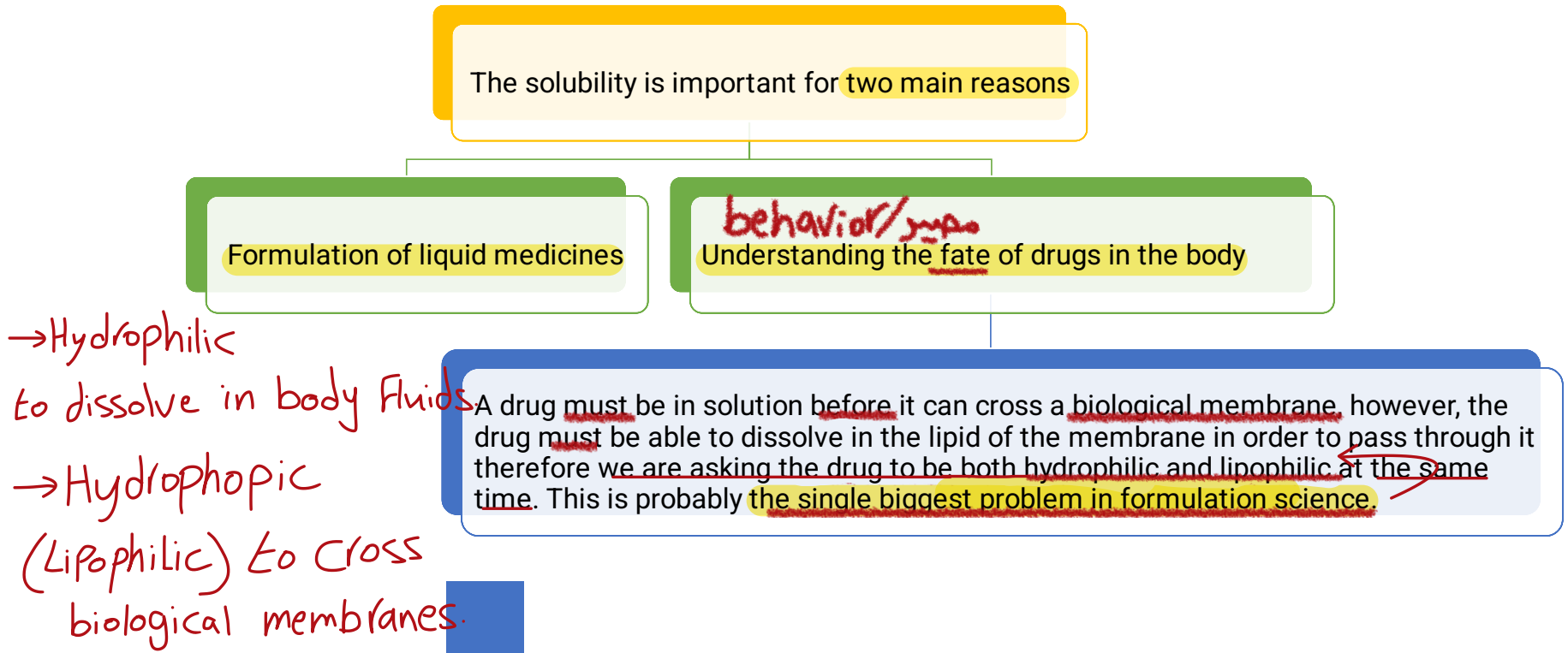
Absorption →

the dissolved drug passes into the bloodstream



Solubility of solids in liquids

- Most drugs are crystalline solids, a solid, when mixed with a liquid, will dissolve until saturation is reached after that that the dissolution process will stop.
- At saturation stage the concentration in the liquid is the solubility.



Formulation of pharmaceutical solutions

Where are solutions used medically?

Solutions can be formulated for different routes of administration:

↳ 8 types

1. Oral dosing
   - Especially for children and the elderly patients
   - Issues with palatability?!! → acceptable taste → we add flavoring agent
   - Usually non-sterile.
   - Wide pH range is acceptable
   - Syrup and elixirs are examples.

2. Mouthwashes / gargles and throat sprays
   - Usually non-sterile.
   - Wide pH range is acceptable

3. Topical lotions / paints
   - usually non-sterile, ie "microbiologically clean"
   - can be non-aqueous

4. Nasal drops
   - Ideally should be isotonic
   - Should be buffered as narrow range of pH is acceptable to avoide irritation of the nasal mucosa.
   - Usually non-sterile

مجال ضيق
محلول منظم لـ pH

5. Ear drops
   - Usually non-sterile.

6. Eye drops
   - Are sterile solutions.
   - Isotonic and buffered

IV → Intravenous في الوريد

IM → Intramuscular في العضلة

SC → Subcutaneous تحت الجلد

7. Parenteral solutions محاليل الحقن
   - IV, IM, and SC injections are examples.
   - Must be sterile.
   - large volumes need to be isotonic.
   - need to be pH-controlled. especially large volumes.

8. Irrigation غسول
   - need to be sterile
   - narrow range of pH acceptable

Medical Solutions Comparison Table

Route / Type	Sterility	Isotonic	pH Control	Notes
Oral	Non-sterile	Not required	Wide range	Children & elderly, palatability
Mouth/Throat	Non-sterile	Not required	Wide range	Local action
Topical	Non-sterile	Not required	Flexible	Aqueous or non-aqueous
Nasal	Usually non-sterile	Yes	Narrow (buffered)	Avoid irritation
Ear	Usually non-sterile	Not required	Not critical	Less sensitive
Eye	Sterile	Yes	Buffered	Very sensitive
Parenteral	Sterile	Yes (large volumes)	Controlled	High risk
Irrigation	Sterile	Often	Narrow	Washing tissues

Advantages of Formulating API as a Solution

Active pharmaceutical ingredient

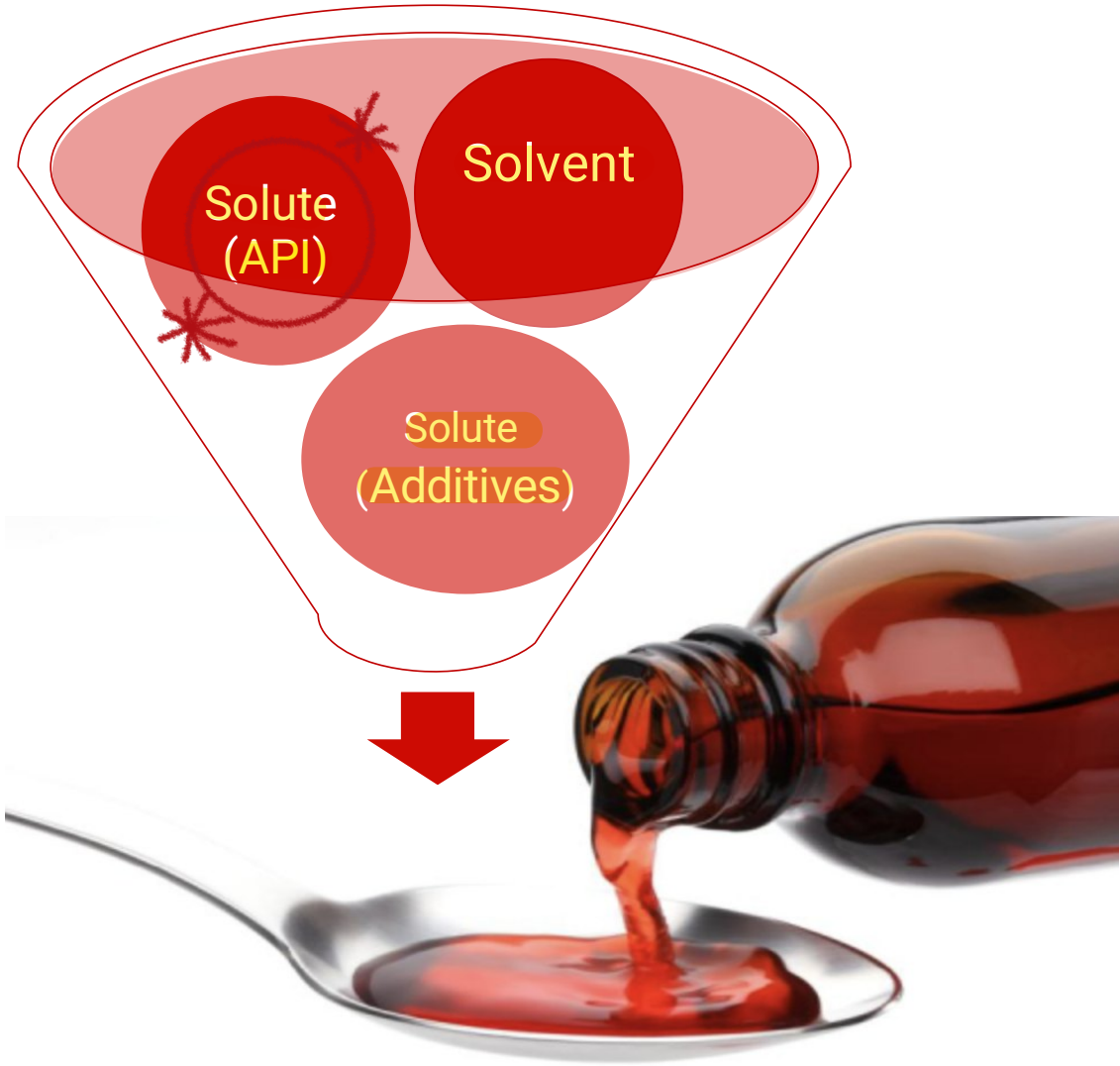
1. Liquids are easier to swallow than solids, therefore are more acceptable for pediatric and geriatric use.
2. Drug administered in the form of solution is immediately available for absorption.
3. The drug is uniformly distributed within the dose since the solution is a homogenous system.
4. Suitable for the administration of drugs that cause stomach irritation if the API was localised in one area as often occurs after ingestion of solid dosage forms, tablets and capsules for instance.

children and elderly

تناول

Solutions reduce Localized gastric irritation

Components of Pharmaceutical solutions



Pharmaceutical solutions are also classified according to solvent composition:

1. Aqueous solutions: water = solvent
- Syrups
- Aromatic waters

2. Hydroalcoholic solutions: water + alcohol
- Elixirs → oral solution
- Spirits → high alcohol concentration
- Tinctures → أصباغ
- Fluid Extracts
- Collodions → تستخدم على الجلد
- Liniments → تفرك على الجلد

3. Non-aqueous solutions: do not contain water

Solubility of solids in liquids

- Many drugs have a poor solubility in water, typically drugs with as solubility ≤ 100 µg /ml consider as poorly soluble
- For example, ibuprofen has a solubility of 0.021mg/ml and it's considered to be insoluble according to bioclassification system
- Up to 90% of the drugs in the pipelines have a solubility of <1µg/ml which results to both formulation and absorption problems. Hence, these drugs might be abandoned despite despite considerable pharmacological potential at the site of action.
- The solubility of many drug substances can be found in the United States Pharmacopeia– National Formulary (USP–NF) in addition to other reference books and websites such as PubChem. Solubility values might be stated also in MSDS.

material safety data sheet

According to the British and the US Pharmacopoeias, drug substances are classified according to their solubility in a quantitative way (Table beside) under defined criteria from "very soluble" to "practically insoluble" regardless of the solvent type used. However, solubility can be expressed in units of concentration, mole fraction, mole ratio, molarity, or any other units

Descriptive term	Part of solvent required per part of solute
Very soluble	Less than 1
Freely soluble	From 1 to 10
Soluble	From 10 to 30
Sparingly soluble	From 30 to 100
Slightly soluble	From 100 to 1000
Very slightly soluble	From 1000 to 10,000
Practically insoluble	10,000 and over

Solutes

Solutes are classified to non-electrolytes and electrolytes.

1. Non-electrolytes:
   - Will not dissociate (ionise) in solvents.
   - Hence their solutions will not conduct electricity.
   - Dextrose, sucrose, glycerin, ethanol, urea are examples.

2. Electrolytes:
   - Will dissociate or ionise when dissolved in a solvent.
   - Hence, their solutions will conduct electricity.

- Strong electrolytes: almost completely dissociate in a solvent (e.g. sodium hydroxide, sodium chloride, potassium chloride, sulfuric acid).
- Weak electrolytes: dissociate in solvents to a lesser extent (e.g. acetic acid, ammonia, and majority of drugs).

dissociate partially

Weak electrolytes are subdivided into weak acids and weak bases.

1. If the salt form of the drug has a sodium (Na^+), potassium (K^+), or calcium ions (Ca^+), then the drugs is an acid (e.g. sodium phenytoin, sodium phenobarbital, buprofen sodium, Diclofenac sodium, Diclofenac potassium).

2. If the salt form of the drug has sulfate (SO_4^{-2}), hydrochloride (HCL), or tartarate ions ($C_4H_4O_6^{-2}$), the drugs is a base (e.g. morphine sulfate, chlorpheniramine maleate, metoprolol tartarate, atropine sulfate).

Solvent

- A widely used rule of thumb is ‘like dissolves like’.
- This refers to the idea that a solute and solvent with similar polarity are likely to allow dissolution.
- Non-polar and dissolves well in oil.
- Polar and dissolves well in water.
- The form a solution (dissolving of solute) crystal lattice has to break to free a molecule, the solvent has to form a hole and then the freed molecule has to go into the hole. Which means molecule-molecule bonds need to break and molecule-solvent bonds needs to form.

Mechanism / خطوات

Solubility

As mentioned previously the formulator (the person) needs to determine the maximum possible concentration to which the solution can be prepared to guarantee the quality and the stability of the formed solution. (ضمان)

* Which varies depending on: (factors affecting Solubility)

1. Chemical constitution of the solute.
2. Chemical constitution of solvent.
3. Type of solvent → water / alcohol / oil
4. pH of the solution → affect ionization
5. Presence of cosolvents or solubilising agents → (مواد إضافية تساعد على الذوبان)
6. Temperature

↑T , ↑ Solubility

To summarise what to consider during solution formulation:

- The information on the solubility and stability of each material (solutes) in the system with regard to the solvent or solvent system must be collected and interpreted.
- Combinations of medicinal or pharmaceutical excipients that might interact chemically and/or physically and affect the therapeutic quality or pharmaceutical stability of the product must be avoided.

What are the formulation issues we need to consider for solutions?

- Solubility of the drug — fully soluble
- Vehicle acceptability — solvent
- pH — for non-sterile ← مواد حافظة
- Sterility (and anti-microbial preservatives)
- Chemical stability (and stability enhancers) — عوامل
- Tonicity (osmatic pressure)
- Viscosity and density — لزوجة وكثافة
- Aesthetic considerations — color / taste / smell
- Reproducibility of dosing — re-produce the dose with same quantity
- Patient acceptability
- Ease of use
- Ease of manufacture and low cost (?) — تصنيع

Solubility of the drug

Main solvent in most pharmaceutical solutions is water:

- Purified Water نقي
- Water for Irrigation غسول
- Water for Injection حقن

Other liquids do appear in formulations but often mixed with water:

- Ethanol
- Industrial methylated spirits
- Glycerin (glycerol)
- Propylene glycol
- Polyethylene glycol
- (PEG 300 to 600)

Polyethylene glycol

Solutions can be of Non-aqueous nature, see examples below:

- Non-aqueous oral formulations:
  - Used to make solutions for oil-soluble vitamins or very non-polar drug
  - Fixed oils eg: soybean oil, arachis oil,sesame oil
  - Volume of oil important
  - Taste is important
- Non-aqueous Intra-muscular depot injections:
  - Long acting
  - Fixed oils eg soybean oil, arachis oil, sesame oil
  - Volume 2 to 5 mL

زيت فول سوبيا — زيت فول — زيت سمسم

Fixed oils → Solvent كـ تستخدم زيوت ثابتة

Controling Manipulating solubility

- When you formulate a drug as a solution you do not want to formulate close to the solubility value, and as many drugs have poor solubility, this presents a problem for preparing solutions.
- Suspensions are a possibility but are not always suitable due to the reasons we will mention in the next chapter of this course.
- How can we change the solubility of a drug material?

avilable choice

A B C D E F

A) Temperature

Not particularly useful – for a product you typically have only two storage options (room temperature, fridge)

- However, elevated temperatures cannot be maintained for pharmaceuticals, and the net effect of heat is simply an increase in the rate of solution rather than an increase in solubility.
- Pharmacists should be careful not to exceed the minimally required temperature to avoid drug deterioration

B) Cosolvents

مذيبات مساعدة

- One approach that can be used is to include cosolvents
- Which means adding miscible solvents of different polarities to form a solvent system of optimum polarity to dissolve the solute.
- These are liquids (ethanol, glycerol + see previous list but NOT methylated spirits for oral formulations) that changes the solvent properties of the water.
- By using a cosolvent it is possible to increase the solubility of a drug significantly.
- Many commonly used liquid medicines contain cosolvents.

Example : a commercially available non-Drowsy Coughs syrup contains the fowling inactive ingredients : Sucrose, Liquid Glucose, Ethanol, Glycerol, Sodium Citrate, Saccharin Sodium, Citric Acid Monohydrate, Sodium Benzoate (E211), Ponceau 4R (E124), Caramel (E150), Carbomer, Raspberry Essence, Natural Sweeteners Enhancer and Water.

C) Manipulation of pH to increase aqueous solubility

- If drug is ionisable, its solubility may vary with pH, as the solubility of a weak base can be increased by decreasing pH while increasing pH increases the solubility of weak acids.
- Use Henderson-Hasselbalch equation to predict pH of maximum solubility.
- Essentially adding / subtracting H+ to / from drug .
- pH is also extremely important for understanding how drugs behave in the body.

↑pH , ↓ S.W. Base , ↑ S.W. acid

(وسط قاعدي) alKaline

ionisable +/− ⇒ more water soluble

1. Narrow range of pH acceptable for ocular, nasal and some injection formulations.
2. Wider range of pH for oral preparations.
3. May need a buffer to maintain pH:
    - Citrate, phosphate, acetate, bicarbonate, gluconate, lactate, tartrate.
    - The effect of buffer on solubility and stability of drug must be studied.
    - The effect of buffer on taste must be taken in consideration.

    - Remember
    - Absorption occurs only in the unionised form, hence in some cases, the bioavailability of drug might be affected by pH of their solutions.
    - Varying pH may affect stability of drug as the stability of drug is table at a pH value that different from the pH value that increases the solubility.
    - Varying pH may affect action of other components.

Example

- For instance, the weak bases, including many of the alkaloids (atropine, codeine, and morphine), antihistamine (diphenhydramine and promethazine), local anesthetics (cocaine, procaine, and tetracaine), and other important drugs, are not very water soluble, but they are soluble in dilute solutions of acids.

مخدر موضعي

↳become anionized form → ↑ Solubility

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D) Salt formation to increase aqueous solubility

- If drug is a weak acid react with a base (strong) and evaporate off the water (تبخير) to give a solid salt.

- If the drug is a weak base react with an acid (strong) and evaporate off the water to give a solid salt.

ملح يتكون من ايون (base من) + وايون (acid من) −

- Acceptable cationic (+) salts: Na+, K+, Ca_2+
- Acceptable anionic (−) salts: Cl-, HCO_3-, SO_4^{2-}, HSO_4-, PO_4^{3-}, HPO_4^{2-}, H_2PO_4-,

  maleate, tartrate, citrate, lactate, succinate, mesylate.

Salt formation to increase aqueous solubility

- About 50% of drugs in solid dosage forms given as salts – can also use for solution formulations especially injections for reconstitution.

more Soluble

الحقن

لإعادة التركيب قبل الاستخدام

TABLE 13.2 WATER AND ALCOHOL SOLUBILITIES OF SOME WEAK ACIDS, WEAK BASES, AND THEIR SALTS

	MILLILITERS OF SOLVENT TO DISSOLVE 1 g OF DRUG	
DRUG	WATER	ALCOHOL
Atropine	455.0	2
Atropine sulfate	0.5	5
Codeine	120.0	2
Codeine sulfate	30.0	1280
Codeine phosphate	2.5	325
Morphine	5000.0	210
Morphine sulfate	16.0	565
Phenobarbital	1000.0	8
Phenobarbital sodium	1.0	10
Procaine	200.0	Soluble
Procaine hydrochloride	1.0	15
Sulfadiazine	13000.0	Sparingly soluble
Sodium sulfadiazine	2.0	Slightly soluble

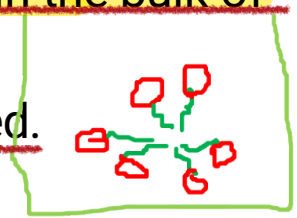
active surface factors

E) Use of surfactants to increase aqueous solubility:

- A surfactant (surface-active agent) is amphiphilic, i.e., it has a hydrophobic tail group and a hydrophilic head group.
- In water, surfactants at low concentrations will form a layer on the surface of the water, i.e., at the air-water interface.
- In water, surfactants at high concentrations will also form micelles in the bulk of the water.
- Above the "Critical Micelle Concentration" (CMC) micelles are formed.

على السطح الملامس للهواء

يحيط بالدواء



- Excess amount may cause toxic effects, product aeration during manufacturing and reduction in bioavailability due to strong adsorption to the micelle.

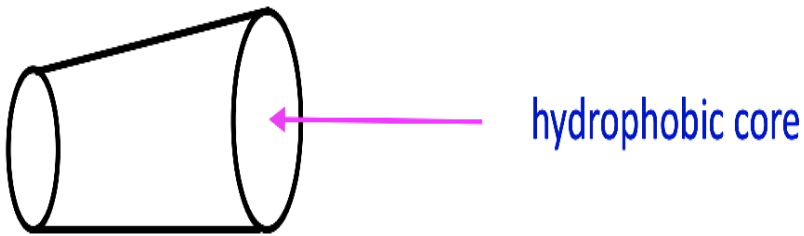
↑ amount زيادة

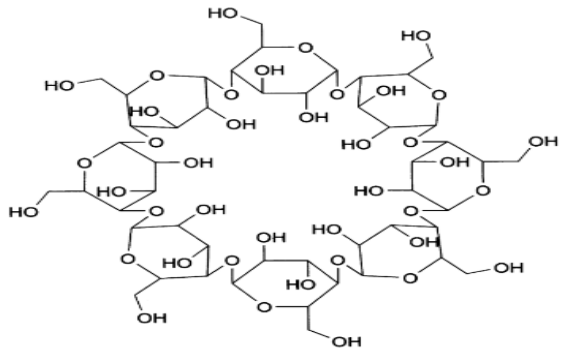
- Insufficient amount may lead to precipitation on storage or dilution of product.

↓ amount غير كافية

F) Use of complexing agents to increase aqueous solubility

- Cyclodextrins which are cyclic glucose polymers are example of complexing agent.
- Cyclodextrins arranged in aqueous solution as a truncated cone. مخروط مقطوع
- Hydrophobic core provides a reservoir for poorly water-soluble drugs, i.e. increases water solubility.





Example on (Complexation):

- iodine granules are soluble in water only to the extent of 1 g in about 3,000 mL. Using only these two agents, the maximum concentration possible would be approximately 0.03% of iodine.

- However, through the use of an aqueous solution of potassium iodide or sodium iodide as the solvent, much larger amounts of iodine may be dissolved as the result of the formation of a water-soluble complex with the iodide salt.

- This reaction is taken advantage of, for example, in Iodine Topical Solution, USP, prepared to contain about 2% iodine and 2.4% sodium iodide.

- Complexation formation: occurs when an insoluble solute reacts with a soluble substance to form a soluble complex (e.g. the complexation of the soluble potassium iodide (KI) to the insoluble iodine molecules (I_2) to form a soluble triiodide complex (KI_3)).

Now to more details about the materials that commonly used as a solvent or a part of the solvent system in pharmaceutical solutions.

Selection factors of solvent

① Solubility

- In addition to the factors of solubility, the selection is based on such additional criteria as:

1. Clarity (شفاف وخالى من الشوائب)
2. Low toxicity
3. Viscosity (تؤثر على سهولة الحقن أو الشرب)
4. Compatibility (التوافق) with other formulative ingredients → do not react with other ingredients
5. Chemical inertness (سكون) / stable / do not react
6. Palatability acceptable taste for oral use
7. Odour / smell
8. Colour
9. Economical factors Low cost

The physiological actions of many solvents limit their use in pharmaceutical solutions.

Most organic solvents in addition to a few exceptions, are irritants and/or toxic which limit the number of solvents that can be used in pharmaceutical solutions.

We lift with only a few solvents (such as glycerin, alcohol, propylene glycol, and fixed oils) that can be employed for the preparations of solutions for internal use. Other solvents, such as acetone, ethyl oxide, and isopropyl alcohol, are too toxic to be permitted in pharmaceutical preparations to be taken internally, but they are useful as reagent solvents in organic chemistry and in the preparatory stages of drug development, as in the extraction or removal of active constituents from medicinal plants.

I. Water

- In most instances, especially for solutions to be taken orally, used ophthalmically, or injected, water is the preferred solvent because it comes closer to meeting the criteria we mentioned than other solvents.
- Naturally occurring water contains various amounts of dissolved inorganic salts, organic matter and microorganisms.
- Ordinary drinking water (tap water) obtained from the tap is not accepted for the manufacture of aqueous pharmaceutical preparations or for the extemporaneous compounding of prescriptions.
- Purified water, USP is obtained by distillation, Ion-exchange treatment, reverse osmosis or other suitable process.
- Purified water, USP is intended for use in the preparation of aqueous dosage forms except those intended for parenteral administration (Injections).
- Water for Injection, USP; Bacteriostatic water for Injection, USP; or Sterile Water for Injection, USP, is used for injections.

II. Alcohol, USP: Ethyl alcohol, Ethanol, C_2H_5OH

- Next to water, alcohol is the most useful solvent in pharmacy.
- When mixed with water, it forms a hydroalcoholic solution that can dissolve both alcohol-soluble and water-soluble materials (drugs).
- Alcohol, USP is 94.9% to 96.0% C_2H_5OH by volume (i.e., v/v) when determined at 15.56°C*.
- When a water-free alcohol is required, Dehydrated Alcohol, USP is the alcohol of choice. Dehydrated alcohol contains not less than 99.5%v/v C_2H_5OH.
- Diluted Alcohol, NF is prepared by mixing equal volumes of Alcohol, USP, and Purified Water, USP.

Con.

خالي من الماء

مجفف

94.9 % → 96 %

Advantages of hydro-alcoholic solutions:	They can dissolve oil soluble drugs (or the free acid or free base form) that cannot be dissolve in aqueous solutions.
	Ethanol at specific content acts as preservative لها مادة حافظة
	They can be used to dissolve either alcohol soluble or water-soluble drugs.
Disadvantages of hydro-alcoholic solutions:	The concentration of ethanol used is not always physiologically inert. غير مضار
	Elixirs are less sweet and less viscous than syrups, hence, less effective in taste masking compared to syrups. elixir أقل فعالية في تحسين الطعم

بدون وصفة طبية

تُقيد

The U.S. Food and Drug Administration (FDA) restrict the use of alcohol in over-the-counter (OTC) oral drug products and include appropriate warnings in the labeling:

1. For OTC oral products intended for children under 6 years of age, the recommended alcohol content limit is 0.5%.
2. For products intended for children 6 to 12 years of age, the recommended limit is 5%.
3. and for products recommended for children over 12 years of age and for adults, the recommended limit is 10%.

Rubbing alcohol:

كحول للتدليك

- Rubbing alcohol contains about 70% ethyl alcohol (ethanol) by volume, the remainder consisting of water, denaturants with or without color additives and perfume oils, and stabilisers.

مواد ضرة

- Each 100 mL must contain not less than 355 mg of sucrose octaacetate or 1.4 mg of denatonium benzoate (bitter substances that discourage accidental or abusive oral ingestion).

- According to the Internal Revenue Service, U.S. Treasury Department, the denaturant employed in rubbing alcohol is formula 23-H, which is composed of 8 parts by volume of acetone, 1.5 parts by volume of methyl isobutyl ketone, and 100 parts by volume of ethyl alcohol. The use of this denaturant mixture makes the separation of ethyl alcohol from the denaturants virtually impossible with ordinary distillation apparatus. This discourages the illegal removal for use as a beverage of the alcoholic content of rubbing alcohol.

Rubbing alcohol is used as:

1. Rubefacient externally. يعزز الدورة الدموية عند تدليك الجلد
2. Soothing rub for bedridden patients. يخفف الالم والتشنجات للمرضى المقعدين
3. Germicide for instruments. مطهر للادوات
4. Skin cleanser before injection. معقم للجلد قبل الحقن
5. Vehicle for topical preparations. مذيب للمستحضرات الموضعية

Storage conditions:

متطاير

Should be stored in a tight container away from fire as it's volatile and flammable liquid.

III. GLYCERIN, USP (GLYCEROL)

Glycerin :

- Is a clear syrupy liquid with a sweet taste.
- Miscible with both water and alcohol.
- Has preservative qualities.
- Is often used as a stabiliser. → مثبت للمحلول (يمنع انفصال مكوناته)
- Glycerin also used as an auxiliary solvent in conjunction with water or alcohol.

مذيب مساعد

IV. Isopropyl rubbing alcohol:

- Isopropyl rubbing alcohol is about 70% by volume isopropyl alcohol the remainder consisting of water with or without color additives, stabilisers, and perfume oils.

V. Propylene glycol, USP:

- Propylene glycol, is a viscous liquid, that is miscible with water and alcohol. It is a useful solvent with a wide range of applications.
- It is sometimes substituted for glycerin in some pharmaceutical formulations.
- Although orally administered propylene glycol has a low toxicity in animals, it may exhibit a weak central nervous system depressant activity.

VI. Fixed oils (vegetable oils)

- A number of fixed oils, such as corn oil, cottonseed oil, peanut oil, and sesame oil, are useful solvents, particularly in the preparation of oleaginous injections, and are recognised in the official compendia for this purpose.
- These are non-volatile oils that consist mainly of fatty acid esters of glycerol.
- As we mentioned previously it's used orally, IM depot and topical solutions.

VII. Liquid paraffin

- It is often used as a solvent for the topical application of drugs.
- Liquid paraffin or mineral oil is a transparent, colourless, odourless, or almost odourless, oily liquid composed of saturated hydrocarbons

Excipients commonly used in solutions

1. Preservatives
2. Buffer → pH control
3. Chemical stability enhancers (ex: antioxidants)
4. Viscosity enhancing agents
5. Isotonicity regulating agents → NaCl
6. Sweeteners
7. Flavors
8. Colors

Anti-microbial preservatives

- Preservatives are for "in use" protection against microbial growth.
- "Single use" sterile solutions do not require preservatives as they should be produced in a "clean" or "sterile" room. Small volume injections, single use eye drops, nebuliser solutions are examples.
- "Multiple use" solutions require preservatives: eye drops, nasal solutions, oral solutions, lotions etc.
- Oral aqueous solutions can support growth especially if sucrose is present.

Methods to preserve solutions:

1. Add a known preservative in the correct concentration that is soluble in the formulation.
2. If absolute alcoholic content is high alcohol can act as preservative: a minimum of 15% absolute alcohol is adequate to preserve products with pH 5, and 18% for neutral or slightly alkaline preparations (tinctures, spirits, and some elixirs require no preservatives)

- Preservative examples: Benzoic acid, sodium benzoate, methylparabens, propylparabens and butylparabens.

- When choosing a suitable preservative, the following points should be considered:

1. No adsorption of the preservative into the container occurs

2. The preservative is not impaired by the pH of the solution or by interaction with other ingredients.

Buffers

- Buffers are compounds that resist changes in pH upon the addition of limited amounts of acids or bases.
- Buffer systems are usually composed of a weak acid or base and its conjugate salt.
- The components act in such a way that addition of an acid or base results in the formulation of a salt causing only a small change in pH.
- Buffer capacity is a measure of the efficiency of a buffer in resisting changes in pH. Conventionally, the buffer capacity (ß) is expressed as the amount of strong acid or base, in gram-equivalents, that must be added to 1 liter of the solution to change its pH by one unit.
- Buffer capacities ranging from 0.01 - 0.1 are usually adequate for most pharmaceutical solutions.

- Once the optimal solution pH for the drug has been determined, buffers are needed to maintain that pH for the expected shelf life of the product.
- The buffer capacity must be large enough to maintain the product pH for a reasonably long shelf life.
- Change in product pH may result from the interaction of components with one another or with the package (glass, plastic, rubber, closure).
- On the other hand, the buffer capacity must be low enough to allow rapid adjustment of the formulation's pH to the physiological pH upon administration.

- Buffer should have low toxicity and compatible with other ingredients.

- As the pH of most body fluids is 7.4, products such as injections, eye drops and nasal drops should , ideally, be buffered at this value.

- Formulating a product at this pH is not always possible because of the drug's solubility, chemical stability, or therapeutic activity. Therefore, some compromise in the formulation pH may be necessary

- However, many body fluids have a buffering capacity and when formulating low volume intravenous injections or eye drops a wider range of pH can be tolerated.
- When a formulation is administered to the eye, it stimulates the flow of tears that is capable of quickly diluting and buffering small volumes of formulations.
- Usually, a compromise between a pH which is physiologically acceptable and a pH of optimum stability and solubility.

Chemical stability enhancers

- To enhance the chemical stability of a drug, the first step is to determine the routes of its degradation. To do so look at chemical structure of drug and predict its route of degradation.

Degradation routs:

1. oxidation
2. reduction
3. hydrolysis

The second step is to consider the potential catalysts for this degradation:

4. pH
5. Oxygen*
6. Water
7. Trace elements*
8. Heat*
9. Light*

The third step is to choose stability enhancer to match the degradation route.

- Acid / base catalysis: use a buffer to maintain pH of maximum stability.
- Oxidation: 1) use an anti-oxidant, 2) reduce O_2 permeation into the package e.g., glass not HDPE. 3) Replace air with nitrogen or CO_2 in package headspace.
- Trace elements: use a chelator to absorb them e.g., EDTA.
- Temperature: Refrigerate?
- Light: use amber glass.

Antioxidants used in solutions includes but not limited to:

1. Ascorbic acid.
2. Citric acid.
3. Sodium metabisulfite.
4. Sodium sulfite.

* Sulfites can cause allergic-type reactions in certain people and so patients should be questioned about this potential reaction before the antioxidant is included in the formulation.

Viscosity enhancing agents

- Oral and parenteral solutions should be of low viscosity to be easily poured / injected
- Increasing viscosity is needed for:
  - Eye drops to promotes retention on surface of eye.
  - Oral solutions for infants to reduces chances of dribble.
- Increase viscosity can be achieved by by adding polymeric material:
  1. Cellulose derivatives such as Methylcellulose and Hydroxypropylmethylcellulose (HPMC, Hypromellose)
  2. Polyvinylpyrrolidone (PVP)
  3. Increasing sugar concentration.
  4. Adding glycerin

Isotonicity modifiers

- Solution 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.

- Other additives should be considered when adjusting tonicity because of their effect on the osmotic pressure of solution.

Additives added for Aesthetic considerations

Does the solution look, smell and taste good ?

1. Colour:

- Added to a formulation for the sole purpose of imparting color to promote patients' acceptance of a formulation via visual appeal
- Colours are contraindicated in all sterile solutions.
- Artificial colourants may have some biological effect.
- Regulations regarding colours are complex, variable and changeable.
- Hence, Best to avoid colours if possible.
- Pleasant fruity colors are generally preferred and should be coordinated with flavors and scents (yellow with lemon, red with cherry).

- Physicochemical reactions with other formulation ingredients must be considered when choosing a colorant. For example, many colors are salts of sulfonic acids and may be incompatible with large cationic compounds such as alkaloids.

- The pharmacists should also consider how pH changes or light exposure alters the color or stability of the product.

- Colours used in pharmaceutical preparations are either natural colors or synthetic dyes.
- Natural colors include red ferric oxide and titanium oxide.

معتمدة

- The synthetic dyes are certified by FDA and are:

1. FD&C dyes: used in food, drug, and cosmetics.
2. D&C dyes: used in drugs and cosmetics.
3. External D&C dyes: Used in externally applied drugs and cosmetics.

2.Flavour

- Drugs tend to taste bitter which will not encourage patient compliance.
- Children prefer sweet, fruity, and candy-like tastes.
- Adults tend to tolerate a reasonable level of bitterness or less sweet, tart, fruity flavors.
- For infants under 3-6 months of age flavoring agents are unnecessary and are not recommended.

In addition to the active drug, formulation components may produce characteristics tastes or odors:

1. Alcohol: biting taste.
2. Glycerin: sweet taste.
3. Methylparaben: floral like aroma.
4. Propylparaben: produces a numbing feel in the mouth.
5. Menthol and mannitol: impart a cooling sensation.

Flavoring techniques:

- Blending: the use of a flavor that blend with drug tastes. Drugs with acidic taste can be blended with citrus fruit flavors.
- Overshadowing (masking, overpowering): involves using a flavor with a stronger intensity and longer residence time in the mouth (e.g. wintergreen oil)
- Physical methods:
- Use insoluble form of drug.
- Make an o/w emulsion of an oily drug and flavor the external aqueous phase.
- Chemical methods: by adsorbing, complexing or making a pro-drug of the drug that eliminate the undesirable taste.
- Physiological techniques:
- Use additives that cause a cooling sensation (e.g. mannitol, menthol).
- Menthol, peppermint oil and chloroform mask the taste also by acting as desensitising agents.

3.Sweeteners

- Low molecular weight carbohydrates and particularly sucrose are traditionally the most widely used sweetening agents in oral solutions.
- Polyhydric alcohols such as glycerol, sorbitol, mannitol and xylitol possess sweetening properties and can be used for diabetic patients.
- Artificial sweeteners (saccharin, aspartame and cyclamates) can be used. Saccharin and cyclamates are suspected to be carcinogenic and so aspartame is the most accepted one.

The main advantages of using sucrose as a sweetener:

- Colorless.
- Very soluble in water.
- Stable over a pH range of about 4 – 8.
- It increases the viscosity of solutions which will give them a pleasant texture in the mouth.
- It masks the taste of both salty and bitter drugs.
- It has a soothing effect on the throat which makes it suitable for antitussive preparations.

مضادات السعال

The main disadvantages of sucrose is that it initiates dental caries and is not suitable for diabetic patients.

تسوس الاسنان

Appendix I
Methods for preparing Purified water

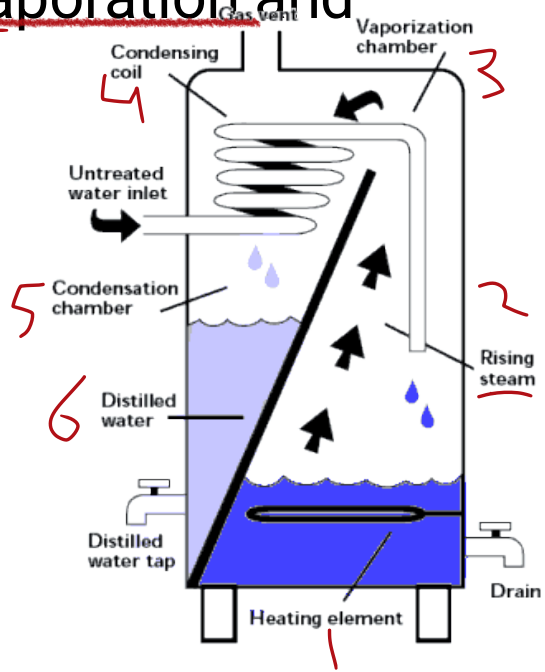
1) Distillation method

- Distillation is a process of separating the component substances from a liquid mixture by selective evaporation and condensation

تكثيف

تبخير

* heat *



Methods for preparing Purified water:

2) Ion- exchange method

- Advantages over distillation method:
  - No heat is required
  - Ease of operation سهولة التشغيل
  - Minimal maintenance صيانة أقل
  - More mobile facility إمكانية التنقل
- The ion exchange equipment involves the passage of water through a column of cation and anion exchangers, consisting of water insoluble, synthetic, polymerized resins of high molecular weight

Methods for preparing Purified water:

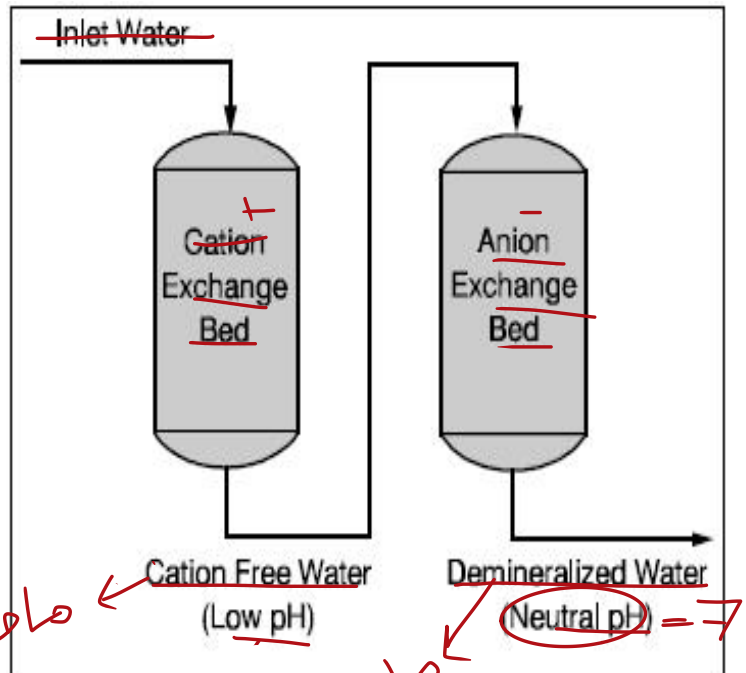
- Water purified using this method is referred to as demineralized or deionized water
- These resins are mainly of two types:
  - A) The cation or acid exchanger, which permit the exchange of cations in solutions with hydrogen ion from the resin
  - B) The anion or base exchangers which permit the removal of anions

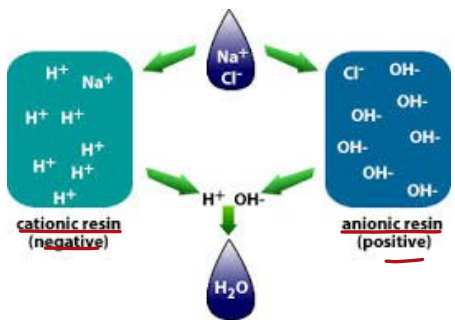
Cation exchange

- $H\text{-Resin} + M^+ + X^- + H_2O \rightarrow M\text{-Resin} + H^+ + X^- + H_2O$ (pure)

Anion exchange

- $\text{Resin } NH_2 + H^+ + X^- + H2O \rightarrow \text{Resin-}NH_2.HX + H_2O$ (pure)

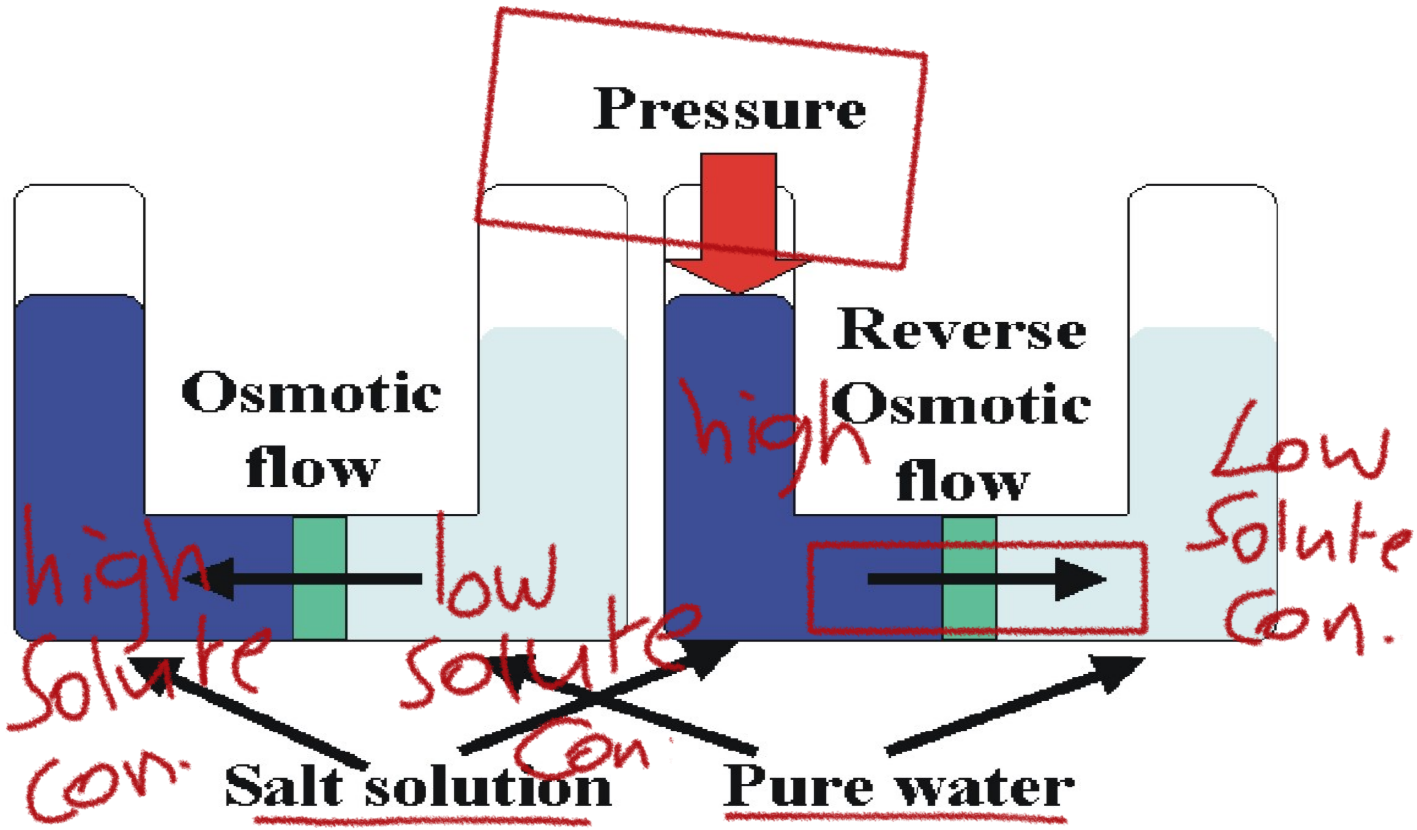

Inlet Water
Cation Exchange Bed
Anion Exchange Bed
Cation Free Water
(Low pH)
Demineralized Water
(Neutral pH) = 7


Na+
Cl-
H+
Na+
H+
H+
H+
H+
H+
cationic resin
(negative)
Cl-
OH-
OH-
OH-
OH-
OH-
OH-
anionic resin
(positive)
H+
OH-
H2O

Methods for preparing Purified water:

3) Reverse osmosis

- Formally, reverse osmosis is the process of forcing a solvent from a region of high solute concentration through a semipermeable membrane to a region of low solute concentration by applying a pressure in excess of the osmotic pressure.
- This is one of the processes referred to in industry as cross-flow (or tangential flow) membrane filtration
- In this process 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
- In the normal osmosis process, the solvent naturally moves from an area of low solute concentration (high water potential), through a membrane, to an area of high solute concentration (low water potential).
- Whereas the flow in this crossflow system is from a more concentrated to less concentrated and therefore it is termed reverse osmosis.



Only Pure Solvent Pass

Methods for preparing Purified water:

- Reverse osmosis can remove many types of molecules and ions from solutions, including bacteria
- The result is that the solute is retained on the pressurized side of the membrane and the pure solvent is allowed to pass to the other side
- Depending on their pore size, cross flow membranes can remove particles defined in the range of:
  - Micro filtration (0.1 – 2 microns)
  - Ultrafiltration (0.01 to 0.1 microns)
  - Nanofiltration (0.001 to 0.01 microns)
  - Reverse osmosis (Less than 0.001 microns) : Reverse osmosis removes virtually all viruses, bacteria, pyrogens, and organic molecules and 90% to 99% of ions


R.O. TACK
Water Technology

RO Membrane

- https://www.youtube.com/watch?v=rK7UVY_7K8w


Thank you!