PHARMACEUTICAL CALCULATIONS

Contents to be covered in this topic

- INTRODUCTION
- ALLEGATION METHOD
- CALCULATIONS INVOLVING PERCENTAGE SOLUTIONS
- PROOF SPIRIT
- ISOTONIC SOLUTIONS BASED ON FREEZING POINT AND MOLECULAR WEIGHT

❑ INTRODUCTION

- **Before dispensing**, a **pharmacist** should **understand** the various types of **calculations**, involve in it.
- Therefore **pharmacist** should have a **thorough knowledge** about **wights and measures,** which are used in the **calculations**.

❖ **Weight** : Weight is a **measure** of the **gravitational force**, acting on a **body** and is **directly proportional to its mass.**

❖ **Measure** : Measure is the **measurement of volume** of any **substance.**

Weight measure

Volume measure

There are two system of weights and measures

1. **The imperial system**
2. **The metric system**

1.The imperial system

- It is an **old system** of **weight and measures** based on **arbitrary** and **unrelated unit** like **grains, drachms, ounces and gallons**
- Imperial system is divided into **two parts** for the purpose of measurement of weight as

(a) Avoirdupois system

(b) Apothecaries system

IMPERICAL SYTEM

Avoirdupois system

Apothecaries system

(a) Avoirduposis system

- In this system the "pound" is the standard unit for weight
- Therefore, all measures of mass are derived from the Imperial standard pound(Lb).

Eg. : (a) 1 pound (Lb) = 16 ounce (oz)

(b) 1 pound = 7000 grains

(c) 1 ounce (oz) = 7000/16 = 437.3 grains (2.1)

Here only weight is primarily used for compounding.

437.5 grain = 1 oz = 28.35 gm

7000 grain = 1 Lb = 16 oz = 454 gm

1 kg = 2.2 Lb

1 gr = 64.8 m

(b) Apothecaries system

- Comprised of both volume and weight. It is used for compounding and for preparing concentration for dilution. In this system, weight is measured in grain and volume in Minim

(i) Volume:

a) 1 teaspoonful (tsp) = 5 milliliters (ml) = 1 dram = 5 cubic centimeters (cc)

b) 1 tablespoonful (tbsp) = 15 milliliters (ml)

c) 29.57 milliliters (ml) = 1 fluid Ounce (fl oz)

d) 473 milliliters (ml) = 1 pint (pt) = 16 fluid ounce (fl oz)

e) 946 milliliters = 1 quart = 2 pints

f) 3784 milliliters = 1 gallon = 8 pints = 128 fl oz

(ii) Weight:

a) 1 grain = 64.8 mg

b) 1 ounce = 31.1 gm = 480 grain

2. Metric System

- The metric system is used for the measurement of weight and capacity
- The metric system in India was implemented from 1st April 1964 in pharmacy profession

- This system was used the Indian pharmacopoeia
- The metric system is based on joining one of a series of prefixes, including **kilo-, hecto-, deka-, deci-, centi-, and milli-,** with a base unit of measurement, such as meter liter, or gram

Measurement of weight in metric system: A kilogram is the standard unit for measurement of weight and all other measures are derived from it.

- **1 kilogram (kg) = 1000 grams**
- **1 gram = 1000 mg**
- **1 milligram (mg) = 0.001 gram**
- **1 microgram (mcg) = 0.000,001 gram**
- **1 hectogram (hg) = 100 grams**
- **1 decagram (dag) = 10 grams**

LATIN TERM	ENGLISH NAME	EQUAL TO
Granum	Grains	1 grain
Scrupulus	Scruple	20 grains
Drachma	Drachm	60 grains
Uncia oz.	Ounce (Avoir)	437.5 grains
Uncia (Troy)	Ounce (Apothe)	480 grains
Libra	Pound (Avoir)	7000 grains
Libra	Pound (Apothe)	5760 grains

Measurement of capacity

1 gallen	160 fluid ounces	1 quart	40 fluid ounces
¼ gallen	1 quart	1 pint	20 fluid ounces
1/8 gallen	1 pint	1 fluid ounces	480 minims
1/60 gallen	1 fluid ounces	1 fluid drachm	60minims

Measurement of weight

1 (kg) kilogram	100 grams (gm)
1 hectogram (hg)	100 grams
1 decagram (dag)	10 grams
1 decigram (dg)	0.1 grams
1 centigram (cg)	0.01 grams
1 milligram (mg)	0.001 grams

CONVERSION TABLES

(a) Weight measurement

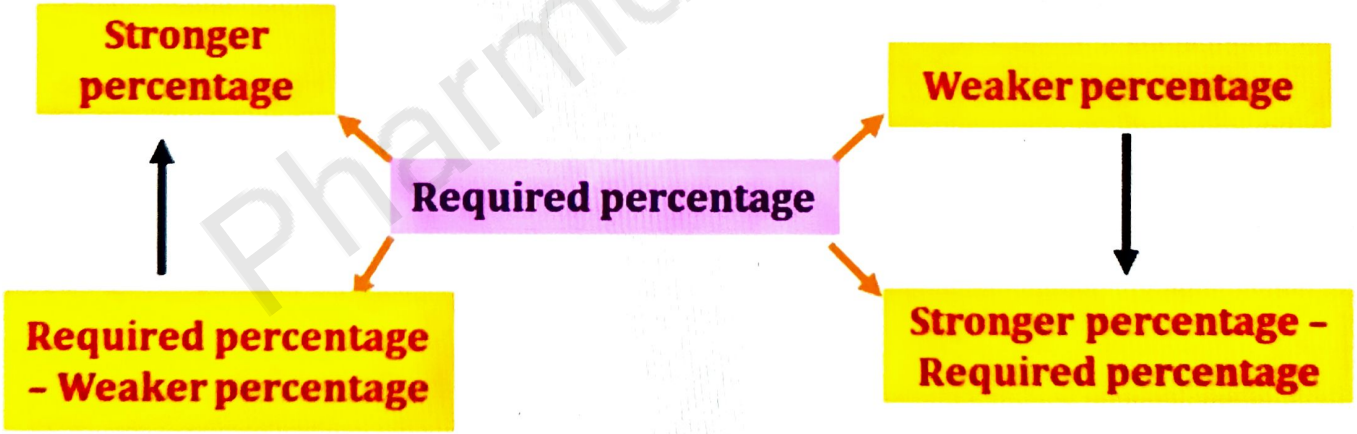
1 kg	2.21 LB (pound)
30 g	1 ounce
450 g	1 pound

(b) Capacity measurement

1000 ml	1 quart
500 ml	1 pint
30 ml	1 fluid ounce
4 ml	1 fluid drachm
1 ml	15 minim
0.06 ml	1 minim

❑ ALLEGATION METHOD

- When the calculation involves **mixing of two similar preparations** of **different strengths**, to produce a preparation of **intermediate strength**, the alligation method is used
- This method is **recommended** for the purpose of **checking the calculations.**

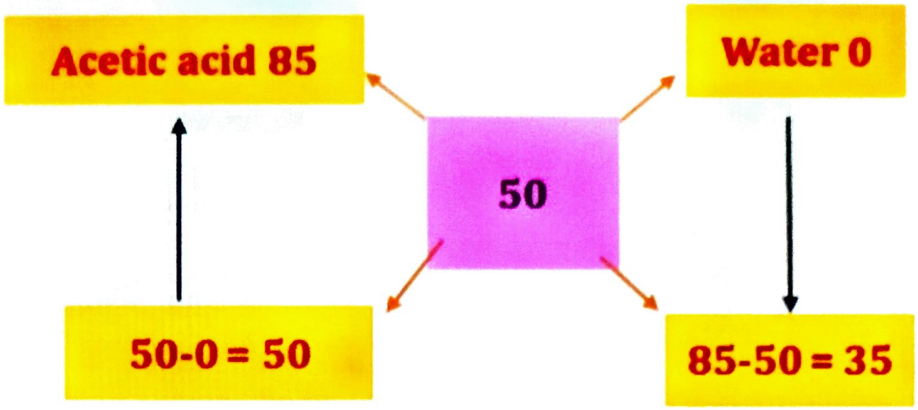


Question : Calculate the **volume of 85% of acetic acid** required to produce 500ml of **50% acetic acid**

Solution : Identify the data given

- ✓ Volume required = 500 ml
- ✓ % of acetic acid required = 50%
- ✓ % of acetic acid used =85%
- ✓ Alligation ratio = ?

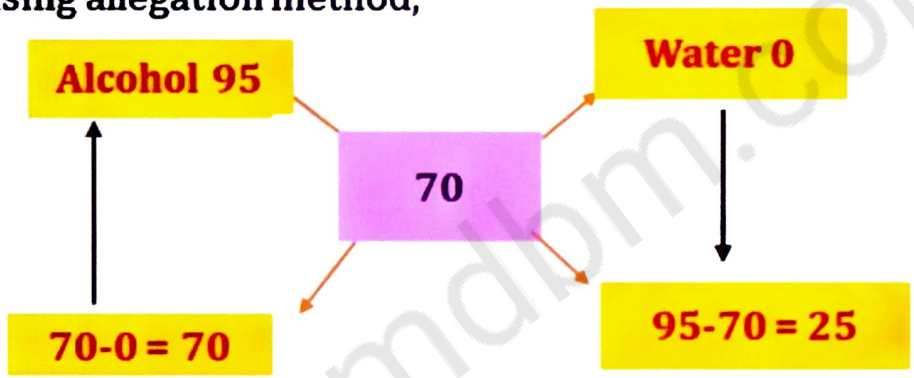
By allegation method



Question : Calculate the volume of 95% alcohol required to prepare 600 ml of 70% alcohol.

- ✓ Volume required = 600 ml
- ✓ Percentage of alcohol required = 70 %
- ✓ Percentage of alcohol used = 95 %

By using allegation method,



70 parts of 95% alcohol and 25 parts of water will produce the required percentage alcohol.

$$\text{Quantity of 95\% alcohol required} = \frac{600 \times 70}{95} = 442.10$$

$$\text{Quantity of water required} = \frac{600 \times 25}{95} = 157.90$$

ANS. 442.10ml

❑ CALCULATIONS INVOLVING PERCENTAGE SOLUTIONS

Four types of percentage solution are used in pharmacy commonly

1. % w/v (%weight in volume)
2. % v/v (% Volume in volume)
3. % v/w (% Volume in weight)
4. % w/W (% weight in weight)

❖ Common formula used in percentage calculation

1. Preparation of 1% w/v solution in imperial system

The formula should be used when the volume of the solution required is small and the strength of the solution required is weak

SOLID	SOLVENT TO PRODUCE
1 gm	110 m
4.375 gm	1 fluid once
3.5 gm	8 fluid once

2. Preparation of 1 % w/v solution

SOLID	SOLVENT TO PRODUCE
1 gm	100 ml

3. Preparation of % solution by diluting the concentrated solution

$$\text{Strenght of dilute solution} = \frac{\text{Strength of concentrate}}{\text{Degree of dilution}}$$

$$\text{Volume of stronger alcohol to be used} = \frac{\text{Volume required} \times \text{Percentage required}}{\text{Percentage used}}$$

$$\text{Volume of stronger acid to be used} = \frac{\text{Weight required} \times \text{Percentage required}}{\text{Percentage used}}$$

❑ PROOF SPIRIT

- Proof spirit is a **mixture of alcohol** and **water** which at **51°F weights 12/13th** of an **equal volume of water.**
- The **strength of alcohol** is **calculated** in proof degrees.
- The Indian standards of **100% proof spirit** is equal to **57%v/v** of **ethyl alcohol.** i.e., **100% p.s = 57%v/v ethyl alcohol.**
- If the value is **more than 57%** then it is said to be as **over proof spirit.**
- If the value is **less than 57%** then it is said to be as **under proof spirit.**

Under proof (U.P.) ← Below this | **100 % Proof 57.1% v/v** | Above this → Over proof (O.P.)

1. **Conversion of % strength to proof strength**

- Multiply the % strength by **1.735** and substract 100 from it.
- If result is **positive** than **over proof**
- If result is **negative** than under proof

Question : Find out the proof strength of alcohol which is 90% v/v and 30% v/v

Solution : 90% v/v = 90 x 1.753 = 157.77

Thus, proof strength = 157.77 – 100 = 57.77° O/P (Over proof) 30% v/v = 30 x 1.753 = 52.59. Thus, proof strength = 52.59 -100 = - 47.41 i.e. 47.41° U/P (Under proof)

2. **Conversion of proof strength to % strength**

- Divide the proof strength by **1.735** and add 100 to it, if **over proof** and substract 100, if under proof

Question : Find % strength of **30° over proof and 40° under proof.**

Solution : **30° over proof**

$$\text{Alcohol strength} = \frac{100+30}{1.753} = 74.15\%\ \text{v/v}$$

$$40^\circ \text{ Over proof} = \frac{100-40}{1.753} = \frac{60}{1.753} = 34.23\%\ \text{v/v}$$

NORMALITY

- It is defined as the presence of **number of gram** equivalent **weight of solute** in **1000 ml or 1 litre of solution**

$$\text{Normality} = \frac{\text{No. of equivalent of solute}}{\text{Liters of solution}}$$

Question : Calculate the normality of 0.321 g sodium carbonate when it mixes in a 250 mL solution.

Solution,
- ✓ N of 0.321-gram Sodium Carbonate
- ✓ The chemical formula is Na_2CO_3

$$N = Na_2CO_3 \times \frac{1mol}{105.99g} \times \frac{2eq}{1mol}$$

$$N = \frac{0.1886eq}{0.2500L} = 0.0755\ N$$

MOLARITY

- It is defined as the presence of **number of moles** of solute in **1000 ml or 1 L** of solution

$$\text{Molarity (M)} = \frac{\text{Moles of solute}}{\text{Liters of solution}}$$

$$\text{Moles of solute} = \frac{\text{Gram}}{\text{Molar mass}}$$

Question : Calculate molarity of 215 g of HCl dissolved in 1000ml of solution

Solution,

$$\text{Moles} = \frac{\text{Gram}}{\text{Molar mass}} = \frac{215}{36} = 5.9g/mol$$

$$\text{Molarity (M)} = \frac{\text{Moles of solute}}{\text{Liters of solution}} = \frac{5.9}{1} = 5.9\,M$$

MOLALITY

- It is defined as the presence of **number of moles** of solute in **1000 gm** of solvent

$$\text{Molality (m)} = \frac{\text{Moles of solute}}{\text{kg of solvent}}$$

Question : Calculate the molality of a solution prepared from 29.1 g of toluene C_7H_8 dissolved in 832 g of benzene C_6H_8

Toluene molar mass : 92g/mol

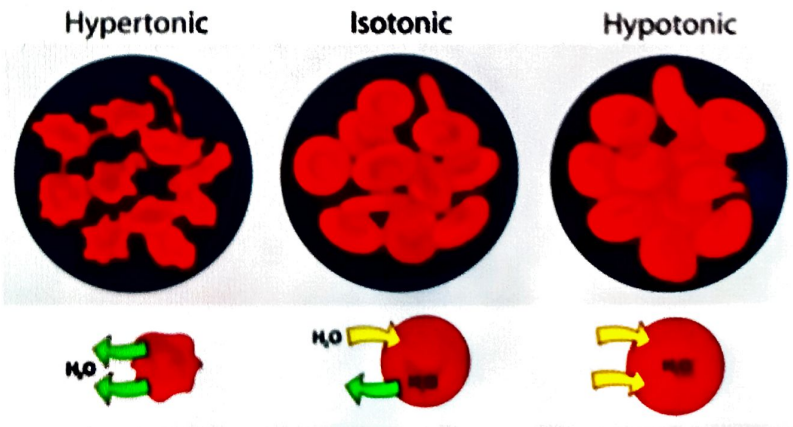
$$\text{Moles of toluene} = \frac{29.1\ \text{g}}{92.0\ \text{g/mol}} = 0.316\ \text{m}$$

$$\text{Molality (m)} = \frac{\text{Moles of solute}}{\text{kg of solvent}} = \frac{0.316}{832} = 0.380$$

❑ ISOTONIC SOLUTIONS BASED ON FREEZING POINT AND MOLECULAR WEIGHT

❖ ISOTONIC SOLUTIONS

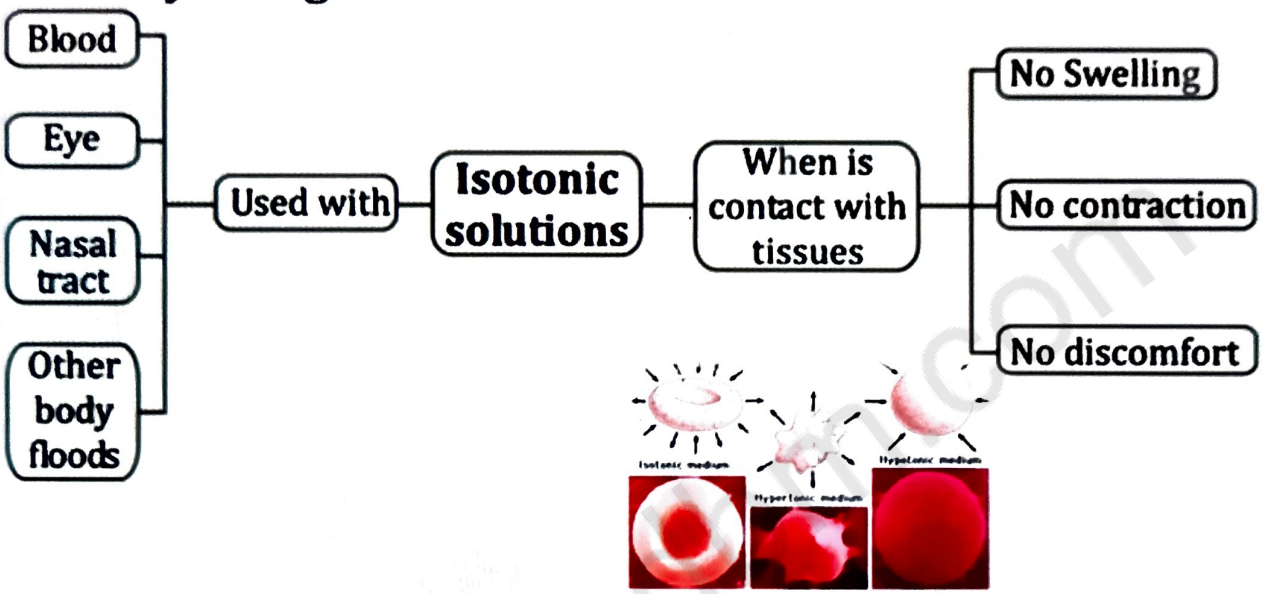
- "When two solutions have **same osmotic pressure** and **salt concentration** are said to be **isotonic solutions**". **Iso (same)** and **tonic (concentration).**
- Physiologically, isotonic solutions are **solutions having** the **same osmotic pressure** as that of the **body fluids** when **separated by a biological membrane.**
- Biological fluids including **blood and lachrymal fluid** normally have an **osmotic pressure** corresponding to that of **0.9% w/v solution of sodium chloride.**
- Thus **0.9% solution of sodium chloride** is said to be **isotonic** with the **physiological fluids.**



❖ Types of Tonicity

HYPOTONIC	ISOTONIC	HYPERTONIC
NaCl 0.2%	NaCl 0.9%	NaCl 2%
Solute > solute Inside outside	Solute = solute Inside outside	Solute < solute Inside outside
Swelling	Equilibrium	Shrinkage

❖ Why using isotonic solutions



1. Freezing point methods

- There are certain **physical properties of solutions** known as **'colligative properties'** which are **independent of the nature** of the dissolved substances. These colligative properties are: **1. Osmotic pressure2. Depression of freezing-point**
- Determination of the **depression of freezing point** is simpler and **more accurate than** direct **measurement of osmotic pressure**. So, this property of the solution is used to compare osmotic pressures.
- The temperature at which **blood plasma and tears freeze** is **-0.52°C**.
- This means that the **dissolved substances** contained in them depress the **freezing point 0.52°C** below that of pure water. So, any other solution which freezes **at -0.52°C** will have the same osmotic pressure as blood plasma and tears.

$$\text{Precentage w/v of adjusting substance needed} = \frac{0.52 - a}{b}$$

Where,

a = Freezing-point of the un-adjusted solution

b = Freezing point of a 1% w/v solution of the adjusting substance

Question : Find out the **proportion of aspirin** which will yield a solution iso-osmotic with blood plasma.

(Given – The freezing point of a 1% w/v solution of aspirin is – 0.122°C)

By the freezing point method,

$$\text{Precentage w/v of adjusting substance needed} = \frac{0.52 - a}{b}$$

$$\text{Precentage w/v of aspirin required} = \frac{0.52 - 0.00}{0.122}$$

$$= 4.26\%$$

Question : Find out the **conc. of sodium chloride required to make a 1% of solution of boric acid, iso-osmotic with blood plasma.** (Given – The freezing point of a 1% w/v solution of sodium chloride is: 0.288°C) The freezing point of 1% w/v solution of sodium chloride is – 0.576°C

$$\text{Precentage w/v of sodium chloride required} = \frac{0.52 - 0.288}{0.576}$$

$$= 0.402\%$$

2. Method based on molecular concentration

- **Molecular concentration** means the **number of units** i.e. **molecules or ions** or both **present in a solution.**
- A solution containing **one gram molecule** of a **non-ionising solute** in **22.4 litres** at **normal temperature** and **pressure** (NTP) has an **osmotic pressure** of one atmosphere. So, a **solution containing one gram molecule in 1 litre** (a mole solution) will have an **osmotic pressure of 22.4 atmosphere.**

- The **osmotic pressure of blood plasma** and lachrymal secretion is approximately **6.7 atmosphere.**

$$\text{Hence molarity of these fluids} = \frac{6.7}{22.4} = 0.3\ \text{M (approx)}$$

- Therefore, a **0.3 M solution** of any **non-ionising solution** will be **iso osmotic with blood plasma and tears**. This knowledge may be used to calculate the concentrations of un-ionised medicaments needed to pro duce iso-osmotic solutions by using the following formula:

Question : Find the **proportion of dextrose** needed to form a solution **iso-**osmotic with blood plasma

$$W = 0.3 \times M$$

Solution, Molecular weight of dextrose = 180

$$W = 0.3 \times 180$$

Question : Find the concentration of sodium chloride required to produce a solution iso-osmotic with blood plasma.

= 54.0 g/litre or 5.4 g/100 ml

Solution: Molecular weight of sodium chloride = 58.5

Sodium chloride is ionising substance and it gets dissociates into 2 ions.

$$W = \frac{0.3 \times M}{N}$$

$$W = \frac{0.3 \times 58.5}{2} = 8.8\ \text{g/litre OR } 0.88\ \text{g/ml}$$

Question: How much boric acid is required to render 200 ml of eyewash containing 1% boric acid are to be dispensed.

(F.P. of 1% boric acid at -0.29°C and E.P. of 1% solution of sodium chloride = -0.58°C).

Applying the above equation:

Thus the working formula for 200 ml of the eyewash will be:

Boric acid (1%, for 200 IL) = 19 x 2 = 2 g.

Sodium chloride (0.39%, for 200 ml) = 0.39 x 2 = 0.78 g.

Purified water q.s. 200 ml

Solution:

However if the pharmacist has been asked to supply **200 ml of eyewash of boric acid,** the calculation will be as follows:

- ✓ Lowering of 0.29°C in F.P. is caused by 1 g of boric acid
- ✓ Lowering of 0.52°C in F.P. will be caused by 1.8 g of boric acid

Therefore, 1.8 g of boric acid is required to make 100 ml of eyewash and the working formula will be : Boric acid (1.8%, for 200 ml) = 1.8 x 2 = 3.6 g. Purified water, **q.s. 200 ml.**

❖ **Important points**

- **Mass Percent** = (mass of solute/mass of solution)100
- **Parts per million** = (mass of solute/mass of solution)10^6
- **Mass/volume percent** = (mass of solute/mL solution)100
- **Volume percent** = (mL solute / mL solution)100
- **Molarity** = moles solute / L solution

POWDERS

Contents to be covered in this topic

- DEFINITION OF POWDER
- CLASSIFICATION OF POWDERS
- POWDERS ENCLOSED IN CACHETS
- COMPRESSED POWDERS OR TABLET TRITURATES
- ISOTONIC SOLUTIONS BASED ON FREEZING POINT AND MOLECULAR WEIGHT

❑ DEFINITION OF POWDER

A powder is a **homogeneous mixture** of more or less finely divided particle or material in dry form. **It is a solid dosage form** of medicament which are **meant for internal and external uses. They** are present in crystalline and amorphous form

❖ Advantages of powder

- They **impart flexibility** with regard to a wide selection of drugs
- They are **stable when compared to other dosage forms**
- They show **rapid therapeutic effect**
- **Ease in administration** to all categories of patients
- They are **economical** because they do not require special technique
- Chances of **incompatibility are less**

❖ Disadvantages

- Drugs having **bitter, nauseous and unpleasant taste** cannot be dispensed in powdered form
- **Deliquescent and hygroscopic** drugs cannot be dispensed in powdered form
- Drugs which get affected by atmospheric conditions are not suitable for dispensing in powder form

❑ CLASSIFICATION OF POWDERS

CLASSIFICATION OF POWDERS

Divided Powders

a) Simple Powder
b) Compound powder

Bulk Powder

a) Dusting Powder
b) Effervescent Powder
c) Dentifrices
d) Insufflations
e) Douche Powder
f) Snuffs

❖ Divided Powder:

These are **unit dose powders** normally packed properly.

(a) Simple powder:

- Contains only **one ingredient** either in **crystalline or in amorphous form**
- Then finely divided powder is weighed wrapped as individual dose

(b) Compound powder:

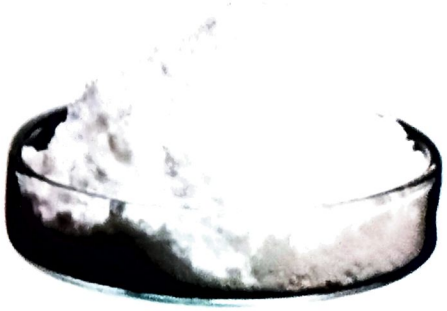
Contains two or more than two substances which are mixed together and then divided into individual doses

❖ Bulk powder for internal use

- Powders are **dispensed in bulk**, when accuracy of dosage is not important.
- Bulk powder contains **several doses of powder**.
- They are supplied in **wide-mouthed containers** that permits **easy removal of a spoonful of powder.**
- The **non potent substances** which are supplied in **bulk are antacids and laxatives** etc.

❖ Bulk powder for external use

- Bulk powder meant for **external use are non potent substances**.
- These powders are supplied in **cardboard, glass or plastic containers**, which are often designed for the specific method of application.
- The dusting powders are preferably supplied in **perforated or sifter top containers.**
- The container should **bear a label** indicating that the **powder is meant for external application.**



The bulk powders which are commonly used for external applications are as follows:

(a) Dusting powders (b) Insufflations (c) Snuffs (d) Dentifrices

(a) Dusting powders

- Meant for **external application** to the **skin**
- Generally applied in a **very fine state of sub division to avoid local irritation.**
- Should be passed through **sieve no. 85 (180 µm)** to **enhance their effectiveness.**
- Dusting powder should **not be applied to broken skin**
- Mainly used for their **antiseptic ,astringent, absorbent, antiperspirant and antipruritic** (anti-itching) action.
- Dusting powder usually contains substances as zinc oxide, starch, magnesium, carbonate, light magnesium oxide, boric acid, talc, kaolin, etc.
- **Dusting powders are of two types:- (i) Medical (ii) Surgical**
- **Medical dusting** powders are used mainly for **superficial skin conditions**, whereas **surgical dusting powder** are used in **body cavities** and also on **major wounds** as a result of **burns and umbilical cords** of **infants** and **sterilised before use**

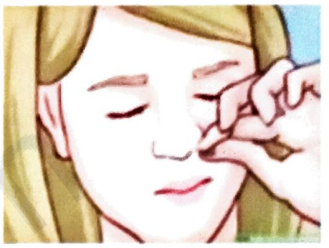
(b) Insufflations

- Meant for introduction into the **body cavities** such as **nose, throat, ears** and **vagina** with the help of an apparatus known as **"Insufflator".**
- It **sprays the powder into a stream** of finely divided particles all over the site of application.
- Used to produce a **local effect**, as in the treat-infection of ear, nose and throat infection with antibiotics or to **produce a systemic effect from** a **drug that is destroyed in the gut.**

- The following difficulties are however generally faced while using the insufflators:
  i. It is difficult to obtain a measured quantity of the drug as a uniform dose.
  i. It gets blocked when it is slightly wet or the powder used is wet.

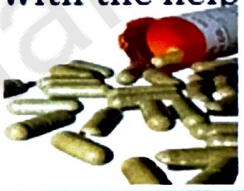
(b) Snuffs

- Finely divided solid dosage forms of medicament which are inhaled into nostrils for its antiseptic, bronchodilator and decongestion action.
- Dispensed in flat metal boxes with hinged lid.



(d) Dentifrices (Tooth powders)

- Dentifrices are bulk powders used to clean teeth.
- They contain a soap or detergent (for cleaning action), mild abrasive and an anti cryogenic agent
- Mild abrasion can be provided by using finely precipitated Calcium Carbonate, Sodium Chloride, Magnesium Chloride etc.
- A strong abrasive substance should not be used as it may cause damage to the tooth
- They are applied with the help of tooth brush for cleaning the surface of teeth



❑ POWDERS ENCLOSED IN CACHETS(WAFER CAPSULE)

- Cachets are the **solid unit dosage form** of drugs.
- These are moulded from rice paper, which is made by pouring a mixture of rice flour and water between two hot, polished, revolving cylinders. The water evaporates and a sheet of wafer is formed.
- Cachets are used to **enclose nauseous** or **disagreeable powders** and are available in different sizes to **hold drugs from 0.2 to 1.5 g of powder.**

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ADVANTAGES AND DISADVANTAGES OF CACHETS

ADVANTAGES	DISADVANTAGES
i. Easily prepared, not required any complicated machines	i. Need to be soften before swallowing
ii. Disintegrate immediately in stomach	ii. Easily damaged
iii. Easily dispense	iii. They cannot protect drug from light and moisture
iv. Large quantity up to 1.5 gm of drug can be swallowed by using cachets.	iv. The shell is very brittle
	v. Not suitable for large scale manufacturing

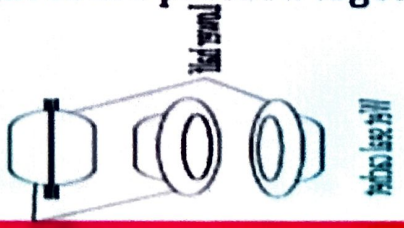
Cachets are of two types:

(a) Wet seal cachets

(b) Dry seal cachets

(a) Wet seal cachets

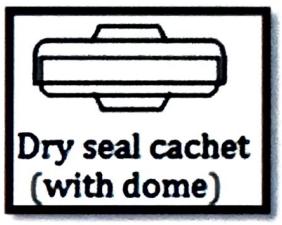
- Made up of **two similar convex halves having flat edges.**
- The weighed of powder drug is placed in one half, the edge of other half are moistened with water & placed exactly over the first half containing the drug.
- The flat edges of both the halves are pressed together in order to seal it perfectly.

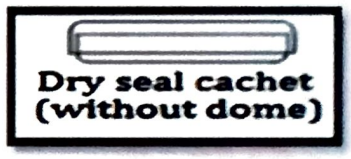


(b) Dry seal cachets

- Consists of **two halves, the upper half & lower half.**
- The diameter of upper half is slightly larger than lower half.
- The powdered drug is filled in lower half & upper half is fitted over it.
- The filled cachets are then sealed in a machine by pressing the two halves, removed & packed in boxes.

B.P.C includes two cachets **sodium amino salicylate & sodium amino salicylate with isoniazid.**


Dry seal cachet (with dome)


Dry seal cachet (without dome)

❑ COMPRESSED POWDERS (TABLETS) OR TABLET TRITURATES (MOULDED TABLETS)

- **Small, usually cylindrical molded or compressed tablets**
- The **drug used were potent** and **mixed** with **lactose** and a **binder** such as **powdered acacia,** after which the mixture was moistened to produce a moldable, compatible mass.
- This **mass was forced** into **holes of a mold board wood or plastic, after** which **tablet where ejected using a peg board, whole pegs matched the hole in the mold, dried and dispensed.**


Tablet Triturates Mould

DISPENSING OF POWDERS

A number of problems arise while dispensing a powder containing **volatile substances, hygroscopic and deliquescent powders, eutectic mixtures, efflorescent powders, liquids, explosive substances** and **potent drugs.** So special considerations are done while dispensing such powders.

❖ Volatile substance

- Certain **vegetable powders contain volatile oils.**
- To **prevent** the **loss of volatile oils**, these vegetable drugs must be **powdered lightly in mortar .**
- Similarly the volatilization of substances like **menthol**; **camphor** and **essential oils** may take place on incorporation in powders.
- This is **prevented** or at **least minimized** by the **use of double wrapping.**
- The **inner wrapper** should be of **wax paper** and **outer wrapper** may be of any **thick paper.**

❖ Hygroscopic and deliquescent powders

- The **powders which absorb moisture** from the atmosphere are called **hygroscopic powders.**
- **Powders absorb moisture to such a great extent that they go into solution** are called **deliquescent powders.**
- **Examples** of such substances include **ammonium chloride, iron and ammonium citrate, pepsin, phenobarbitone, sodium bromide, sodium iodide, potassium citrate, zinc chloride etc.**
- Such **substances** are usually **supplied in granular form** in **order to expose less surface area to the atmosphere.**
- These powders **should not be finely powdered** and **double wrapped.**
- In **humid weather** or when **dealing** with very **deliquescent substances**, further **wrapping** in **aluminium foil** or **plastic cover** is advisable.

❖ Hygroscopic and deliquescent powders

Hygroscopic substances	Deliquescent substances
• When exposed to the atmosphere at ordinary temperature, they absorb moisture and do not dissolve.	• When exposed to the atmospheric air at ordinary temperature, they absorb moisture and dissolve
• Hygroscopic substance do not change its physical state on exposure to air.	• Deliquescent substance change its physical state on exposure to air.
• Hygroscopic substance may be amorphous solids and liquids.	• Deliquescent substance may be crystalline solids
• Calcium chloride ($CaCl_2$), Caustic soda (NaOH), Caustic potash (KOH) and Ferric chloride ($FeCl_3$).	• Conc. Sulphuric acid (H_2SO_4),Phosphorus Pentoxide (P_2O_5),Quick lime (CaO),Silica gel (SiO_2),Anhydrous calcium chloride ($CaCl_2$).

❖ Efflorescent powders

- Some crystalline substances **liberate water of crystallisation** wholly or partly on **exposure to humid atmosphere** or **during trituration** and thus **become wet or liquefy.**
- Example of such substances **include caffeine, citric acid, ferrous sulphate** etc.
- This **difficulty may be overcome** by using either **corresponding anhydrous salt** or an **inert substance may be mixed with efflorescent substance before incorporating with other ingredients.**

Ferrous Sulphate Powder

❖ Eutectic mixtures

- When two or more substances are mixed together they liquefy due to the formation of a compound which has a lower melting point than the individual substances are called eutectic substances.
- Example of such substances include menthol, thymol, camphor, phenol, salol, aspirin, phenacetin, chloral hydrate etc.

➢ These substances can be dispensed by two methods:-

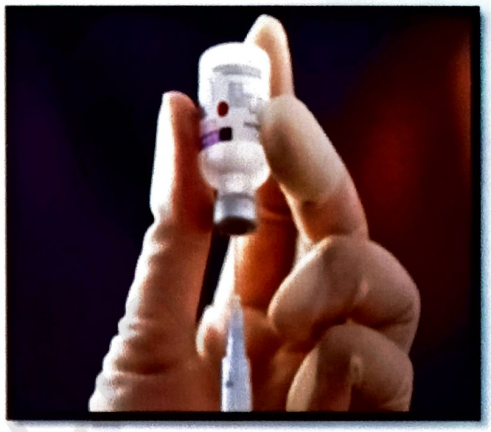
i. Dispense as separate set of powders with directions that one set of each kind shall be taken as a dose.

ii. An equal amount of any of inert absorbent like magnesium carbonate, light magnesium oxide, kaolin, starch, lactose, calcium phosphate etc. may be mixed with eutectic substance and then blended together lightly with a spatula on a sheet of paper. When in addition to liquefying substances, other ingredients are also present, the liquefiable substances should first be triturated together to form the eutectic mixture. Then the remaining ingredients of the prescription are incorporated and mixed together.

❖ Liquids

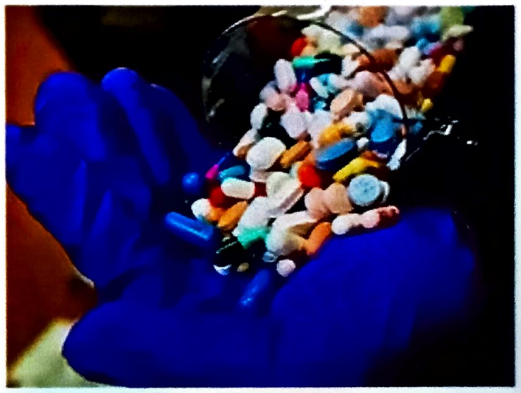
- In certain prescriptions, the liquid medicaments are also incorporated in dispensing powders.
- If the quantity of the liquid is small, it may be triturated with an equal amount of powder, then the rest of the ingredients are incorporated in small portions with continuous trituration.
- If the quantities of liquids are large than an absorbent must be added.

- Liquid extracts and tinctures are **evaporated to syrupy mass in a China dish.**
- Lactose or some other suitable diluent is mixed and then **continue** the **evaporation to dryness.** Mix other ingredients.
- Another alternative is to substitute a **liquid extract by a dry extract.**



❖ Potent drugs

- The substances having a **maximum dose of less than one grain (60 mg)** and **poisonous substances** are regarded as the potent drugs.
- **Small quantities** of potent drugs should **not** be **weighed on dispensing balance.**
- The potent drug is **triturated** with some **diluent** such as lactose in definite proportion to **make a weighable quantity** for each powder.
- Generally potent drug is **reduced to fine powder** and to this an **equal quantity of diluent is mixed** by through **trituration in a mortar.**
- Then the **rest of diluent is incorporated in successive portions** with thorough trituration each time.
- The **whole of the diluent** should **never** be **added** to the **drug at one time** otherwise the potent drug will not be mixed uniformly and thoroughly in the diluent.



MIXING OF POWDERS

The powders may be mixed by any one of the following methods:

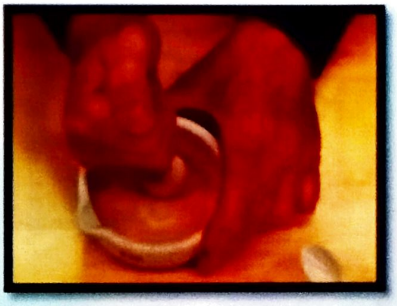
1. **Spatulation**
2. **Trituration**
3. **Geometric dilution**
4. **Shifting**
5. **Tumbling**

❖ Spatulation

- In this method, mixing of powders is done by the **movement of a spatula** throughout the powders on a **sheet of a paper** or on a **porcelain tile**.
- The method is very useful in mixing:—
  - **(a) Small amount of powder.**
  - **(b) Solid substances** that **liquefy** or **form eutectic mixtures**, when **in close** and **prolonged contact with one another** since **very little compression** or **compact** results.
- The **method is not suitable for large quantities** of powders or for powders containing one or more potent substances because homogenous blending may not occur

❖ Trituration

- Trituration is the process of **grinding the powder in Motar and pestle** to reduce its particle size.
- If particle size reduction is desired along with mixing of powders, a **porcelain mortar with a rough inner surface** is preferred to a **glass mortar with a smooth working surface.**



- A **glass mortar** may be preferred for **chemicals that may stain a porcelain surface** and for **simple mixture of substances without special need for comminution.**
- A **glass mortar cleans more readily after use.**

❑ Geometric dilution

- The method is used when **potent substances are to mixed with a large amount of diluent.**
- The potent drug is placed upon an approximately **equal volume of the diluent in a mortar and the substances are slightly mixed by trituration.**
- A second portion of **diluent equal in volume to the powder mixture in the mortar is added and trituration is repeated.**
- The process is continued, **adding diluent equal in volume to the mixture in the mortar at each step, until all the diluent is incorporated.**
- **For example,**

if 100 mg of potent drug is required to be mixed with 900 mg of lactose, then according to geometric dilution, the following procedure should be followed:

100 mg of a potent drug + **100 mg** of lactose = 200 mg of mixture

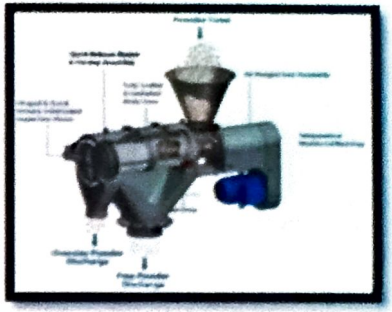
200 mg of the mixture + **200 mg** of lactose = 400 mg of mixture

400 mg of the mixture + **400 mg** of lactose = 800 mg of mixture

800 mg of the mixture + **remaining portion** = 1000 mg of mixture of lactose

❖ Sifting

- The powders are **mixed by passing through sifters.**
- This process results in a **light fluffy product** and is generally **not acceptable for incorporation of potent drugs into a diluent base**



Centrifugal Sifter

❖ Tumbling

- Tumbling is the process of **mixing powders in a large container rotated by an electric motor.**
- These **blenders are widely employed** in **industry as large volume powder mixers.**

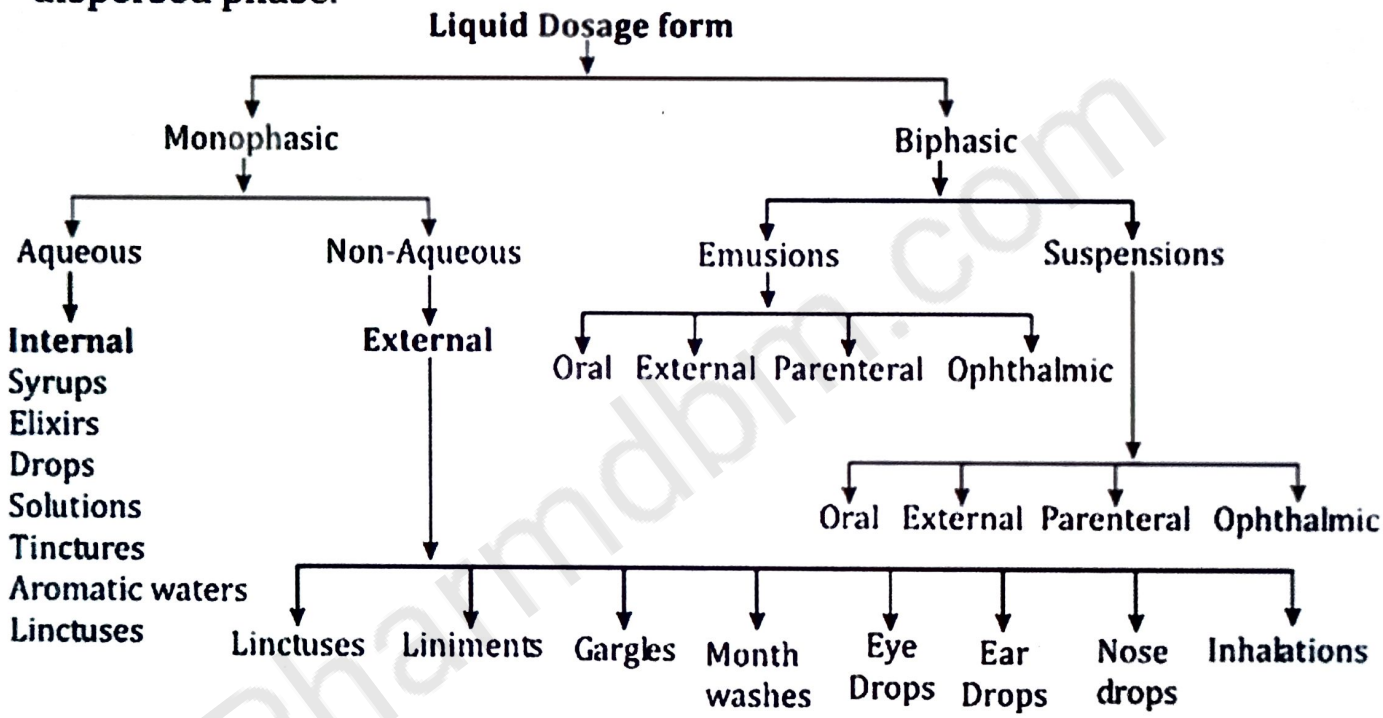
LIQUID DOSAGE FORMS

Contents to be covered in this topic

- LIQUID DOSAGE FORM
- EXCIPIENTS USED IN FORMULATION OF LIQUID DOSAGE FORMS
- SOLUBILITY
  - Techniques of solubilization

LIQUID DOSAGE FORM

- Dosage forms meant either **for internal, external or parenteral use** may be sub-classified into **monophasic or biphasic liquid** dosage forms.
- The **monophasic liquid dosage** forms consists of either true or colloidal solutions or solubilized system. All these consists of only a **single phase** and may have either **aqueous or non-aqueous solvents** as the base
- **Biphasic dosage forms** are represented by **emulsions and suspensions** and consist of two immiscible phases, the continuous phase and the dispersed phase.



➢ **Merits of liquid dosage forms:**

1. **Onset of action is quick as compared to tablets and capsules**
2. **Certain medicaments can only be given in liquid form, e.g., castor oil**
3. **Certain drugs are to be given in suspended form to produce maximum surface**
4. **A few drugs if taken in dry form may cause pain and irritation**
5. **Psychological satisfaction to a patient of something is in the bottle**

➢ **Demerits of liquid dosage forms:**

1. **Dose has to be measured.**
2. **Stability and preservation possess a problem.**
3. **Storage should be proper.**

4. Possibility of breaking the containers during transport.
5. Costly dosage form than the solid dosage form.

EXCIPIENTS USED IN FORMULATION OF LIQUID DOSAGE FORMS

EXCIPIENTS	EXAMPLES
SWEETENING AGENT	Some of the most commonly used sweeteners include sucrose, sorbitol, mannitol, liquid glucose, honey molasses, saccharin, aspartame, sucralose
VISCOSITY CONTROLLING AGENTS	Polyvinylpyrrolidone and cellulose derivatives (e.g., methylcellulose or sodium carboxymethylcellulose).
BUFFERS	Phosphates, acetates, citrates, and glutamates.
ANTIOXIDANTS	citric and ascorbic acids, ethylene diamine tetra acetate (EDTA), butylated hydroxytoluene (BHT) and butylated hydroxyanisole (BHA)
FLAVOURS	

TASTE SENSATION	RECOMMENDED FLAVOUR
SALT	maple, apricot, peach, vanilla, wintergreen mint.
BITTER	Wild cherry, walnut, chocolate, mint combinations, passion fruit, mint spice, anise
SWEET	Fruit and berry, vanilla.
SOUR	Citrus flavors, liqorice, root beer, raspberry

PRESERVATIVE

CLASS	USUAL CONCENTRATION (%)
Acidic	
Phenol	0.2-0.5
Chlorocresol	0.05-0.1

O-phenyl phenol	**0.005-0.01**
Alkyl esters of parahydroxybenzoic acid	0.001-0.2
Benzoic acid and its salts	0.1-0.3
Boric acid and its salts	0.5-1.0
Sorbic acid and its salts	0.05-0.2
Neutral	
Chlorobutanol	0.5
Benzyl alcohol	1
o-phenylethyl alcohol	0.2-1.0

Mercurial	
Thiomersal	0.001-0.1
Phenylmercuric acetate and nitrate	0.002-0.005
Nitromersol	0.001-0.1
Quaternary Ammonium Compound	
Benzalkonium chloride	0.004-0.02
Cetylpyridinium chloride	0.01-0.02

SWEETENING AGENT

- Sweeteners are often classified as either **nutritive (caloric) or non-nutritive (non caloric)**
- Sucrose is the most widely used sweetener, with a long history of use

SUCROSE

- It is a **white crystalline powder, soluble in water and alcohol.**
- It **inhibits the growth of microorganisms** in solution at sucrose concentrations above **65 wt%**
- Official simple syrup is an 85% w/V solution of sucrose in water.
- One of the manifestations of the sucrose crystallization is "cap-locking

SACCHARIN

- It is a **non-nutritive synthetic sweetening agent.** It has approximately **500 times the sweetening** power of sucrose

SUCRALOSE

- Sucralose (Splenda) is approximately 600 times sweeter than sucrose, Sucralose is heat stable
- Acesulphame-K is **approximately 200 times sweeter** than sucrose, This sweetener is also heat stable

VISCOSITY CONTROLLING AGENT

- Viscosity can be achieved by **increasing the sugar concentration** by **incorporating viscosity controlling agents** such as polyvinylpyrrolidone or various cellulosic derivatives
- Carboxymethylcellulose may be used in solutions containing high concentrations of alcohol (up to 50%) without precipitating.
- **Methylcellulose polymers do not form insoluble salts** with metal ions, but can be salted out of solution when the concentration of electrolytes or other dissolved materials exceed certain limits.

BUFFERS

- During storage of liquid preparations, **degradation of the product,** interactions with container components or dissolution of gases and vapors causes change in their pH level, which can be **prevented by addition of buffer**
- A suitable buffer system should have **adequate buffer capacity** to maintain the pH level of the product
- The ionic strength contributions of the buffer systems can **affect stability**

ANTIOXIDANTS

- Various drugs in solution are subject to oxidative degradation. Oxidation is defined as a loss of electrons from a compound leading to change in the oxidation state of the molecule.
- Agents with an oxidation potential lower than that of the drug in question are called **antioxidants.**

FLAVOUR

- Flavouring can be divided into two major categories: **selection and evaluation**
- The four basic taste sensations are **salty, bitter, sweet, and sour**
- A combination of **flavoring agents** is usually **required to mask these taste sensations effectively**
- **Menthol, chloroform, and various salts** frequently are used as flavour adjuncts
- **Menthol and chloroform** are sometimes referred to as **desensitizing agents**

PRESERVATIVE

Ideal preservative can be qualitatively defined as one that meets the following three criteria:

- It must be effective against a **broad spectrum of microorganisms**
- It must be physically, chemically and **microbiologically stable** for the lifetime of the product
- It must be **non-toxic, non-sensitizing, adequately soluble,** compatible with other formulation components, and acceptable with respect to taste and odour at the concentrations used

SOLUBILITY

- Solubility is defined as **amount of solute that can be dispersed molecularly in the given amount of solvent under standard conditions of temperature, pressure and pH**

The following questions related to solubility must be resolved before formulating solution dosage form:

(a) Will the drug(s) dissolve in the vehicle?
(b) How much drug will dissolve?
(c) How long will dissolution take?
(d) What is optimum pH for dissolution?

To determine the solubility of solute in solvent following points are to be considered :

(a) Temperature must be controlled
(b) The **solute and the solvent** should be **pure**
(c) A saturated solution of the solute should be prepared before withdrawing the sample for analysis
(d) A proper method of separation of saturated solution from the undissolved solute

Method of determination:

An excess powder is added in the solvent to achieve the saturated solubility and constant stirring is given for long duration at required temperature till the equilibrium is achieved.

Solubility of the solute in the solvent is determined by the analyzing the sample by suitable method.

Terms	Expression of solubility Part by volume of solvent required to dissolve 1 part by weight 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, or insoluble Greater than 10,000

During compounding of a solution the solids will need to go through a dissolution phase, so it is worth remembering that rate of dissolution generally increases with:

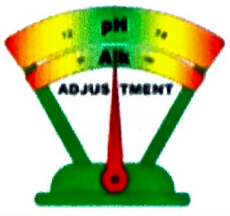
(1) Effective stirring
(2) Lower viscosity
(3) Increasing temperature
(4) Decreasing particle size

❑ TECHNIQUES OF SOLUBILIZATION

Solubilization is the technique by which the **desired solubility of a poorly water-soluble substance is achieved**. Since, **water** is the most commonly used solvent in pharmaceutical liquids, the following techniques have been aimed at increasing the solubility of a drug substance in water

Pharmaceutical Approach :

pH ADJUSTMENTS



- The aqueous solubility of a weak acid or a weak base is greatly **influenced by the pH of the solution**. Hence, the solubility of drug that is either a weak base or a weak acid may be altered by adjusting the pH of the solution.

- The solubility of a weak base can be increased by lowering the pH of its solution whereas the solubility of a weak acid can be improved by increasing the pH

pH adjustment for improving the solubility can be achieved in two ways:

(a) Salt formation

(b) Addition of buffers to the formulation

e.g. The solubility of various chemotherapeutic agents such as Methotrexate, Fluorouracil, Cytrabine etc. also gets affected by the alteration in pH changes

COSOLVENCY

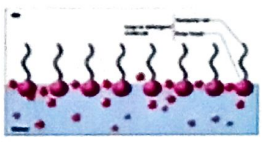
- Cosolvency is the **technique of increasing the solubility** of poorly soluble drugs in a liquid by addition of a solvent miscible with the liquid in which the drug is also highly soluble
- Cosolvents such as **ethanol, glycerol, propylene glycol or sorbitol decreases the interfacial tension** or alter the dielectric constant of the medium and increases the solubility of weak electrolytes and non-polar molecules in water.

Example: Formulation of Diazepam injection using propylene glycol as cosolvent

COMPLEXATION

- **Increase the solubility of a poorly soluble drug** by allowing it to interact with a soluble material form a soluble intermolecular complex.
- **Complex formed** is easily reversible so that the free drug is released readily during or before contact with biological fluids.

e.g. Interaction of **Iodine with Povidone** to **form water soluble complex** and preparation of Itraconazole injection by forming inclusion complex of itraconazole with hydroxy propyl beta cyclodextrin



SURFACE ACTIVE AGENT

- A surface active agent is a substance which **reduces the interfacial tension** between the **solute and the solvent** to form thermodynamically stable homogeneous system.
- Involves micelle formation

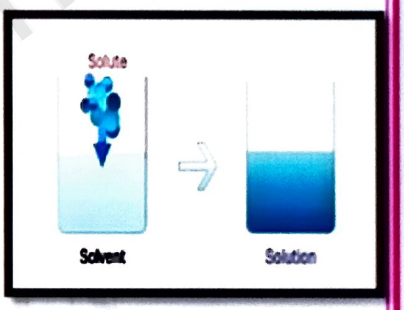
- At a certain concentration known as the **Critical Micelle Concentration (CMC)**, the dispersed surfactant molecules tend to aggregate into groups of 100 to 150 molecules known as micelle
- Surfactants that are used as **solubilising agents** generally have **HLB values in excess of 13**

Examples Include polysorbate-80, polyoxyl 40 stearate, sodium lauryl sulphate and **PEG-40-Castor oil** (Cremophor)

HYDROTROPISM

- Describe the increase in aqueous solubility of a drug by the use of large concentrations (20% to 50%) of certain additives.

  e.g.: Increase in solubility of caffeine and theophylline by addition of **sodium benzoate and sodium salicylate** respectively



MICRONIZATION

- Surface area and particle size are **inversely related to each other**
- Smaller the drug particle, **larger the surface area and greater is the solubility**
- A decrease in particle size achieved through Micronization, will result in **higher solubilization of drug**

SOLID SOLUTIONS

- Solid solutions **are prepared by melting of physical mixture** of solute
- Solid solutions are also called as **molecular dispersions or mixed crystals**

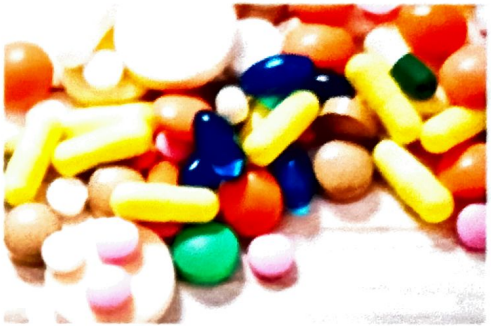
e.g. : Griseofulvin from succinic acid solid solution dissolves 6 to 7 times faster than pure griseofulvin and Digitoxin-PEG 6000 solid solution showed **enhanced solubility**

This is often achieved by **salt formation**; for instance, **alkaloids are poorly soluble in water** whereas **alkaloidal salts are freely soluble in it.**

Alternatively, a molecule may be modified to produce a new chemical entity or prodrug

STABILITY

Physical, chemical and microbiological stability of the preparation will need to be taken into consideration.



CHEMICAL MODIFICATION

- Solubility of a substance can be improved by chemically modifying the substance

  For example, aqueous solubility can be improved by **increasing the number of polar groups in a molecule.**