SHAMBHUNATH INSTITUTE OF PHARMACY, JHALWA, ALLAHABAD

LECTURE NOTES
ON

PHARMACEUTICS -I

UNIT -II

(BP-103T)

B. PHARM. 1st Year 1st Sem

BY

SAURAV GHOSHAL
Asst. Prof.

UNIT II

Pharmaceutical Calculations

Weights and Measures:
There are two systems of weights and measures:

A. The imperial system
B. The metric system

IMPERIAL SYSTEM
It is an old system of weights and measures.
Measurements of weights in imperial system
Weight is a measure of the gravitational force acting on a body and is directly proportional to its mass.
The imperial systems are of two types:
(a) Avoirdupois system and
(b) Apothecaries system

(a) Avoirdupois system
In this system **pound (lb)** is taken as the standard of weight (mass).
TABLE:

1 pound avoir (lb)	= 16 oz avoir	**oz** is pronounced as *ounce*.
1 pound avoir (lb)	= 7000 grains (gr)	

(b) Apothecary or Troy system
In this system **grain (gr)** is taken as the standard of weight (mass).
TABLE:

1 pound apoth (lb)	= 12 ounces (℥)	1 pound apoth (lb) = 5760 grains (gr)
1 ounce (℥)	= 8 drachms (ʒ)	
1 drachm (ʒ)	= 3 scruples (ɜ)	
1 scruple (ɜ)	= 20 grains (gr)	

Measurements of volumes.
TABLE:

1 gallon (c)	= 4 quart
1 quart	= 2 pint (o)
1 pint (o)	= 20 fluid ounce
1 fluid ounce	= 8 fluid drachm
1 fluid drachm	= 3 fluid scruple
1 fluid scruple	= 20 minims

Exercise:
Convert (i) *quart to minim*

1 quart = 2 pint
= 2x (20 fluid ounce)
= 2x20x (8 fluid drachm)
= 2x20x8x (3 fluid scruple)
= 2x20x8x3x(20minims)
= 19200 minims

(ii) pint to fluid ounce, (iii) fluid ounce to minim, fluid drachm = minim

THE METRIC SYSTEM

'**Kilogram**' is taken as the standard weight (mass).

1 kilogram (kg)	= 1000 grams (g)	Kilo = 1000 Greek word
1 hectogram (hg)	= 100 grams (g)	Hecto = 100 Greek word
1 dekagram (dg)	= 10 grams (g)	Deka = 10 Greek word
1 gram (g)	1 gram (g)	
1 decigram (dcg)	1/10 gram (g)	Deci = 1/10 Latin word
1 centigram (cg)	1/100 gram (g)	Centi = 1/100 Latin word
1 milligram (mg)	1/1000 gram (g)	Milli = 1/1000 Latin word
1 microgram (μg, mcg)	10^{-6} gram (g)	Micro = 10^{-6}.
1 nanogram (ng)	10^{-9} gram (g)	Nano = 10^{-9}.

Measurement of volume

'Litre' is taken as the standard of volume.

1 liter (L, lit)	1000ml	
1 microliter (μl)	1/1000 ml	

CONVERSION TABLE

Domestic measures	Metric System	Imperial system
1 drop	0.06ml	1 minim
1 teaspoonful	5 ml	1 fluid drachms
1 desert spoonful	8 ml	2 fluid drachms
1 tablespoonful	15 ml	4 fluid drchms
1 wine-glassful	60 ml	2 fluid ounces
1 teacupful	120 ml	4 fluid ounces
1 tumblerful	240 ml	8 fluid ounce

Weight measure conversion table

1 kilogram	= 2.2 pounds (lb)	
1 ounce apoth.	= 30 g	
1 pound avoir.	= 450 g	
1 grain	= 65 mg	

PERCENTAGE SOLUTIONS

The concentration of a substance can be expressed in the following three types of percentages:

1. Weight in volume (w/v) : Required to express concentration of a solid in liquid.
2. Weight in weight (w/w) : Required to express concentration of a solid in solid mixture.
3. Volume in volume (v/v) : Required to express concentration of a liquid in another liquid.

Weight in volume (w/v)

In this case the general formula for 1%(w/v) is:

		The formula is actually:	
Solute	1part by weight	Solute	1 g
Solvent upto	100 parts by volume	Solvent upto	100 ml

Exercise1: Calculate the quantity of sodium chloride required for 500ml of 0.9% solution.

Ans: 0.9%w/v solution of sodium chloride = $\frac{0.9\text{g Sodium chloride}}{100\text{ml solution}}$

So 500ml solution will contain $\frac{0.9\text{g Sodium chloride}}{100\text{ml solution}} \text{ x } 500\text{ml} = \frac{0.9\text{g x } 500\text{ml}}{100\text{ml}} = \frac{0.9 \text{ x } 500}{100}\text{g} = 4.5\text{g}$ sodium chloride

Weight in weight (w/w)

In this case the general formula for 1%(w/w) is:

		The formula is actually:	
Solute	1part by weight	Solute	1 g
Solvent upto	100 parts by weight	Solvent up to	100 g

Problem: Prepare 100ml Phenol Glycerin BPC. It contains 16%w/w phenol in glycerol. Sp.gr. of glycerol = 1.26

Let us assume that phenol is not increasing the volume of the solution.

So the final solution: Volume = 100ml

Volume of glycerol = 100ml

Weight of glycerol = 100ml x 1.26 g/ml = 100 x 1.26 g = 126g

So the working formula will be:

Ingredient	Quantity for 100g	Quantity required for 100ml
Glycerol	84g	126g
Phenol	16g	$\frac{16\text{g}}{84\text{g}} \text{x } 126\text{g}$ = 24g

Volume in volume (v/v)

In this case the general formula for 1%(w/w) is:

		The formula is actually:	
Solute	1part by volume	Solute	1 ml
Solvent upto	100 parts by volume	Solvent upto	100 ml

Problem: Prepare 600ml of 60%v/v alcohol from 95% v/v alcohol.

In this problem: V1 = ? S1 = 95% V2 = 600ml S2 = 60%

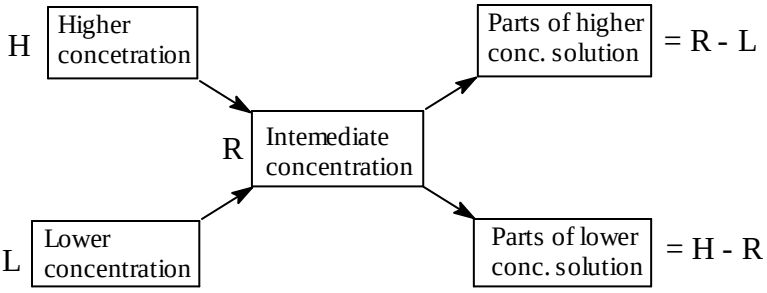
$$V1 \times S1 = V2 \times S2 \quad \text{or, } V1 = \frac{V2 \times S2}{S1} = \frac{600ml \times 60\%}{95\%} = 379ml$$

Ans: 379 ml of 95% alcohol is diluted to 600ml to obtain 60% alcohol.

CALCULATION BY ALLIGATION METHOD

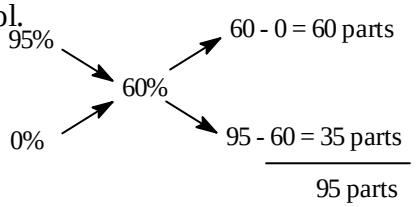
This types of calculation involves the mixing of two similar preparations, but of different strengths, to produce a preparation of intermediate strength. The name is derived from the Latin *alligatio,* meaning the act of attaching and hence referes to the lines drawn during calculation to bind quantities together.

Method:



Example:

Prepare 600ml of 60%v/v alcohol from 95% v/v alcohol.



Higher concentration = 95%
Required concentration = 60%
Lower concentration = 0% (i.e. water)
So from alligation method it is obtained:
Volume of 60% alcohol solution = 600ml

$\therefore$ the volume of 95% alcohol required =

$$\frac{\text{Parts of 95\% alcohol}}{\text{Parts of water + parts of 95\% alcohol}} \times 600ml = \frac{60}{35+60} \times 600\,ml = 379ml$$

PROOF SPIRITS

For excise (tax) purpose, the strength of alcohol in indicated by *degrees proof*.

The US System: **Proof spirit** is 50% alcohol by volume (or 42.49% by weight).
The British / Indian system: **Proof spirit** is 57.1% ethanol by volume (or 48.24% by weight.

Definition: **Proof spirit** is that mixture of alcohol and water, which at 51^0F weighs $12/13^{th}$ of an equal volume of water.
[N.B. Density of proof spirit = 12/13 of density of water at 51^0F = 0.923 g/ml]

This means that any alcoholic solution that contains 57.1%v/v alcohol is a proof spirit and is said to be 100 proof.

100 degree proof alcohol = 57.1% v/v alcohol

If the strength of the alcohol is above 57.1%v/v alcohol then the solution is called "*over proof*".

If the strength of the alcohol is below 57.1%v/v alcohol then the solution is called "*under proof*".

In India, the excise duty is calculated in terms of Rupees per litre of proof alcohol. So any strength of alcohol is required to be converted to *degree proof* . We shall follow the British System

*Conversion of strength of alcohol from **%v/v** to **degrees proof** as per Indian system.*

$$\text{Strength of alcohol} = \frac{\%v/v \text{ strength}}{57.1\%v/v} \times 100$$

*Conversion of strength of alcohol from **degrees proof** to **%v/v** as per Indian system.*

$$\text{Strength of alcohol in \%v/v} = \frac{\text{Strength of alcohol in degree proof} \times 57.1}{100}$$

Example 1:Find the strength of 95%v/v alcohol in terms of proof spirit.

Strength of alcohol = $\frac{95\%v/v}{57.1\%v/v} \times 100$ = 166.34 degree proof = (166.34-100) degrees over proof = 66.34^0 op

Example 2:Find the strength of 20%v/v alcohol in terms of proof spirit.

Strength of alcohol = $\frac{20\%v/v}{57.1\%v/v} \times 100$ = 35.03 degree proof = (100-35.03) degrees under proof = 64.97^0 up

Example 3:Calculate the real strength of 30^0op and 40^0up.

30^0op = (100 + 30) = 130 deg proof Therefore the strength of alcohol = $\frac{130 \times 57.1}{100}$ = 74.23%v/v

40^0op = (100 – 40) = 60 deg proof Therefore the strength of alcohol = $\frac{60 \times 57.1}{100}$ = 34.26%v/v

ISOTONIC SOLUTIONS

Osmosis: If a solution is placed in contact with a semipermeable membrane the movement of the solvent molecules through the membrane is called *osmosis*.

An ideal *semipermeable* membrane only lets the solvent molecules to pass through it but not the solute molecules. The biological membranes are not ideal semipermeable membranes. They are selectively permeable; they give passage to some solutes while stop the passage of others. In case of biological membranes another term *tonicity* is used.

Isotonicity: A solution is isotonic with a living cell if there is no net gain or loss of water by the cell, when it is in contact with this solution.

If a living cell is kept in contact with a solution and there is no loss or gain of water by the cell then the solution is said to be *isotonic* with the *cell*.

- It is found that the osmotic pressure of 0.9%w/v NaCl solution is same as blood plasma. So 0.9%w/v NaCl solution is *isotonic* with plasma.

Tonicity– A. Isotonic – When a solution has same osmotic pressure as that of 0.9%w/v NaCl solution.

B. Paratonic – Not isotonic

(a) Hypotonic – The osmotic pressure of the solution is higher than 0.9%w/v NaCl solution

(b) Hypertonic – The osmotic pressure of the solution is lower than 0.9%w/v NaCl solution

Test of tonicity

A red blood corpuscle is placed in a solution and after some time it is viewed under microscope.

Observation	**Conclusion**	**Mechanism**
The shape and size of the cell remained unchanged	The solution is isotonic	Osmotic pressure of the cell fluid and the solution are same. No movement of water occurs across the cell membrane.
The size of the cell increased and may burst.	The solution is hypotonic.	Osmotic pressure of the cell fluid is more than the solution. Water molecules moved from the solution to the interior of the cell, so the cell swelled.
The size of the cell is reduced or shrinked.	The solution is hypertonic.	Osmotic pressure of the cell fluid is less than the solution outside. Water molecule moved from the interior of the cell to the solution.

N.B. If the red blood cell bursts then the hemoglobin comes out of the cell and the plasma become red in color. This phenomenon is called haemolysis.

Importance of adjustment of tonicity in pharmaceutical dosage forms

1. *Solution for intravenous injection*: The injection must be isotonic with plasma, otherwise the red blood corpuscle may be haemolysed.
2. *Solution for subcutaneous injection*: Isotonicity is required but not essential, because the solution is coming in contact with fatty tissue and not in contact with blood.

3. *Solution for intramuscular injection*: The aqueous solution may be slightly hypertonic. This will draw water from the adjoining tissue and increase the absorption of the drug.
4. *Solution for intracutaneous injection*: Diagnostic preparations must be isotonic, because a paratonic solution may cause a false reaction.
5. *Solutions for intrathecal injection*: Intrathecal injections are introduced in the cavities of brain and spinal chord. It mixes with the cerebrospinal fluid (CSF). The volume of CSF is only 60 to 80ml. So a small volume of paratonic injection may change the osmotic pressure of the CSF, which may lead to vomiting and other side effects.
6. *Solutions for nasal drops*: Aqueous solutions applied within the nostril may produce irritation if it is paratonic. So nasal drops must be isotonic with plasma.
7. *Solutions for ophthalmic use*: Only one or two drops of ophthalmic solutions are generally used. So it is not essential for eyedrops to be isotonic. Slight paratonicity will not produce great irritation because the eyedrops will be diluted with the lachrymal fluid.

Calculations for adjustment of tonicity

It is difficult and time consuming to determine the osmotic pressure of a solution. So some indirect methods are adopted to compare between two isotonic solutions. Two solutions will produce same osmotic pressure if both contain the same numbers of *ultimate units*. These units may be as follows:

1. These units may be molecules in case of substances those do not ionize.
2. These units may be ions in case of substances those ionize.
3. These units may be both ions and unionized molecules in case of weak electrolytes.

Some physical properties of these solutions depend on this number (or, collection) of units, such as osmotic pressure, freezing point depression (ΔT_f), vapor pressure etc. – these physical properties are called *colligative properties* of the solutions.

Since these colligative properties are inter-dependent, so osmotic pressures of two solutions can be compared from their colligative properties like freezing point depression.

Tonicity of a solution can be adjusted by the following methods:

1. Freezing Point Depression Method (ΔT_f)
2. Molecular Concentration Method

1. Freezing Point Depression Method

Theory: Freezing point of pure water is 0^0C. When any impurities are there (like salt, drug etc.) the water freezes at some lower temperatures (like -0.18^0C). In case of a solution the solute units reduces the freezing point of water.

So the freezing point depression, ΔT_f = Freezing point of pure water – Freezing point of the solution

This ΔT_f is proportional to the number of units of solutes present in the solution.

ΔT_f is also proportional to the osmotic pressure of the solution.

Now while preparing an injection or ophthalmic solution the drug is given in a certain percentage (i.e. %w/v)

The concentration of the adjusting substance to be added is calculated according to the formula below

%age (v/v) of adjusting substance= (0.52-a)/b
Where a= freezing point of unadjusted solution
b= freezing point of 1%w/v solution of adjusting substance

2. Based on Molecular Concentration:

In this method the concentration of the adjusting substance to be added is calculated according to the formula below

%age (v/v) of adjusting substance= (0.03*M)/N
Where M= Molecular Weight of adjusting substance
N= Number of ions into which the substance ionizes in solution.

POWDERS

Powders are mixtures of dry, finely divided drugs and/or chemicals that may be intended for internal or external use.

The term '**Powder**' may be used to describe:

The physical form of a material, that is, a dry substance composed of finely divided particles or, it may be used to describe a type of pharmaceutical preparation, that is, a medicated powder intended for:

- ✓ internal (i.e., oral powder)
- ✓ external (i.e., topical powder) use.

Although the use of medicated powders in therapeutics is limited, the use of powdered substances in the preparation of other dosage forms is extensive.

For example:

1. Powdered drugs may be blended with powdered fillers and other pharmaceutical ingredients to fabricate solid dosage forms as tablets and capsules
2. They may be dissolved or suspended in solvents or liquid vehicles to make various liquid dosage forms
3. They may be incorporated into semisolid bases in the preparation of medicated ointments and creams.

Advantages

- More stable than liquid
- More convenient to swallow than tablet or capsules.
- Used in blending with medicated application as ointments, suppositories and pastes.
- Can be prepared into granules for use in preparing tablets and or reconstituted to liquid form.
- Rapid therapeutic effect due to large surface area.
- Useful for bulky drugs with large dose.

Disadvantages

- Unpleasant tasting of drugs

- It is difficult to protect powders containing hygroscopic, deliquescent (tending to melt or dissolve in humid environment), or aromatic materials from decomposition.

- Time and expenses require in the preparation of uniform powders are great

- Patient may misunderstand the correct method of use. Without clear instruction, patients may inhale through the nose a drug intended for oral administration.

CLASSIFICATION OF POWDERS

Powders are subdivided solids which are classified based on the manner of their dispensing.

1. Bulk powders for external use:

(a) Dusting powders (b) Snuffs (c) Dental powder (d) Insufflations

2. Bulk powders for internal use.

3. Simple and compound powders for internal use.

4. Effervescent granules

5. Cachets

1. Bulk powders for external use

External bulk powders contain non-potent substances for external applications. These powders are dispensed in glass, plastic wide mouth bottles and also in cardboard with specific method of application. Bulk powders for external used are of four types.

(a) Dusting powders (b) Snuffs (c) Douche powders (d) Dental powder (e) Insufflation

2. Bulk powders for internal use

Bulk powders contain many doses in a wide-mouth container that is suitable to remove the powder by a teaspoon. The non-potent substances are used in bulk powder form such as antacid, laxative, purgative, etc.

Rhubarb powder

Light magnesium carbonate

Heavy magnesium carbonate

Ginger powder

Make a powder.

3. Simple and compound powders for internal use.

These are unit dose powders normally packed in properly folded papers and dispensed in envelopes, metal foil, small heat-sealed plastic bags or other containers.

Usually for the preparation of simple powders, the ingredients are weighed correctly and blended by geometrical mixing in ascending order of weights. The mixture is then either divided into blocks of equal size, numbers of blocks representing the number of powders to be dispensed or each dose is weighed separately and placed on a powder paper. The paper is then folded according to the pharmaceutical art and placed in either an envelope or a powder box.

4. Effervescent granules

This class of preparations can be supplied either by compounding the ingredients as granules or dispensed in the form of salts. The ingredients whether in granular form or present as salts, react in presence of water evolving carbon dioxide gas.

For evolution of the gas two constituents are essential, a soluble carbonate such as sodium bicarbonate and an organic acid such as citric or tartaric acid. The preparation can be supplied either as a bulk powder or distributed in individual powders.

5. Cachets

Cachet as a unit dosage form was very popular sometime back. Presently cachets are seldom used and have been replaced by capsules. Cachets, like capsules, can be easily filled and sealed at the dispensing counter.

This dosage form holds larger quantity of the medication as compared to capsules. Since the cachets are made of flour and water they are easily damaged in handling. Further this dosage form offers little protection against light and moisture.

CLASSIFICATION ON THE BASIS OF PARTICLE SIZE

Powders of vegetable and animal origin drugs are officially classified as follows:

- **Very coarse (No. 8):** All particles pass through a No. 8 sieve and not more than 20% pass through a No. 60 sieve.
- **Coarse (No. 20):** All particles pass through a No. 20 sieve and not more than 40% pass through a No. 60 sieve.

- **Moderately coarse (No. 40):** All particles pass through a No. 40 sieve and not more than 40% pass through a No. 80 sieve.
- **Fine (No. 60):** All particles pass through a No. 60 sieve and not more than 40% pass through a No. 100 sieve.
- **Very fine (No. 80):** All particles pass through a No. 80 sieve. There is no limit to greater fineness.

SIMPLE AND COMPOUND POWDERS:

A powdered drug on its own can be a dosage form for taking orally (called a simple powder), when they are usually mixed with water first, or for external application as a dusting powder. Alternatively, the drug may be blended with other ingredients (called a compound powder).

Powders for oral administration will comprise the active ingredients with excipients such as diluents, sweeteners and dispersing agents. These may be presented as undivided powders (bulk powders) or divided powders (individually wrapped doses).

Individually wrapped powders tend not to be official formulae and are rarely prescribed these days.

OFFICIAL PREPARATIONS

Magnesium Trisilicate Powder Compound BP and Compound Kaolin Powder BP are examples of bulk powders for internal use. Proprietary powders and granules include Dioralyte®, Electrolade® (both oral rehydration salts), Normacol® (sterculia) and Fybogel® (ispaghula husk).

Supplying as an undivided powder is useful for non-potent, bulky drugs with a large dose, e.g. antacids, or when the dry powder is more stable than its liquid-containing counterpart. A bulk powder can be supplied to the patient although this is rarely seen nowadays because the dosage form is inconvenient to carry and there are possible inaccuracies in measuring the dose.

Individually wrapped powders are used to supply some potent drugs, where accuracy of dose is important. Extemporaneously produced powders are wrapped separately in paper. They are convenient dosage forms for children's doses of drugs which are not commercially available at the strength required, such as levothyroxine (thyroxine) or ibuprofen. Sealed sachets of powders are available commercially, e.g. Paramax® (paracetamol and metoclopramide) and oral rehydration salts. They are mixed with water prior to taking and are useful for patients who have difficulty swallowing or where rapid absorption of the drug is required.

DUSTING POWDERS

These are used externally for local application not intended for systemic action. The desired characteristics of powders include- (a) homogeneity, (b) non-irritability, (c) free flow, (d) good spreadability and covering capability, (e) adsorption and absorption capacity, (f) very fine state of subdivision, and (g) capacity to protect the skin against irritation caused by friction, moisture or chemical irritants.

Dusting powders usually contain substances such as zinc oxide, starch and boric acid or natural mineral substances such as kaolin or talc.

Talc may be contaminated with pathogenic microorganisms such as - Clostridium tetani etc., and hence it should be sterilized by dry heat. Dusting powders should not be applied to broken skin. If desired, powders should be micronised or passed through a sieve # 80 or 100. Dusting powders should preferably be dispensed in sifter-top containers. Such containers provide the protection from air, moisture and contamination as well as convenience of application. Currently some foot powders and talcum powders have been marketed as pressure aerosols.

Dusting powders are employed chiefly as lubricants, protectives, absorbents, antiseptics, antipruritics, astringents and antiperspirants.

Zinc oxide 20 parts

Salicylic acid 2 parts

Starch powder 78 parts

EFFERVESCENT GRANULES

This class of preparations can be supplied either by compounding the ingredients as granules or dispensed in the form of salts. The ingredients whether in granular form or present as salts, react in presence of water evolving carbon dioxide gas.

For evolution of the gas two constituents are essential, a soluble carbonate such as sodium bicarbonate and an organic acid such as citric or tartaric acid. The preparation can be supplied either as a bulk powder or distributed in individual powders.

There are three alternative methods of dispensing depending upon the nature of prescription.

(i) If the effervescent salts are prescribed to be the dispensed in bulk form, no granulation is necessary. The ingredients are mixed uniformly and directions stated on the label to add the prescribed quantity to water, before use.

(ii) If the effervescent salt is prescribed in divided doses, the ingredients which cause effervescence on mixing with water are enclosed separately in papers of different colour. The patient is advised to take one powder of each colour and add to water, before use. Quantities of the sodium bicarbonate and the organic acid, citric or tartaric, are equimolecular in proportion.

(iii) In the third case the product contains all the ingredients mixed together in a granular form. Preparation of granular products requires pharmaceutical technique. If sodium bicarbonate and citric acid are taken in equimolecular proportion and mixed to make granules, the quantity of water of crystallization liberated from the citric acid is large enough to make the mass wet and carbon dioxide may be liberated during the preparation itself. If one tries to substitute citric acid by tartaric acid, which contains no water of crystallization; it may not be possible to form a mass necessary for granulation.

Therefore both citric and tartaric acids are taken in suitable proportions leaving a little acid in surplus than the quantity required to neutralize sodium bicarbonate. This surplus is necessary to give the final preparation an acidic taste that is more palatable. There is a certain loss in weight of such a preparation due to the loss of water in drying the granules and partial loss of carbon dioxide due to its release during preparation.

Heating is done on a water bath keeping all the ingredients thoroughly mixed in a porcelain dish. Gentle application of heat liberates the water of crystallization from citric acid and the mass tends to be coherent.

Prolonged heating may result in complete evaporation of the released water leaving the product in the form of a dry lump which cannot be rendered into granules. The coherent mass is transferred from the porcelain dish to an inverted sieve of suitable aperture size kept over a glazed paper.

The mass is pressed through the sieve taking care to change the position of the sieve over the paper to prevent the formation of a lump of the sieved granules. The granules are dried in an oven taking care to regulate the temperature which should be generally kept below 80°C.

The operation requires considerable skill and experience to obtain granules of uniform size and an elegant product. If necessary, the dry granules are passed through a sieve of appropriate size to break larger granules which result due to sticking of the sieved wet granules[-].

The water of crystallization of the citric acid and the water from the reactions make the material coherent. Loss of weight occurs during granulation due to (a) evaporation from the damp mixture, and (b) loss of carbon dioxide. The losses constitute approximately one-seventh of the weight of powder used and must be allowed for when calculating the amount to be prepared.

HYGROSCOPIC AND DELIQUESCENT POWDER

They absorb moisture from air leading to partial or complete liquefaction.
This problem is solved by
A- Applied in a granular form to decrease the exposed surface to air.
B- Packed in aluminum foil or in plastic film packets
C- Addition of light magnesium oxide to reduce the tendency to damp
D- Addition of adsorbent materials such as starch
Examples: - halide salts (ex. Sod. Iodide)
- Certain alkaloids (physostigmine HCl)

EFFLORESCENT POWDERS

Crystalline substances which during storage loose their water of crystallization and change to powder (to be efflorescent). The liberated water convert the powder to a paste or to a liquid.
This problem is solved by:
Using the anhydrous form, and treating it in a manner similar to hygroscopic powders
Examples: Alum- atropine sulfate- citric acid- codeine phosphate…

EUTECTIC MIXTURES

Mixture of substances that liquefy when mixed, rubbed or triturated together. The melting points of many eutectic mixtures are below room temperature.
This problem is solved by:
A- using inert adsorbent such as starch, talc, lactose to prevent dampness of the powder
B- dispensing the components of the eutectic mixture separately.
Examples:
Menthol- thymol- phenol- salol- camphor…….

Homogenous Mixture

The processes used to reduce particle size are also used to mix solid particles into a homogenous mixture. Powders that have been blended with a protectant to prevent the formation of a eutectic mixture must be mixed carefully with little to no pressure. **Spatulation,** or the mixing of particles with a spatula on an ointment slab, will result in a light, well-mixed powder without interfering with the protectant. **Trituration** serves the dual purpose of reducing particle size and mixing powders. It is especially effective for mixing small quantities of potent drugs with larger amounts of diluent. Hazardous substances can be effectively mixed by a process called **tumbling**. The powders are sealed in zipper-sealed bags or clear bottles with a lid and tumbled until they are well mixed. The addition of a coloring agent can assist in determining when the mixture is homogenous.

GEOMETRIC DILUTION

When the powders being combined are unequal in quantity, **geometric dilution** is the preferred method for mixing them. Begin by placing the powder with the smallest quantity in the mortar and adding an equal amount of each of the other powders. Continue adding each powder in an amount that is equal to the powder in the mortar and triturate well after each addition to form a homogenous mixture. To mix powders of equal volumes, add small, equal amounts of each powder and mix well after each addition. Equal dispersion of each ingredient is important to provide the proper therapeutic effect.

LIQUID DOSAGE FORMS

Liquid form of a dose of a chemical compound used as a drug or medication intended for administration or consumption.

May be administered systematically by mouth or injected, by using different techniques, into the skin, muscles, or veins.

ADVANTAGE OF LIQUID DOSAGE FORM:

1. Better for patients who have trouble swallowing.
2. Faster absorption than solids.
3. More flexibility in achieving the proper dosage of the medication.

DISADVANTAGE OF LIQUID DOSAGE FORM:

1. Shorter life before expiration than other dosage forms.
2. Bad taste.
3. More difficult to administer.
4. Harder to measure accurately.
5. May have special storage requirements.

EXCIPIENTS USED IN LIQUID DOSAGE FORMS:

The common excipients generally required for any liquid formulation are vehicles (base), viscosity builders, stabilizers, preservatives, colours and flavours. In addition, solubilizers are required in case of clear liquids, suspending agents are needed for suspensions and emulsifying agents for emulsions.

VEHICLES

Vehicles, in pharmaceutical formulations, are the liquid bases that carry drugs and other excipients in dissolved or dispersed state. Pharmaceutical vehicles can be classified as under;

Aqueous vehicles: Water, hydro-alcoholic, polyhydric alcohols and buffers. These may be thin liquids, thick syrupy liquids, mucillages or hydrocolloidal bases.

Oily vehicles: Vegetable oils, mineral oils, organic oily bases or emulsified bases.

Aqueous Vehicles

Water

Natural water contains large number of dissolved and suspended impurities. The dissolved impurities include inorganic impurities like salts of sodium, potassium, calcium, magnesium and

iron as chlorides, sulfates and bicarbonates. Drinking water, termed as potable water in many texts, contains less than 0.1% of total solid.

However, drinking water is not usable in pharmaceutical formulation, obviously due to the possible incompatibility of formulation components with dissolved impurities in water. Purified water USP is allowed for usage as vehicle or as a component of vehicle for aqueous liquid formulations except for those intended for parenteral administration (injections). It is obtained by distillation, ion exchange treatment, reverse osmosis or any other suitable process from water.

Alcohol (Ethyl Alcohol)

Next to water, alcohol is the most useful solvent in pharmacy. It is invariably used as hydro-alcoholic mixture that dissolves both water soluble and alcohol soluble drugs and excipients. Diluted alcohol NF, prepared by mixing equal volumes of Alcohol USP and purified water USP is a useful solvent in various pharmaceutical processes and formulations.

Glycerol

Glycerol (or Glycerin) is a clear, colorless liquid, with thick, syrupy consistence, oily to the touch, odourless, very sweet and slightly warm to the taste. When exposed to the air, it slowly abstracts moisture. Glycerol is obtained by the decomposition of vegetable or animal fats or fixed oils and containing not less than 95 percent of absolute Glycerin. Glycerin is used as vehicle in various pharmaceutical products like Elixir of Phosphoric acid, Solution of Ferric Ammonium Acetate, Mucilage of Tragacanthae, Glycerin of boric acid, Glycerin of tannic acid, and in many Extracts, Fluid Extracts, Syrups and Tinctures.

Propylene Glycol USP

Pharmaceutical grade of Propylene Glycol is monopropylene glycol (PG or MPG) with a specified purity greater than 99.8%. Propylene glycol is an outstanding solvent for many organic compounds. It is colourless and odourless and has a very slight characteristic taste which is not objectionable. These properties make propylene glycol particularly suitable as a solvent for flavourings and dyes in cosmetics, toothpastes, shampoos, and mouthwashes. Propylene glycol is non-allergenic and may be used in cosmetics and other toilet goods specifically formulated for sensitive skin. Propylene glycol is a general solvent and antimicrobial preservative used in a wide range of pharmaceutical preparations including oral liquid, topical and parenteral preparations.

Lipid-Based Vehicles

These are obtained from vegetable, animal or mineral origin and are quite commonly used in formulations. Vegetable Oils are mainly used in preparation of emulsions e.g. Corn Oil, Cotton seed oil and castor oil. They may develop rancidity upon storage or may cause allergic reactions in certain patients. Mineral oils like liquid paraffin are more stable but the vegetable oils are

preferred for parentral preparations. Animal oils such as Lard are rarely used. Oils are rarely used in oral preparations due to their disagreeable taste and odour.

Certain Esters (RCOOR') such as Ethyl Oleate, Isopropylmyristicate and benzyl benzoate and Silicones (-O-Si-O-Si-) such as dimethylpolysiloxane are being used as substitute for the conventional oil based vehicles.

Wetting Agents and Surfactants

Wetting agents are routinely used in pharmaceutical formulations, especially in liquid dosage forms to create a homogeneous dispersion of solid particles in a liquid vehicle. This process can be challenging due to a layer of adsorbed air on the particle's surface. Hence, even particles with a high density may float on the surface of the liquid until the air phase is displaced completely. The use of a wetting agent allows removal of adsorbed air and easy penetration of the liquid vehicle into pores of the particle in a short period of time. For an aqueous vehicle, alcohol and glycerin are frequently used to facilitate the removal of adsorbed air from the surface of particles. Whereas for a non-aqueous liquid vehicle, mineral oil is commonly used as a wetting agent.

Typically, hydrophobic API particles are not easily wetted even after the removal of adsorbed air. Hence, it is necessary to reduce the interfacial tension between the particles and the liquid vehicle by using a surface-active agent. Structurally, wetting agents comprise branched hydrophobic chains with central hydrophilic groups or short hydrophobic chains with hydrophilic end groups. For example, sodium lauryl sulfate is one of the most commonly used surface-active agents. Such surfactants, when dissolved in water, lower the contact angle of water and aid in spreadability of water on the particles surface to displace the air layer at the surface and replace it with the liquid phase. Wetting agents have a hydrophilic-lipophilic balance (HLB) value between 7 and 9.

pH Modifiers and Buffering Agents

The pH of an oral liquid formulation is a key point in many regards. Control of the formulation pH, could prevent large changes during storage. Therefore, most formulations utilize a buffer to control potential changes in the solution pH. The selection of a suitable buffer should be based on:

(i) Whether the acid-base forms are listed for use in oral liquids,

(ii) The stability of the drug and excipients in the buffer, and

(iii) The compatibility between the buffer and container. A combination of buffers can also be used to gain a wider range of pH compared to the individual buffer alone. However, not all buffers are suitable for use in oral liquids. For example, a boric acid buffer may be used for optical and IV delivery but not in oral liquids because of its toxicity.

ANTIOXIDANTS

The oxidation of an API in an oral liquid formulation is difficult to control due to low activation energies (2-12kcal/moL) for oxidation and photolysis compared to solvolysis, dehydration, and polymorphic transformations (10-56kcal/mol). Trace amounts of impurities, which are invariably present in the API or excipient catalyses the oxidation reaction. Most drugs exist in a reduced form, show increased instability when the solution is consistently introduced into an atmosphere of 20% oxygen.

Antioxidants can be compounds that can reduce a drug that has been oxidized, or compounds that are more readily oxidized than the agents they are to protect (oxygen scavengers). Many of the lipid-soluble antioxidants act as scavengers. Antioxidants can also act as chain terminators, reacting with free radicals in solution to stop the free-radical propagation cycle. Anti-oxidants generally used in liquid formulations are listed below:

Oil Soluble: Butylated Hydroxy Toulene (BHT), Butylated Hydroxy Anisole (BHA), Lecithin.

Water Soluble: Ascorbic Acid, Citric Acid, Tartaric Acid and Phosphoric Acid

COLORING AGENT:

Coloring agents or colorants are employed in pharmacy solely for the purpose of imparting colour which gives a pleasing appearance to the dosage form. They are used as sensory adjuvants. The coloring principles are divided into two broad categories:

1. Natural Colouring Agents: These are obtained from mineral, plant and animal sources. They are used as colours for foods, drugs and cosmetics and for other psychologic effects.

(a) Mineral Colors: These are also known as pigments and are used as colours for lotions, cosmetics and other preparations. Eg. red and yellow ferric oxide, titanium dioxide, carbon black, lead chromate, Prussian blue.

(b) Plant Colors: Coloring principles from plants are normally obtained by extraction. Egs. **Chlorophyll**, **Beta-Carotene**, Alizarin from Madar, **Indigo**, anthocyanin, flavones, Rutin and Hesperidine from Citrus plants & **Saffron** from *Crocus sativus.*

(c) Animal Colors: Cochineal obtained from the insect *Coccus cacti* contains the bright red coloring principle, carminic acid. Tyrian purple is obtained by the oxidation of snails. These colors have a lot of side effects hence are not generally used. (Carminic acid causes salmonella infection).

2. Synthetic Colors: Mauveine or Perkin's Purple was accidentally discovered while trying to synthesize quinine. The earliest synthetic colours were prepared from aniline. Synthetic dyes

prepared from coal tar were frequently used in food and beverages to enhance their appearance, without considering their toxicity. However since all these colors are not suitable for human consumption hence only certain colors have been approved by Govt. of various countries.

In India the following colours may be used in drugs:

i) Natural Colours: Annatto, **Carotene**, **Chlorophyll**, Cochineal, Curcumin, Red Oxide of Iron, Yellow Oxide of Iron, **Titanium Dioxide**.

ii) Artificial Colours: **Caramel**

iii) Coal Tar Dyes: Tartazine, Sunset Yellow- Yellow Colours

Amaranth, Eosin YS or Eosin G- Red Colours

Indigo Carmine- Blue

Napthol Blue Black- Blue

iv) Lakes: These aluminium or calcium salts of the coal tar dyes. They are insoluble in water and organic solvents. They are used in powder, food packaging and candles.

Selection of Colouring Agent:

The selection of appropriate coloring agent is based on the following points:

1. The aesthetics and certification status of the dye.

2. Physical and chemical properties of the dye.

3. In case of liquid preparation the pH and the pH stability of the preparation to be coloured.

4. Photostability of the dye.

5. Personal preference of the consumer population.

The amount of the colorant added ranges from 0.0005 to 0.001% for liquids, 0.1% for powders.

FLAVORING AGENT:

The term flavor refers to the mixed sensation of taste, smell, touch, sight and sound, all of which produce an infinite number of gradations in the perception of a substance. Flavouring is particularly significant in case of liquid dosage forms intended for oral use. By suitably

flavouring the medication the bad taste can be effectively masked. Chewable tablets are often flavored to improve patient acceptance.

Taste is percepted due to physiological and psychological action; the impulse for taste is carried by the 7^{th}, 9^{th} and 10^{th} Cranial Nerves. However the smell has a more significant role in taste perception and in general people are more sensitive to odour than to taste.

Flavouring agents may belong to the following categories:

Simple Ester- Methyl Salicylate

Alcohol-Glycerin

Aldehyde-Vanillin

Carbohydrates-Honey

Volatile Oil-Fennel, Anise, etc..

Synthetic Flavours-Cinnamaldehyde, Benzaldehyde

Selection of flavouring agent: The selection of appropriate flavouring agent is done on the following basis:

1. The taste qualities of the flavor.
2. Suitability of the flavor, colour and sweetener
3. Type of preparation- Internal Use or External Use
4. Age of the patient
5. Likings and Disliking of the user
6. Patient condition and Psychology. Eg. A nauseating patient feels a cool flavor more relaxing
7. Knowledge of allergies of the patient.

Correlation of Flavour and Odour with taste:

1. Sour Taste (in acids and lipid soluble drugs) is masked by Raspberry and fruit syrups
2. Salty Taste (in ion containing drugs) is masked by Cinnamon, Orange and Cherry Syrup.
3. Sweet Taste (due to poly hydroxyl groups) generally not masked but may be accompanied with a spicy or lemon like flavor to overcome the sweetness.
4. Bitter taste (due to free bases) polyhydroxy compounds like saccharine and cyclamates mask the bitter taste.
5. Oily Taste is masked by peppermint oil

Significance of Flavours

1. In Liquid dosage forms:- Flavours like Vanilla, Vannillin, syruop, honey, peppermint, cherry syrup ,etc are often used for drugs with pungent odour or taste.
2. Chewable Tablets: The antacid and antidiarrhoeal drugs have a chalky taste, mannitol is generally used in this case which gives a cooling effect and masks the taste. Vanilla, Raspberry and Cherry are also used as flavours in the case of vitamins and antibiotics.

SWEETENING AGENTS:

Sweetening agents (sweeteners) are used to impart sweetness to a preparation. Like smell, taste is also a chemical sense, the appreciation of which results from the contact between the taste possessing material and the taste buds in the mouth. The four primary tastes are sweet, bitter, sour and salty for which the taste buds are located in the different parts of the mouth. The perception of taste depends upon the actual taste and the "body" (viscosity) of the formulation.

All drugs for oral use may not have an agreeable taste often the taste has to be masked. Sweet taste is most appreciated and sweeteners are often employed in formulations. The following types of sweeteners are often employed in formulations.

1. Sugar (or Sucrose): It is obtained from cane sugar and is available in highly pure form at a reasonable cost. It is stable in the pH range of 4.0-8.0. It is generally used along with sorbitol and glycerol to prevent the **Cap Locking** which occurs due to crystallization of Sucrose. It is however prone to microbial attack and is not suitable for diabetic patients.
2. Liquid Glucose: It is prepared by partial hydrolysis of starch with strong acid. It provides body and sweetness to formulations.
3. Invert Sugar: It is obtained by the hydrolysis of sucrose and is a mixture of glucose and fructose. The fructose present in it prevents crystallization and is sweeter than sucrose. However it is thermolabile and darkens in cold weather.

4. Sorbitol or D-glucitol: It is a hexahydric alcohol (with 6 –OH) groups and is used as a 70% w/w soln. and is half as sweet as simple syrup. It doesn't raise the blood sugar level, hence can be used by diabetics. It also prevents cap locking
5. Saccharin: It is an artificial sweetener and purely synthetic in nature. It is 250-500 times as sweet as sugar but it leaves a bitter after taste. It undergoes hydrolysis and the product is bitter (thus bitter aftertaste). It is available as Saccharin Sodium and Saccharin Calcium, 1 to 10% solutions are generally used in formulations. It is used as sweetener in vehicles for liquid dosage form, canned foods, beverages, tooth paste, chewable tablet and preparations for diabetic patients. It is non toxic and excreted unchanged in urine in 24 hrs.

6. Cyclamates: They were widely used due to high stability, absence of bitter after taste and good sweetening properties. They are sodium or potassium salts of cyclohexanesulphamic acid. They are approximately 30 times sweeter than sucrose. However their use is now banned because of their cancer causing property (Carcinogen).
7. Asparatame: It is the methyl ester of aspartic acid and phenylalanine. It is 200 times sweeter than sucrose but its calorie content is very low. It is generally regarded as safe but is not allowed in patients with phenylketonuria.

CO-SOLVENTS

The solubility of a compound in a solvent depends upon the dielectric constant of that solvent. Thus as the dielectric constant of a series of solvent increases, the probability of dissolving a substance in that solvent also increases. When a substance is poorly water soluble it becomes necessary to design a solution system which achieves an adequate concentration for a solution dosage form. One of the common approaches to increase the solubility of drugs is the use of co-solvents or mixed solvents eg. Ethanol, glycerin, propylene glycol and isopropyl alcohol.

Cosolvency is the process of enhancing the solubility of a very poorly soluble drug in water by adding water miscible solvents in which the drug is very soluble. The Cosolvents generally act by increasing the solubility as a result of additive effect of the solubility of the substance in the primary solvent and the cosolvent. Some of the commonly used cosolvents are described below:

1. Alcohol: Ethanol or Ethyl Alcohol is an important solvent next to water. It can be stored for an indefinite period due to lack of hydrolysis. Microbial growth doesn't occur in ethanol. It is used to dissolve resins, volatile oils, alkaloids, glycoside, etc.. Preparations containing a mixture of water and alcohol are known as hydroalcoholic preparations.
2. Glycerine: It is the most popular cosolvent after alcohol. Its higher concentrations have preservative action. It is used to dissolve a large number of salts, vegetable acids, pepsin, tannin, plant constitutents, etc.. It is added as a preservative and stabilizer of solutions that have been prepared with other solvents.
3. Propylene Glycol: It is used as a substitute for glycerine. It is miscible with water, with acetone and with chloroform in all proportions. It dissolves many essential oils but is immiscible with fixed oils. It is as effective as ethanol in preventing microbial growth.
4. Isopropyl Alcohol: Its solvent properties are similar to that of ethyl alcohol. Its avantage over ethyl alcohol is that the commonly available isopropyl alcohol contains not more than 1% water while the commonly available ethanol contains about 5% water which is often a disadvantage.

PRESERVATIVE

Preservatives are substances which are added to preparation to prevent bacterial growth and subsequent spoilage of the preparation which are intended to be stored for prolonged periods of time. Emulsions and Suspensions which have water and carbohydrates are good nutrient media and should be preserved from microbes and thus require the use of preservatives.

Non sterile pharmaceutical preparations are particularly prone to microbial attack. The presence and subsequent growth of microbes may lead to many chemical changes and spoilage of the product and hence pharmaceutical preparations are to be preserved.

Products intended for multiple use must contain antimicrobial compounds and bacteriostatic compounds.

MODE OF ACTION:

They interfere with the growth, multiplication and metabolism of the microbes by one or more of the mechanisms:

1. They modify the membrane permeability.
2. They cause the denaturation of enzymes and other cellular proteins.
3. They oxidize cellular contents.
4. Cause hydrolysis of the cell contents.

Few examples of commonly employed preservatives in pharmaceutical preparations are:

BENZOIC ACID: It is the simplest aromatic acid. Its sodium or potassium salt in 0.1% w/v concentration is permitted as a preservative in foodstuffs, drugs and cosmetics. It is non toxic at this concentration value but is not effective at pH above 5.0.

PARAHYDROXY BENZOATES: These are the derivatives of benzoic acid especially, the esters of p-hydroxy benzoic acid and are used in concentration ranging from 0.005% to 0.05%. They are referred to as parabens and include methyl paraben, ethyl paraben, propyl paraben, butyl paraben and benzyl paraben. They are commonly used in syrups and other pharmaceutical preparations. The free ester is generally poorly soluble in water but their sodium salt shows good solubility in water.

SALICYLIC ACID AND SALICYLATES: Salicylic acid exerts a slight antiseptic action. It is not as popular as benzoic acid and is usually combined with benzoic acid in Whitfield ointment. It is normally used as sodium salicylate in 1:1000 ratio.

PHENYL MERCURIC NITRATE AND ITS SALTS: These are mercury compounds exhibiting antimicrobial action in concentrations as low as 1 in 10,000. Nitrate and acetate salts are both effective against bacteria and fungi. Acetate is slightly more soluble than the nitrate.

They can be used as sterilizing agent in concentration of 0.002% and as preservative in concentration of 0.001%. Their disinfectant action is due to the phenyl mercuric ion.

PHENOL: Its germicidal properties were discussed by Lister. It is used as a standard for comparing the disinfectant properties of substances. It is used in 0.5%w/v concentration in multi dose injections, in gargles and mouthwashes, in ear drops (6.4%w/v). It is commonly used as sterilizing agent in concentration of 0.5%.

QUARTERNARY AMMONIUM COMPOUNDS

FORMALDEHYDE

PARACHLORO METACRESOL

PARACHLORO METAXYLENOL

DICHLORO METAXYLENOL

Some other commonly used preservatives are

Hexachlorophene (in soaps, detergents, shaving creams, etc..), **Dichlorophene (G-4)**(in hair lotions, athlete foot preparation, not used systemically as it is toxic), **Actamer** (in soap and skin cosmetics), **Anobial** (in soaps and skin cosmetics).

Choice of a Preservative: The following are the characteristics of an ideal preservative:

1. It should have a wide range of activity against various organisms.
2. It should be effective in low concentrations
3. It should be compatible with all the ingredients of the formulation.
4. It should be soluble, odourless, tasteless, colourless.
5. It should be stable and unaffected by pH or chemical environment.
6. It should be non toxic and non irritant.

No single preservative satisfies all these criteria and thus often the formulator has to choose a combination of preservatives to achieve the desired results.

SOLUBILITY ENHANCEMENT TECHNIQUES:

Solubility may be defined as the maximum quantity of any given solute which can be dissolved in a given quantity of solvent at a fixed temperature and pressure. Certain descriptive terms are used for solubility which are mentioned below:

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

Some of the techniques which can be used to improve the solubility of any given substance are mentioned below:

1. **Micronization:** Particle size reduction leads to increase in the effective surface area resulting in enhancement of solubility and dissolution velocity of the drug. Micronization technique is used to improve dissolution rates of drugs into the biological environment, in order to improve the oral bioavailability. Particle size reduction methods include recrystallization of the solute particles from solutions using liquid antisolvents, along with labor intensive techniques like crushing, milling, grinding, freeze drying and spray-drying.
2. **Micellar Solubilization:** The use of surfactants to improve the dissolution performance of poorly soluble drug products is probably the basic, primary, and the oldest method. Surfactants reduce surface tension and improve the dissolution of lipophilic drugs in aqueous medium. They are also used to stabilise drug suspensions. When the concentration of surfactants exceeds their critical micelle concentration (CMC, which is in the range of 0.05–0.10% for most surfactants), micelle formation occurs which entrap the drugs within the micelles. This is known as micellization and generally results in enhanced solubility of poorly soluble drugs. Surfactant also improves wetting of solids and increases the rate of disintegration of solid into finer particles. Commonly used nonionic surfactants include polysorbates, polyoxyethylated castor oil, polyoxyethylated glycerides, lauroyl macroglycerides, and mono- and di-fatty acid esters of low molecular weight polyethylene glycols. Surfactants are also often used to stabilize microemulsions and suspensions into which drugs are dissolved. Examples of poorly soluble compounds that use Micellar solubilization are antidiabetic drugs, gliclazide, glyburide, glimepiride, glipizide, repaglinide, pioglitazone, and rosiglitazone.
3. **Hydrotrophy:** Hydrotrophy is a solubilisation process, whereby addition of a large amount of second solute, the hydrotropic agent results in an increase in the aqueous

solubility of first solute. Hydrotropic agents are ionic organic salts, consists of alkali metal salts of various organic acids. The mechanism by which it improves solubility is more closely related to complexation involving a weak interaction between the hydrotrophic agents like sodium benzoate, sodium acetate, sodium alginate, urea, and the poorly soluble drugs. The hydrotropes are known to self-assemble in solution. Specific examples may include ethanol, aromatic alcohols like resorcinol, pyrogallol, catechol, α and β -naphthols and salicylates, alkaloids like caffeine and nicotine, ionic surfactants like diacids, SDS (sodium dodecyl sulphate), and dodecylated oxidibenzene.

4. **Co-Solvency:** The solubility of a poorly water soluble drug can be increased frequently by the addition of a water miscible solvent in which the drug has a good solubility known as cosolvents. Cosolvents are mixtures of water and/ or more water miscible solvent used to create a solution with enhanced solubility for poorly soluble compounds eg., of solvents used in co-solvent mixture are PEG 300, propylene glycol or ethanol. Dimethyl sulfoxide (DMSO) and dimethyl acetonamide (DMA) have been widely used as cosolvent because of their large solubilization capacity of poorly soluble drugs and their relatively low toxicity.
5. **Complexation:** Complexation is the association between two or more molecules to form a non bonded entity with a well defined stoichiometry. It relies on relatively weak forces such as London forces, hydrogen bonding and hydrophobic interactions. There are many types of complexing agents. Complexation generally works because the substance forms a complex with the additive and the total solubility is given by the sum of the uncomplexed drug and the complexed drug. Cyclodextrin is very commonly used as a complexing agent.
6. **pH Adjustment:** Poorly water soluble drugs with parts of the molecule that can be protonated (base) or deprotonated (acid) may potentially be dissolved in water by applying a pH change. pH adjustment can in principle be used for both oral and parental administration. Ionizable compounds that are stable and soluble after pH adjustment are best suited. It can also be applied to crystalline as well as lipophillic, poorly soluble compounds.
7. **Chemical Modification:** In this method water soluble derivatives of drugs are prepared and used eg. Betamethsone disodium phosphate ester is 1500 times more water soluble than Betamethasone.