MONOPHASIC LIQUIDS

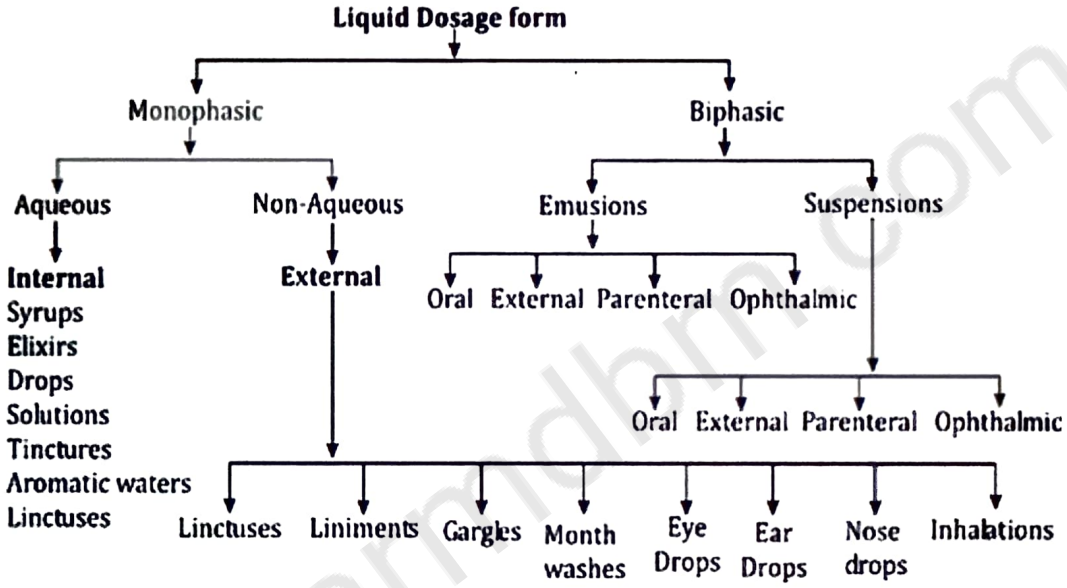
Contents to be covered in this topic

- INTRODUCTION
- DEFINATION AND PREPARATION OF :
  - MIXTURE
  - SYRUPS
  - ELIXIRS
  - LINCTUSES
  - AROMATIC WATERS
  - LINIMENTS
  - LOTIONS
  - GARGLES
  - MOUTH WASH
  - THROAT PAINTS
  - DOUCHES
  - EAR DROPS
  - NASAL DROPS
  - NASAL SPRAYS
  - INHALATIONS

MONOPHASIC LIQUIDS

❖ INTRODUCTION

- Monophasic liquid dosage form refers to **liquid preparation** in which there is only **one phase**
- It is represented by **true solution**
- A true solution is a **clear homogenous mixture** that is prepared by dissolving a **solid, liquid or gas in a liquid.**
- The component of solution present in **large amount** is known as **'solvent'** and the component present in small amount is known as **'solute'.**



LIQUIDS MEANT FOR INTERNAL ADMINISTRATION

MIXTURE

❖ INTRODUCTION

- A mixture is a **liquid preparation**
- meant **for oral administration** in which medicament or medicaments are dissolved or suspended in a suitable vehicle.
- Generally, several doses are dispensed in a bottle. In case, a bottle contain one dose, it is called **draught.**
- So the mixtures should be **extemporaneously prepared** and supplied only for **small number of doses** which can be used up **within a short period.**
- In case further need arises, then a fresh mixture is prepared for the patient

Mixtures are classified into:-

(1) Simple mixtures containing soluble substances
(2) Mixtures containing diffusible solids
(3) Mixtures containing indiffusible solids
(4) Mixtures containing precipitates forming liquids
(5) Mixtures containing slightly soluble liquids

❖ **Simple mixtures containing soluble substances:** Simple mixtures contains only **soluble ingredients** e.g., carminative mixture, diarrhoea mixture and expectorant mixture.

Example- Prepare and dispense 90 ml of the following mixture.

Potassium bromide - 4.0 g
Tincture nux vomica - 4.0 ml
Chloroform water - add up to 90 ml
Prepare a mixture

METHOD OF PREPARATION:

Dissolve potassium bromide in 3/4th of chloroform water.

↓

Filter the solution to remove foreign particles.

↓

Add tincture nux vomica.

↓

Incorporate more of chloroform water to make required volume. Transfer the

↓

mixture to a bottle.

↓

Cork, label and dispense.

SYRUPS

❖ INTRODUCTION

- The **syrup is a saturated or concentrated, viscous aqueous solution** of **sucrose/sugar** substitute with or **without flavor/medicinal substances** in purified water.
- **Simple syrup contain 85% w/v (65% w/w); specific gravity 1.313 (USP)** or **66.7% w/w as per Indian Pharmacopeia/BP.**

❖ FORMULATION OF SYRUP

✓ **Most syrups contain the following components(Adjuncts) in addition to the purified water and drug :-**

(a) Sugar, usually sucrose or other sugar substitutes are used to provide sweetness and viscosity, (Sugar-free alternative- Sorbitol, Saccharine, Aspartame)

(b) Antimicrobial preservatives

(c) Flavorants & Colorants

(d) Syrups may also contain solubilizing agents, thickeners.

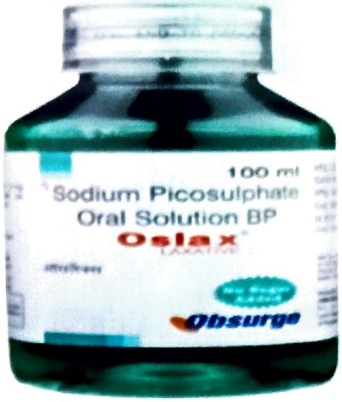
Advantages of Syrups :

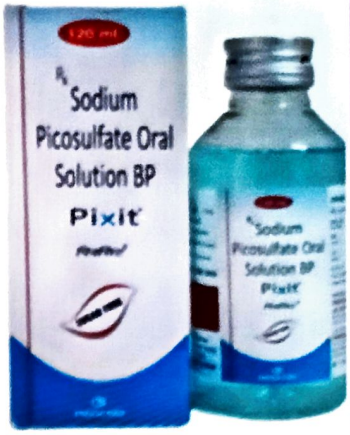
(1) Syrup **retards oxidation** because it is partly hydrolyzed into reducing sugars such as, laevulose and dextrose.

(2) It prevents **decomposition of many vegetable substances.** Syrups have high osmotic pressure which **prevents growth of bacteria, fungi and moulds**

(3) They are **palatable.** Due to sweetness of sugar

❖ TYPES OF SYRUP





- ✓ Simple Syrup
- ✓ Medicated Syrups
- ✓ Flavored Syrups

➢ SIMPLE SYRUPS

- It's a **basic combination of sugar and water.**
- Simple syrup offers an easy way to **add sweetness to a cocktail** without having to dissolve granular sugar in the glass.

➢ MEDICATED SYRUPS

- A liquid preparation of **medicinal or flavoring substances** in a concentrated aqueous solution of a sugar, usually sucrose; when the syrup **contains a medicinal substance,** it is termed a **medicated syrup.**

➢ FLAVORED SYRUPS

- Flavored syrups **typically consist of a simple syrup,** that is sugar, with naturally occurring or artificial flavorings also dissolved in them.
- A sugar substitute may also be used.

❖ PREPARATION METHODS OF SYRUPS

- ✓ Solution with Heat
- ✓ Agitation without Heat
- ✓ Addition of Medicating or Flavouring Liquid to Syrup
- ✓ Percolation

❖ PREPARATION METHODS OF SYRUPS

➢ Solution with Heat

- This **method is a suitable preparation method,** if the constituents are not volatile or degraded by heat. **Purified water is heated to 80–85°C,**
- and then removed from its heat source. **Sucrose is added with vigorous agitation.**

- Then, other **required heat-stable components** are added to the hot syrup, **the mixture is allowed to cool,** and its volume is adjusted to the **proper level by the addition of purified water.**
- In instances in which **heat-labile agents or volatile substances,** such as flavors and alcohol, are added, they are incorporated into **the syrup after cooling to room temperature.**

➢ Agitation without Heat

- This method is used for the preparation of **syrups containing volatile** substances. In this process **active substance is added** in solution & agitated in **glass-stoppered bottle. This method involves these steps :-**
- **Sucrose and other ingredients are weighed properly.**
- **Dissolved in purified water.**
- **Kept in a bottle of about twice** the volume of syrup followed by continuous agitation.
- **Prepared syrup volume is made up to q.s.**

➢ Addition of Medicating or Flavouring Liquid to Syrup

- **This method is used when fluid extracts,** tinctures, or **other liquids are to be added to syrup. Alcohol is added to dissolve the resinous or oily substances. Alcohol acts as a preservative also.**

➢ Percolation Method

The process in **which a comminuted drug** is **extracted of its soluble constituents** by slow passage of suitable **solvent through a column of drug.**

- **Sucrose is placed in percolator.**
- **Water is passed through sucrose slowly.**
- **The neck of the percolator is packed with cotton.**
- **The rate of percolation regulates rate of dissolution.**
- **After complete dissolution, final volume is made.**

ELIXIRS

❖ INTRODUCTION

- **An elixir is a sweet liquid** used for medical purposes, to be taken orally **and intended to cure one's illness.**
- **When used as a pharmaceutical preparation,** an elixir contains at least one active ingredient designed to be taken orally.
- **Elixirs contain 4-40% of alcohol (ethanol).**
- They may **contain glycerin & syrup for increasing solubility** of medicament/for sweetening purposes.
- **Elixirs may also contain suitable flavoring & coloring agents.**
- Preservatives are not needed in elixirs as alcohol **content is sufficient to act as a preservative.**

❖ FORMULATION OF ELIXIR

1. **Vehicles:** The elixirs are usually prepared by using water, alcohol, glycerin, sorbitol, and propylene glycol. Certain oils are easily soluble in alcohol where alcohol is used as cosolvent. 30-40% of alcohol may be used to make a clear solution.
2. **Adjuncts**

(a) **Chemical stabilizer:** The various chemicals or special solvents are used in many elixirs to make suitable elixir. E.g. For neomycin elixir - citric acid is added to adjust pH.

(b) **Colouring agent:** Amaranth, compound tartrazine dyes are used for colouring purpose.

(c) **Flavouring agent:** Black current syrup, raspberry syrup, lemon syrup etc.

(d) **Preservatives:** Alcohol 20% or more propylene glycol or glycerol as a vehicle is used as preservative. Chloroform desirable strength, benzoic acid may also be used

❖ METHODS OF PREPARATION

- **Alcohol soluble and water soluble** components are generally dissolved **separately in alcohol and water.**
- Aqueous solution is added to the alcoholic solution, so minimal separation of alcohol soluble components occurs.
- **Mixture is made up to the volume** by the specific solvent or vehicle.
- **Talc to remove excess amount of oil.**
- **Filter the preparation.**
- **Pour it in clean bottle.**
- **Label the bottle.**

LINCTUSES

❖ INTRODUCTION

Linctuses are **viscous, liquid and oral preparations** that are generally prescribed for the **relief of cough.** They **contain medicaments** which have **demulcent, sedative or expectorant action.** Linctuses should be taken in small doses, sipped and swallowed slowly **without diluting it with water** in order to have the maximum and prolonged effect of medicaments

AROMATIC WATERS

Aromatic waters are the **clear saturated solution** of volatile oil or volatile substances in purified water. They are also known as **medicated water e.g.** Camphor water, concentrated Peppermint water.

❖ METHODS OF PREPARATION

Distillation -

- In this method, crude drug containing volatile oil is subjected to distillation.
- The distillate is collected in the receiver.
- The distillate collected have two layers; the upper layer is of volatile oil and lower layer is separated and on clarification, clear aromatic water is produced.

Simple solution method-

- The volatile oil or volatile substance is **dissolved in purified water** by shaking in order to convert volatile oil into small oil globules

Dilution method:

- In this method, **concentrated water is diluted with purified water**
- The concentrated waters are alcoholic solution of volatile oil and volatile substances
- These are 40 times stronger than simple aromatic waters.
- The aromatic waters are **prepared by diluting one volume of concentrated water** with thirty nine volume of purified water.
- Many volatile oils consists of aromatic part and non-aromatic parts.
- When alcoholic solution of volatile oil is diluted with water the non aromatic portion gets separated as fine precipitate which interfere with clarity of the aromatic water

LIQUIDS TO BE APPLIED TO THE SKIN

LINIMENTS

- They are **liquid or semi-liquid preparations**
- meant for **application to unbroken skin** by **friction** or rubbing of skin.
- They may be **alcoholic or oily or soapy solutions or emulsions.** **Alcoholic liniments** are used generally for their **rubefacient, counterirritant, mildly astringent, and penetrating effects.**
- The oily or soapy liniments are milder in their action but are more useful when massage is required.

- Liniments should never be applied to the skin areas that are broken or bruised. E.g. camphor liniment, turpentine liniment.

LOTIONS

- Lotions are **liquid or semi-liquid preparations** meant for application to unbroken skin **without friction.**
- They are either dabbed on the skin or applied on a suitable dressing and covered with water proof material to reduce evaporation.
- An evaporating vehicle like **alcohol may be used** when a cooling effect is desired on application to the skin.
- Lotions generally contain **antiseptic, astringent, anaesthetics, germicides, protectives or screening agent** for prevention or treatment of various skin diseases.

e.g. calamine lotion, hydrocortisone lotion

LIQUIDS TO BE USED IN MOUTH

GARGLES

- Gargles are aqueous solution used to **prevent or treat infection**
- They are usually available in concentrated form with direction for dilution with warm water for use
- They are used to **relieve soreness** in mild throat infection.
- **Phenol or thymol** is used as **antibacterial agent** in gargles. Phenol or thymol may be present in low concentrations which exert mild anaesthetic effect; KCl is included in gargle preparation for its weak astringent effect
- Gargle differs from mouth washes in that they are light medicated oral mixture be diluted with water before use

For example: Phenol gargle, $KClO_3$ gargles

Formula: Phenol gargle

Rx

Phenol glycerin - 5 ml

Amaranth solution - 1 ml

Purified water - q.s. to 100 ml

PREPARATION

Mixing amaranth solution (1% w/v in chloroform water) with a small quantity of water

↓

Adding Phenol glycerin (16% w/w phenol and 84% w/w glycerin) to it

↓

The solution is stirred

↓

Made up to volume with purified water

↓

The gargle is meant to be diluted with equal quantity of warm water before use

Uses: Antibacterial effect, astringent effect, **mild anaesthetic effect**

MOUTH WASH

- These are **aqueous solutions** with a pleasant taste to clean, deodorize the buccal cavity
- Mouthwashes have refreshing, antiseptic and antibacterial activity and prevent Halitosis.
- They may also **contain alcohol, glycerin, synthetic sweeteners, surfactants, flavouring and colouring agents.**

  For example: Compound sodium chloride mouth wash, Zinc chloride mouth wash, Fluoride mouth wash.

Formula:

Rx

Zinc sulphate and zinc chloride mouth wash B.P.C.

Zinc sulphate - 20 g

Zinc chloride - 10 g

Dilute hydrochloride acid - 10 ml

Compound tartarzine solution - 10 ml

Chloroform water to produce - 1000 ml

PREPARATION

made by **dissolving Zinc sulphate and Zinc chloride** in small quantity of Chloroform solution

↓

To this is added dilute hydrochloric acid and compound tartrazine solution

↓

The final volume is made up with water

THROAT PAINTS

- **Solution or dispersion of one or more active agents.** Throat paints are **viscous liquid** preparations used for mouth and throat infections.
- Glycerin is commonly used as a base because being viscous it adheres to mucous membrane for a long period. Glycerin prolongs the action of medicaments.
- **Glycerin also provides sweet taste to preparation.**

For example: Boroglycerin, Phenol glycerin throat paint, Compound Iodine paint (Mandl's paint)

Formula:

RX

Potassium iodide - 2.5 gm

Iodine - 1.25 gm Alcohol - 4 ml

Water - 2.5 ml

Peppermint oil - 0.4 ml

Glycerin - 100 ml

PREPARATION

Dissolve the potassium iodide in water.

↓

Add the iodine and stir until completely dissolved.

↓

Dissolve peppermint oil in alcohol 90% in a small container and transfer it into iodine solution.

↓

Transfer paint into a measuring cylinder

↓

Make up the volume to q.s.

↓

PAINT are applied with soft brush

LIQUIDS TO BE INSTILLED INTO BODY CAVITIES

DOUCHES

- A douche is a medicated solution meant for rinsing a body cavity
- The word douche is often used for **vaginal solutions**
- Solutions are generally called **irrigations**
- Douches are also used to **irrigate the other body cavities**, such as **eyes, ear or nasal cavities** for cleaning or removing the foreign particles or discharges from them.
- Douches are generally dispensed in the form of a powder or tablet with a specific directions for dissolving it in a specific quantity of warm water
- They are also dispensed as concentrated solutions with direction to dilute it in a specific quantity of warm water before use.
- Vaginal douches must be sterile

EAR DROPS

- Ear drops are **liquid preparations** meant for **instillation into the ear**
- In these preparations, the drug is usually dissolved or suspended in a suitable solvent such as propylene glycol, polyethylene glycol, glycerol alcohol and water or a mixture of these.
- **Aqueous vehicle is generally not preferred** because the secretions in the ear are fatty in nature and as such these do not easily mix with water
- Used for their cleansing, **pain relieving and antiseptic actions.**
- The main classes of drugs include analgesics like benzo ne, antibiotics like neomycin and chloramphenicol and anti-inflammatory agents such as cortisone and dexamethasone.
- Wax softening agents include hydrogen peroxide and sodium bicarbonate.
- Ear drops are usually supplied in amber coloured, glass bottles with a teat and dropper closure or plastic squeeze bottles

Example : Chloramphenicol Ear Drops

Chloramphenicol – 5g

Propylene glycol q.s to 100 ml

PREPARATION

Chloramphenicol ear drops may be **prepared by dissolving Chloramphenicol** in sufficient quantity of **Propylene glycol** and finally making up the final volume with it

NASAL DROPS

- These are aqueous solutions of drops that are instilled into the nose with a dropper
- The oily vehicle is not used nowadays because oily drops inhibit the movement of cilia in the nasal mucosa and if used for long periods, may reach the lungs and cause lipoid pneumonia
- Nasal drops should be isotonic with 0.9% sodium chloride having neutral pH and viscosity similar to nasal secretions by using 0.5% methyl cellulose.

- The buffering capacity of nasal mucosa is quite low and strong alkali solutions can cause considerable damage to cilia. To prevent this, it is advisable to use a phosphate buffer of pH 6.5 as a vehicle.

EXAMPLE- Prepare and dispense 100 ml of ephedrine nasal drops

Ephedrine Hydrochloride - 0.05 g

Chlorobutol – 0.05 g

Sodium Chloride – 0.05g

Purified water q.s to 100 ml

METHOD OF PREPARATION

Dissolve the ephedrine hydrochloride, chlorobutol, and sodium chloride in warm water

↓

Cool, filter if necessary and make to volume through the filter.

↓

Transfer the nasal drops to the container, label and dispense.

NASAL SPRAYS

- Nasal sprays are used to **reduce nasal congestion** and to **treat infections**
- The main aim of nasal spray is to **retain the nasal solution** in the droplet form in the nasal tract
- For this purpose, the **nasal solution is sprayed in the form of coarse droplets** by using scent spray type of atomizer or a plastic squeeze bottle.
- The nasal spray should be **isotonic and buffered at pH 6.2.**
- They may contain **antibiotics and antihistamines**

INHALATIONS

- These are liquid preparations containing **volatile substances** and are used to relieve congestion and inflammation of the respiratory tract.
- Substance are volatile at room temperature may be placed on an absorbent pad or handkerchief to inhale there from.
- In other cases **inhalations are added to hot, but not boiling water** (about 65°C) and **vapours are inhaled** for about **10 minutes**

- Aerosol inhalations are **solutions, suspensions or emulsions of drugs in a mixture of inert propellants** held under pressure in an aerosol dispenser
- The dose of the medicament in the form of droplets of **50 µm diameter or less** is released from the container by using the **metering valve.**

BIPHASIC LIQUID DOSAGE FORM- SUSPENSION

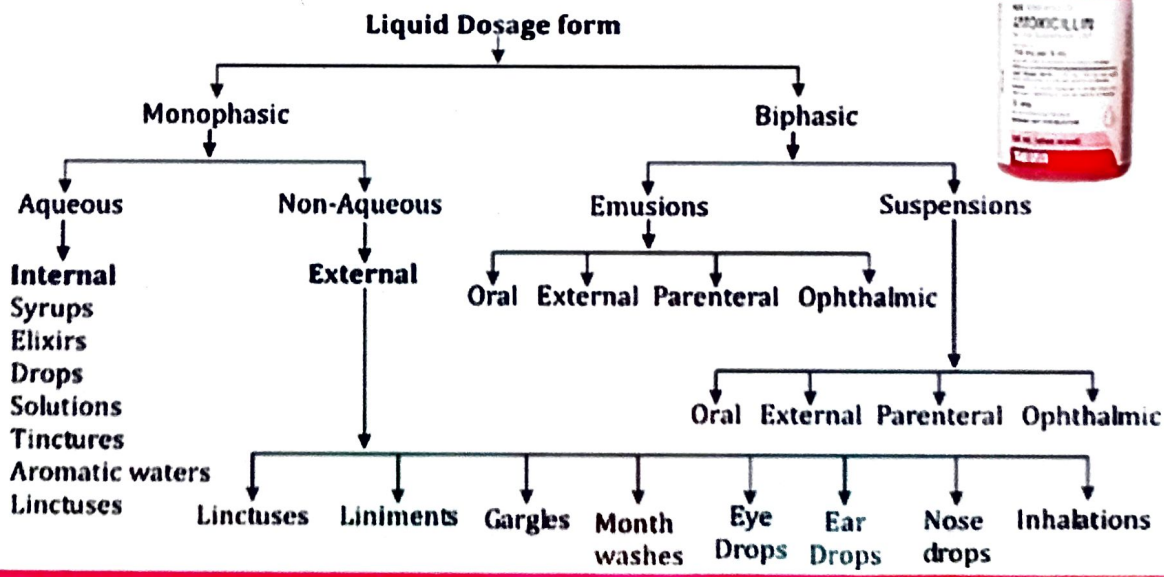
Contents to be covered in this topic

- INTRODUCTION
- CHARACTERISTICS OF AN IDEAL SUSPENSION
- CLASSIFICATION OF SUSPENSION BASED ON ROUTE OF ADMINISTRATION
- TYPES OF SUSPENSION BASED ON ELECTROKINETIC NATURE OF SOLID PARTICLES
- FORMULATION OF SUSPENSION
- STAGES IN FORMULATION OF SUSPENSION
- EVALUATION OF SUSPENSION STABILITY
- METHODS OF DISPENSING SUSPENSIONS

SUSPENSIONS

❑ INTRODUCTION

- Suspensions are the **biphasic liquid dosage form** of medicament in which the finely divided solid particles ranging from **0.5 to 5.0 micron** are dispersed in a **liquid or semisolid vehicle**
- The **solid particles act as disperse phase** whereas **liquid vehicle acts as the continuous phase.**
- Suspensions are generally taken **orally or by parenteral route**
- The particle size of the disperse phase is **very important** in the formulation of suspensions
- The suspensions which are **meant for external application**, should **have small particle size** to avoid gritty feeling to the skin and to cover a greater area of the application.
- it also helps **penetration of solid medicament into the skin** because its **smaller particle size** gives a **faster rate of dissolution**
- The suspensions which are **meant for parenteral administration** should have a **particle size** that can **pass through the needle**
- The **suspensions which are instilled into the eye,** should be **free from gritty particles** to avoid irritation pain and discomfort
- The particle size of the suspended drug particles should **not go beyond 10 micron.**



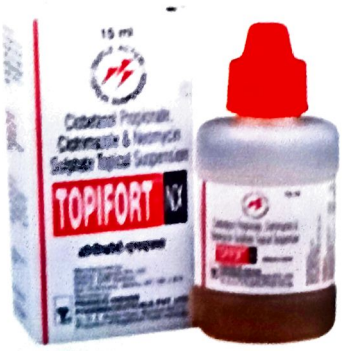
❑ CHARACTERISTICS OF AN IDEAL SUSPENSION

- It should be capable of being easily incorporated **into the material to be suspended.**
- **Should be non-toxic and compatible** with other formulation ingredient.
- **Should be free from microbial contamination.**
- **It should be readily available and inexpensive.**
- **It should have an acceptable, odour, colour and taste.**
- It should readily dispersed on mixing with an appropriate **vehicle without resource to special techniques.**

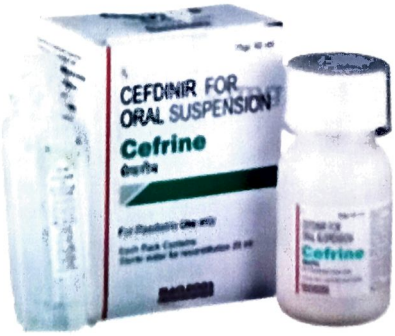
❑ CLASSIFICATION OF SUSPENSION BASED ON ROUTE OF ADMINISTRATION

❖ **Oral suspension**

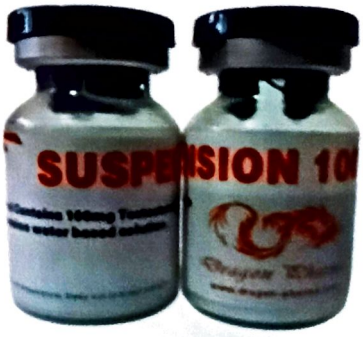
- It contains **antibiotic preparation,** antacid and **radiopaque suspension.**
- It contains high amount of suspension for administration as compare to other suspension.



Topical suspension



Oral suspension



Parenteral suspension

❖ Topical suspension

- This type of suspension are **applied topically, "shake lotion"** is the oldest example for these suspension.
- It contains **Calamine lotion USP** and other **dermatological preparation.**
- For protective as well as cosmetic action it should contain high amount of dispersed phase often in excess 20% (w/v).
- Therefore, topical lotion are the best example of suspension **which exhibit lo settling rate.**

❖ Parenteral suspension

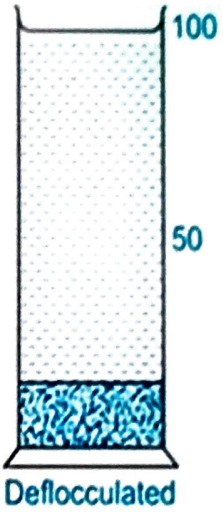
- Solid content of parenteral suspension is usually **between 0.5 and 0.5% (w/v),** except for **insoluble form of penicillin,** where **concentration of antibiotic may exceed 30% (w/v).**
- The type of suspension are sterile and designed for **intramuscular, intra-articular, subcutaneous or intradermal administration.**

❑ TYPES OF SUSPENSION BASED ON ELECTROKINETIC NATURE OF SOLID PARTICLES

❖ FLOCCULATED SUSPENSION

- Particles forms loose aggregates and form a network like structure.
- Particles from light fluffy conglomerates called flocs.
- Rate of sedimentation is high.
- Sediment is rapidly formed.
- Sediment volume is high.

- **Sediment is loosely packed & doesn't form hard cake.**
- **Sediment is easy to redisperse.**
- **Suspension is not pleasing in appearance.**
- **The floccules stick to the sides of the bottle.**



❖ **DEFLOCCULATED SUSPENSION**

- **Particles exist as separate entities.**
- **The particle in the suspension remains individually.**
- **Rate of sedimentation is slow.**
- **Sediment is slowly formed.**
- **Sediment is very closely packed & hard cake is formed.**
- **Sediment is difficult to redisperse.**
- **Suspension is pleasing in appearance.**
- **They don't stick to the sides of the bottle.**

❑ FORMULATION OF SUSPENSION

➢ **Flocculating agents -**

- **Agents that can be added** to the medium to promote flocculation by counteracting the effect of the **protective layer are termed** as **flocculating agent.**
- Act by reducing the surface tension. **e.g. SLS, Tweens, Span, Carbowax.**

➢ **Suspending agent, Thickening agent –**

- Added to the dispersion medium to lend its structure to assist in the suspension the dispersed phase.

(a) Polysaccharide -

- Natural - Acacia, Starch, Tragacanth, sodium alginate || Semisynthetic – Methyl cellulose, HPMC, Sodium carboxymethyl cellulose, Microcrystalline cellulose

(b) Inorganic agents - Clay, $Al(OH)_3$

(c) Synthetic - Carbomer, Colloidal SiO_2

➢ **Protective Colloids –**

- A protective colloid can be defined as a **lyophilic colloid** that when present in small quantities **keeps lyophobic colloids** from precipitating under the coagulating action of electrolytes.
- **E.g. - Gelatin, natural gum and cellulosic derivatives.**

➢ **Wetting agent -**

- Decrease interfacial tension between **solid particles and liquid medium.**
- **Types of wetting agent used** - Surfactant, Hydrophilic polymer, Solvent-Water and Alcohol.
- **E.g. Alcohol in tragacanth mucilage, Glycerin in sodium alginate.**

➢ **Preservative -**

- A preservative is a **substance or a chemical** which is added in any suspension products to preserve the particles from being contaminated from microorganism or microbial growth in the product.
- **E.G. :- Benzoic acid, Methyl paraben, Benzoic acid, Sodium benzoate.**

❑ STAGES IN FORMULATION OF SUSPENSION

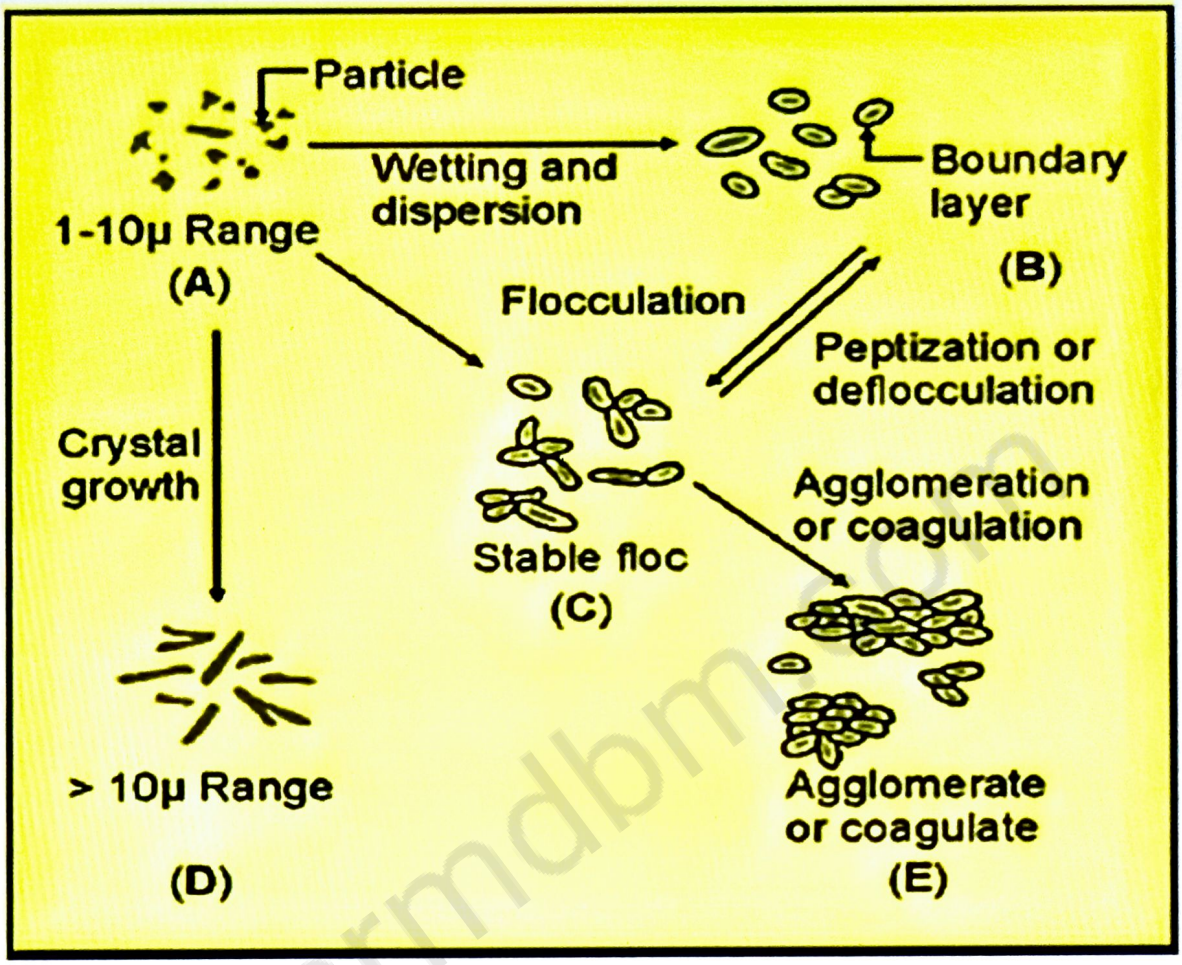
➢ **Selection of particle** - Particles within range of 1-10μ are selected

➢ **Deflocculated state** - This stage is **reached by wetting** and dispersion of the particle, **where a boundary is formed around the particle**

➢ **Flocculated state** - This stage may be formed by either directly wetting and dispersing hydrophobic particle **with a suitable flocculating** agent or by first wetting **and then dispersing** with a suitable surfactant (preparing deflocculated state) and then flocculating with suitable agents **like hydrophilic colloid** or polyelectrolyte. **This state is considered** as pharmaceutically stable and can **be always redispersed.**

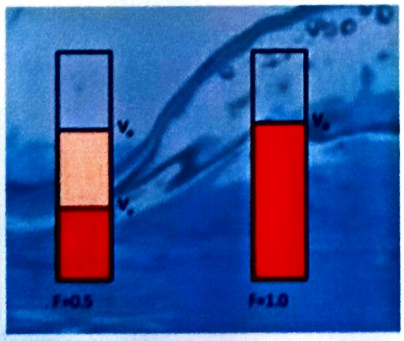
➢ **Crystal growth state** - This stage **indicates process of crystal growth in absence of a protective colloids**

- **Agglomeration/Coagulated irreversible system** - Addition of too much flocculating agent results as overflocculation and laids to produce this system.

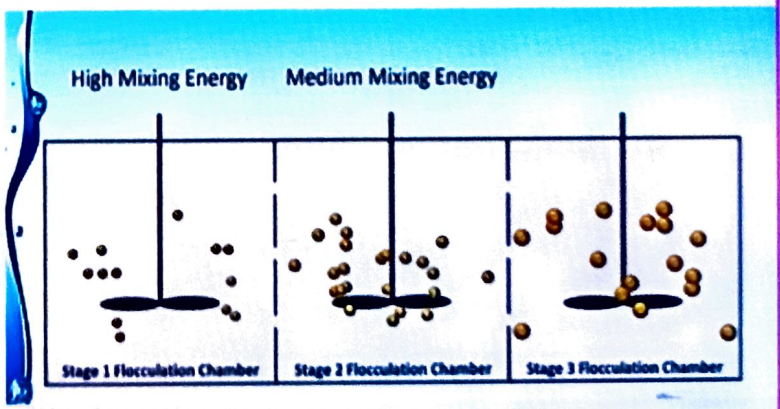


❑ EVALUATION OF SUSPENSION STABILITY

- **Sedimentation Volume**
- **Degree of Flocculation**
- **Redispersibility**
- **Electrokinetic Techniques**



Sedimentation Volume

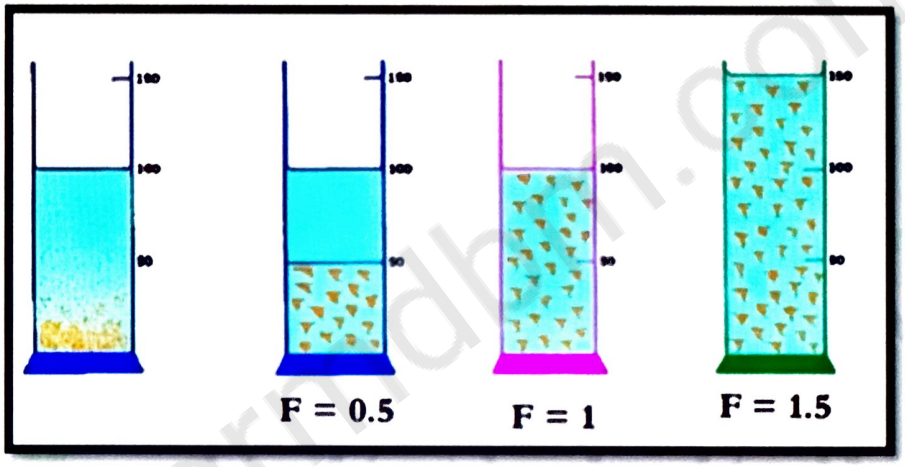


Degree of Flocculation

Sedimentation Volume

- Since redispersibility is one of the major considerations in assessing the **acceptability of a suspension,** and since the sediment formed should be easily dispersed by moderate shaking to **yield a homogeneous system.**
- Measurement of the sedimentation volume and its ease of redispersion form two of the most common basic evaluation procedures.
- **The concept of sedimentation volume is simple.**
- In short, it considers the ratio of the **ultimate height (Hu)** of the sediment to the **initial height (Ho) of the total suspension** as the suspension settles in a **cylinder under standard conditions.**

Sedimentation volume = H_u / H_o



Degree of Flocculation

- One additional concept should also be **considered by the formulator.**
- In all the **comparisons just mentioned,** the screening technique results only in a **relative ranking which indicates which preparations** are the better ones.
- **It is also useful, however, to consider the possibility** of making an absolute evaluation; which may be done as follows:
- **The degree of flocculation is the ratio of sedimentation volume** of the flocculated suspension **(F) to the sedimentation volume** that would be produced in the **ultimate dispersed state (F_∞).**

Degree of flocculation = F/F_∞

➢ Redispersibility

- As noted, the evaluation of **redispersibility is also important.**
- To help quantitate this parameter to some extent, a **mechanical shaking device may be used.**
- It **simulates human arm motion during the shaking process** and can give reproducible results when used under controlled conditions.
- It should be remembered, however, that the test conditions are not the same as those encountered under actual use, and further testing should be considered.
- **Nevertheless, the test results are useful and provide guidance during screening procedures.**

➢ Electrokinetic Techniques

- **Microelectrophoresis apparatus permits** the measurement of the migration velocity of the particles with respect to the **surface electric charge or the familiar zeta potential.**
- The latter has **units of viscosity times** the electrophoretic mobility, or more familiarly, volts.
- **Stanko and DeKay also evaluated suspensions by electrokinetic methods** and showed that the zeta potential changes upon the addition of additives and is related to stability.
- They correlated the **zeta potential to visually observed caking;** zeta potential was again determined by microscopic electrophoresis.
- It was found that **certain zeta potentials produced more stable suspensions** because aggregation was controlled and optimized.

➢ Rheological method

- The viscosity of the suspension is studied at different time intervals by using a **good quality of viscometer**. provides useful information about the stability of suspension.

➢ **Micromeritic method**

- The stability of a suspension depends on the **particle size**
- The size of the particle in a suspension may grow and may ultimately lead to the formation of lumps or caking
- A change in particle size distribution and crystal habit may be studied by microscopy and **Coulter counter method**

❑ METHODS OF DISPENSING SUSPENSIONS

The suspensions are divided into 4 types according to method of dispensing:-

(1) Suspensions containing diffusible solids

(2) Suspensions containing indiffusible solids

(3) Suspensions containing precipitate-forming liquids

(4) Suspensions produced by chemical reactions

BIPHASIC LIQUID DOSAGE FORM - EMULSION

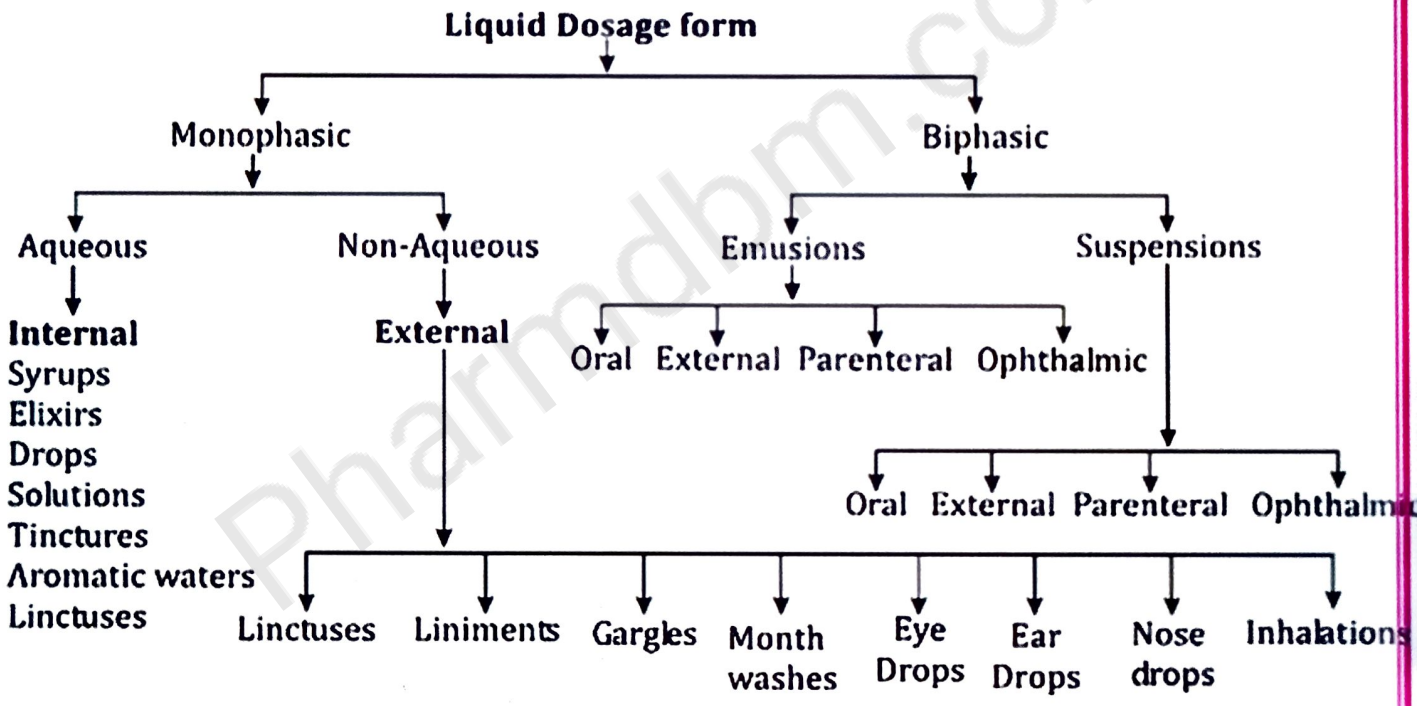
Contents to be covered in this topic

- INTRODUCTION
- TYPES OF EMULSION
- THEORIES OF EMULSIFICATION
- FORMULATION OF EMULSION
- METHODS FOR PREPARATION OF EMULSION
- TESTS FOR IDENTIFICATION OF TYPE OF EMULSION
- INSTABILITY OF EMULSION
- EVALUATION OF EMULSION

EMULSION

❑ INTRODUCTION

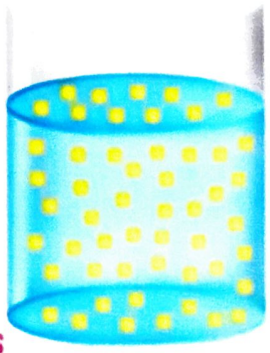
- An emulsion is a biphasic liquid preparation containing two immiscible liquids, one of which is **dispersed as minute globules into the other**
- The liquid which is converted into minute globules is called the **'dispersed phase'** and the liquid in which the globules are dispersed is called the **'continuous phase'**
- So, an emulsifying agent is added to the system. It forms a film around the globules in order to scatter them indefinitely in the continuous phase, so that a stable emulsion is formed.
- The globule size in emulsion varies from **0.25 to 25 µm diameter**



❑ TYPES OF EMULSION

➢ Oil in Water Emulsion

- Oil in water emulsions are **colloidal systems that have oil droplets dispersed throughout water.**
- Therefore **water acts as the continuous phase** of this **colloid while oil is the dispersed phase.**
- **Oil does not mix with water under normal conditions**



➢ Water in Oil Emulsion

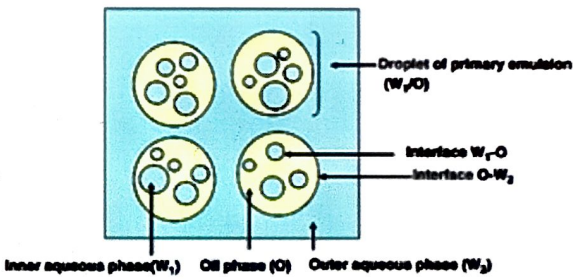
- Water in oil emulsions are colloidal systems having **water droplet dispersed** throughout oil.
- Therefore **oil acts as the continuous phase** of this colloid while **water is dispersed phase.**

➢ Microemulsion

- A **Microemulsions are clear, thermodynamically stable, isotropic liquid mixtures oil, water, and surfactant.**
- The particle size of microemulsions **ranges from about 10–300 nm.**
- The **solubilities of the drugs** in the microemulsion were **found to be higher in comparison to the solubilities** in the **individual microemulsion components.**

➢ Multiple emulsion

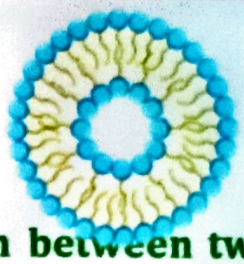
- Multiple emulsion are complex system which consist of both w/o and o/w at the same time. **Multiple emulsion can be of 2 types :-**
- **O/W/O – Small oil droplets** are entrapped within **larger water droplets** and they are **dispersed in continuous oil phase**
- **W/O/W – Small water droplets** are entrapped within **larger oil droplets** and they are disperse in **continuous water phase**



➢ Nanoemulsion

- In nanoemulsion particles are in the range of 10 nm to 75 nm. They do not refract therefore they **appear as transparent emulsion.**
- **These are the thermodynamically stable isotropic system** in which two immiscible liquids are mixed to form a single phase by means of **an emulsifying agent, i.e., surfactant and co-surfactant.**

❑ THEORIES OF EMULSIFICATION



➢ **Reduction of interfacial tension –**

- **Adsorption of surfactant lowers the interfacial tension between two different liquids.**
- **Reduction in the attractive force of dispersed liquid lowers the interfacial free energy of the system which will prevent coalescence or phase separation .**

➢ **Interfacial Film formation -**

It is **considered as an extended interfacial tension theory,** in which the adsorbed emulsifier at the **interface surrounds the dispersed droplets forming a monolayer or multimolecular film, which prevents the coalescence as the droplets approach each other.**

➢ **Monomolecular Film Formulation**

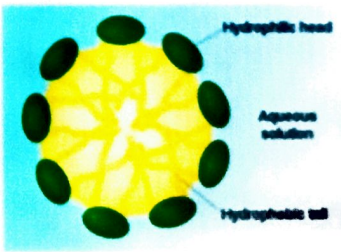
- This theory is **based on presumption** that certain **emulsifying agent orient themselves** about and within a liquid in a manner reflective of their solubility in that particular liquid.
- This theory **assumes monomolecular layer of emulsifying agent curved around a droplets of the internal phase.**

❑ FORMULATION OF EMULSION

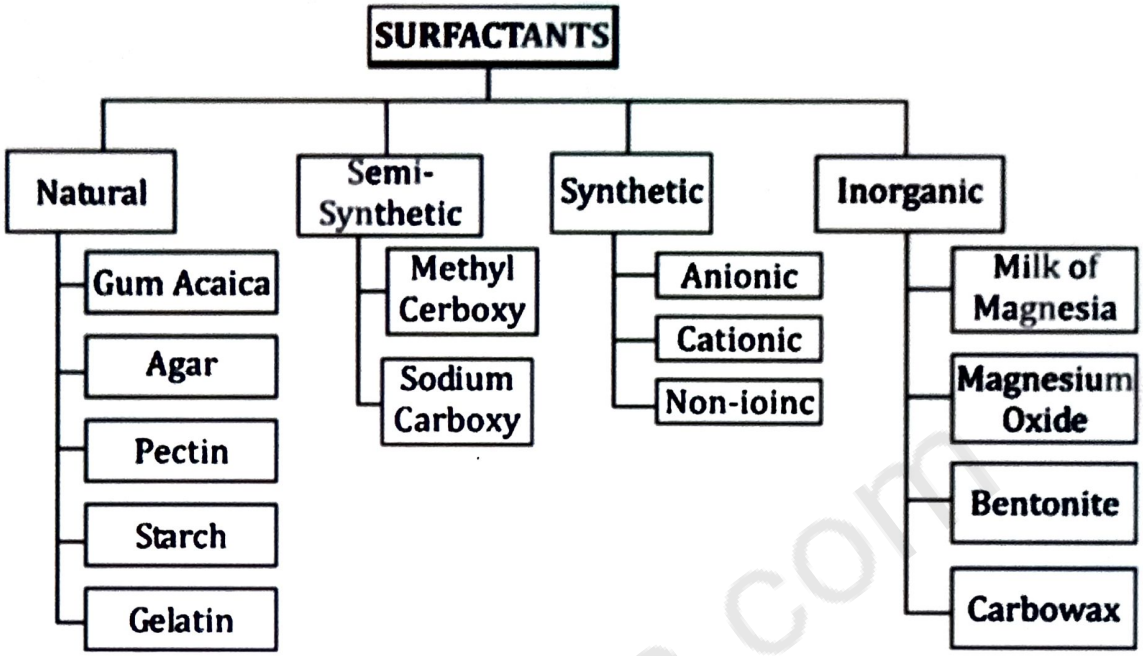
Emulsion are formulated by using following components

➢ **Surfactants**

- Substances having **both hydrophilic and, hydrophobic regions** in their molecular structures are **called surface active agents or surfactants.** These materials are **soluble in both water and oil.** Upon addition of the

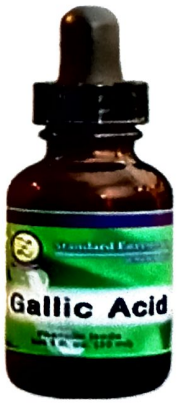


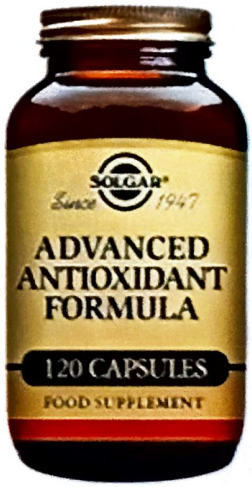
surfactants into the dispersed system, the hydrophilic (polar) and hydrophobic (non polar) groups orient themselves in a mono molecular layer facing the polar (i.e. water) and non-polar (i.e. oils) solvents, respectively..



➢ Antioxidants

- In emulsions antioxidants are used to prevent the product from being oxidized
- Example – Gallic acid, Propyl gallate, Ascorbic acid, Tocopherol, Butylated hydroxytoluene (BHT), Butylated hydroxyanisol (HTA).





➢ Preservatives

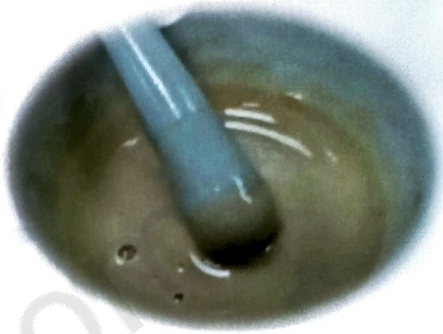
- A preservative added to emulsion products to prevent decomposition by microbial growth or by undesirable chemical changes.
- Example :- Paraoxybenzoate, Benzalkonium chloride.

➢ Flavouring agents

- The Flavouring agents are added to mask the unpleasant taste of drugs present in the product.
- **For example, orange oil, lemon oil,** distilled lime oil, grapefruit oil, and other citrus oils, clove oil, peppermint oil, ginger oil, dill oil.

❑ METHODS FOR PREPARATION OF EMULSION

➢ Wet-gum method :-



- Wet-gum method is used for preparing emulsions containing volatile and other non-viscous oils
- **In a mortar, add measured quantity of water**
- **Add weighed quantity of gum, E.G. Acacia**
- Triturate to **disperse lumps** add oil in small **amounts while triturating**
- **When whole of oil is added**, triturate vigorously to **produce thick cream.**
- Used for making emulsions of oleo-resins.

➢ Dry-gum method :-

- In dry mortar, add measured quantity of oil
- **Add weighed quantity of gum, e.g. Acacia**
- Triturate to disperse the lumps
- **Add water all at once**
- Triturate to produce thick cream.
- **This is the most commonly used method.**

➢ Bottle method :-

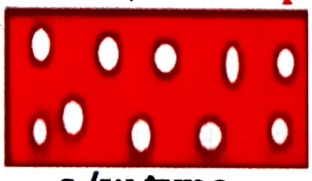
- **All the ingredients are added to a bottle and shaken vigorously.**
- **This method is used for making emulsions of volatile oils.**

❑ OIL : WATER : GUM RATIO FOR EMULSION PREPARATION

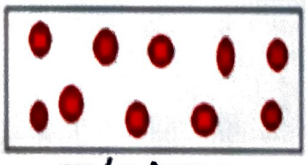
PROPORTION	OIL	WATER	GUM	METHOD
Fixed Oil (Castor Oil, Cod liver Oil, Olive Oil, Almond Oil)	4	2	1	F (4:2:1) Dry/ Wet gum method
Mineral Oil (Paraffin Oil)	3	2	1	M (3:2:1) Bottle method
Volatile Oil (Turpentine Oil, Sandal wood Oil, Cinnamon Oil)	2	2	1	V (2:2:1) Bottle method
Oleo Resin (Balsam of peru)	1	2	1	O (1:2:1)

❑ TESTS FOR IDENTIFICATION OF TYPE OF EMULSION

1. **DILUTION TEST:** The emulsion is diluted with water. In case the emulsion remains stable after its dilution, it is o/w emulsion. The **w/o emulsion breaks** on its dilution with water but remains stable when diluted with oil
2. **DYE TEST:** The scarlet red dye is mixed with the emulsion. Place a drop of the emulsion on a microscopic slide, cover it with a cover-slip, The reverse and examine it under a microscope. If the disperse **globules appear red** and the 'ground' colourless, the **emulsion is o/w type.** condition occurs **in w/o type emulsion** i.e., the **disperse globules appear colourless** in the red 'ground'.



o/w type



w/o type

1. **CONDUCTIVITY TEST: Water is a good conductor of electricity**, whereas **oil is non-conductor of electricity**. The conductivity test can be performed by dipping a pair of electrodes connected through a low voltage bulb in the emulsion. If the bulb glows on passing the electric. current, the emulsion is o/w type, because water is in the continuous phase. In case the bulb does not

4. FLUORESCENCE TEST: Certain fixed oils possess the physical property of **fluorescing in the presence of ultraviolet radiation**. On microscopic observation of emulsion under ultraviolet radiation, the whole field fluorescence indicates that oil is present in continuous phase (w/o type emulsion) and droplets fluorescence indicates that oil is present in dispense phase (o/w type emulsion)

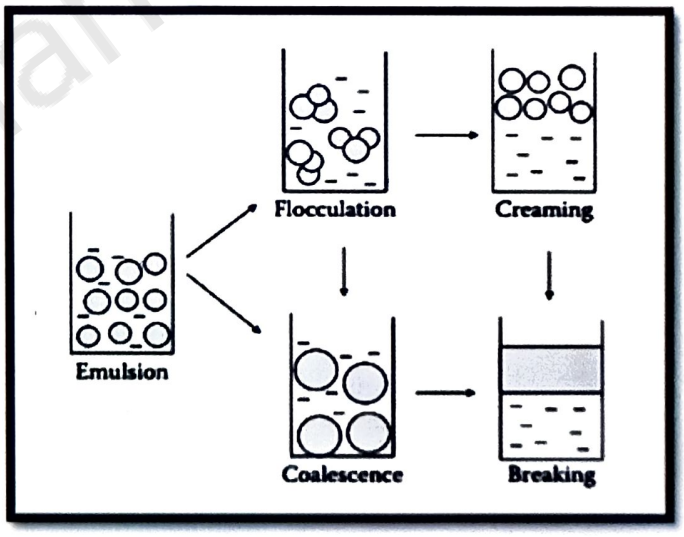
❑ INSTABILITY OF EMULSION

➢ Coalescence

- Coalescence of emulsions is an **irreversible process** by which **two or more droplets merge during** contact to form a single daughter droplet.
- Coalescence is the growth process in which **small particles merge with each other to form larger particle.**
- **Coalescence is followed by creaming stage.**
- **Mainly occurs due to insufficient emulsifying agent.**

➢ Flocculation

- In these **globules comes closer to each other** and form **flocs in the external phase.**



- Leads to instability

✓ Extent of flocculation of globules depends on

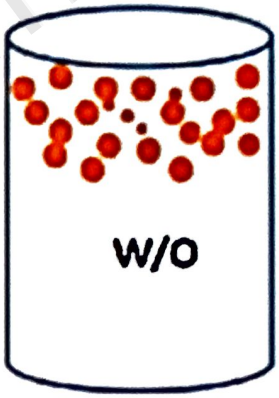
- Globule size distribution – Uniform – Prevent flocculation.
- Changes on globular surface – achieved by ionic emulsifying – Changes exert repulsive force.
- Viscosity of the external medium – Globule be immobile and prevent flocculation.

➢ Creaming

- It is the concentration of globules at the top or bottom of emulsion
- Rate of creaming is determined by Stoke's equation
- Leads to instability

✓ Prevented by

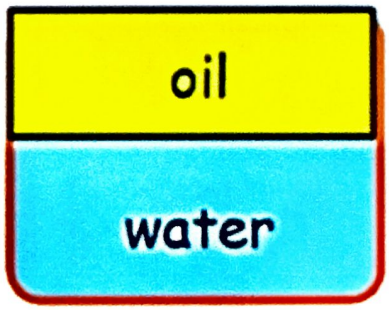
- Reducing particle size by homogenization.
- Increasing viscosity by adding thickening agent.
- Reducing the difference in densities.



Creaming

➢ Breaking or Cracking

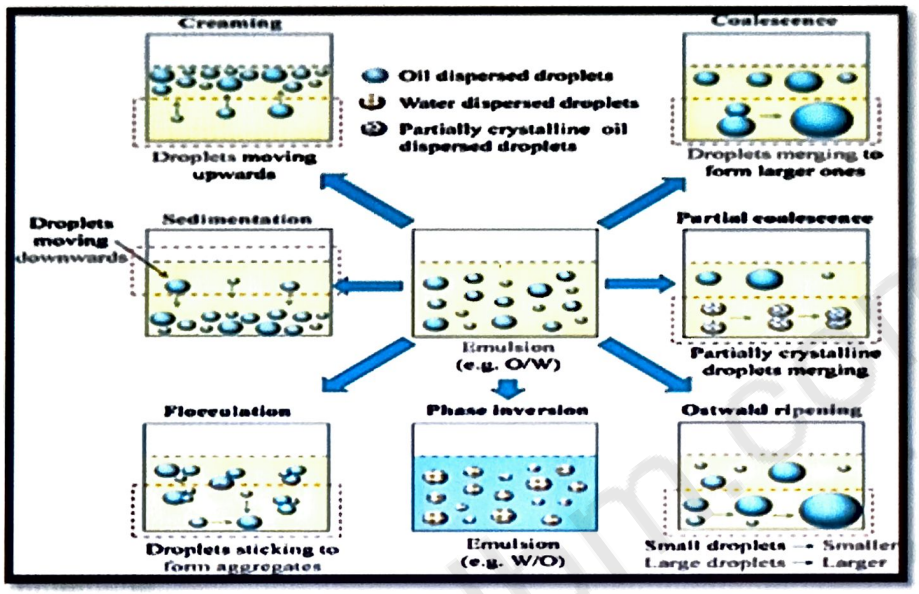
- Complete separation of oil and aqueous phase, irreversible.
- When ammonium chloride is gradually & slowly mixed into emulsion containing ammonium oleate, emulsion gets Cracked.
- When sodium chloride is gradually & slowly mixed into emulsion containing sodium oleate, emulsion gets Destabilize.
- Occurs due to addition of incompatible emulsifying agent; e.g - Monovalent soap + Divalent soap



Breaking

➢ Phase inversion

- In phase inversion, **o/w type emulsion** changes **into w/o type and vice versa**
- Brought about by **changing the phase volume ratio**, temperature change or by **addition of electrolyte.**
- When **stoichiometric amount of $CaCl_2$** is added to an **emulsion stabilized with sodium alginate, it will change nature from w/o to o/w.**



❑ ELAVUATION OF EMULSION

METHOD	DESCRIPTION
	STRESS CONDITION
Centrifugation	• **Centrifugation is a separative technique used in phase separation of dispersions, emulsions, and other formulations across many industry sectors.** • **In some cases, it can be used for accelerated stability analysis because it enables to apply strong gravitational stress on the sample, which results in faster separation** • **It gives idea about separation of disperse phase due to either creaming or coalescence.**

Agitation	• The stronger the agitation of a liquid phase, the more it is dispersed in the form of droplets. • The transformation of a mixture into an emulsion requires agitation in order to reduce the size of the drops and achieve the desired balance. • It gives idea about Brownian motion of emulsion.
Aging & temperature	Storing final product for varying period of time at temperature higher than normal, after specific period of time samples are withdrawal from preparation and tested for viscosity, rancidity, phase inversion etc.

PHYSICAL PARAMETERS	
Viscosity	• The viscosity of an emulsion depends on the initial viscosity of the bulk phase, η 0 and the volume fraction of the drops, φ. • Many equations are used to describe this dependence and three are shown here. • The Einstein equation obviously is the standard for solid particles. • Brookfield or cone and plate viscometer are used.
Zeta potential	• Emulsions with high zeta potential (negative or positive) are electrically stabilized while emulsions with low zeta potentials tend to coagulate or flocculate, possibly leading to poor physical stability. • Zeta sizer is used to determine viscosity, desired value for viscosity ±25mV.
Phase separation	• The main mechanism which leads to phase separation of emulsions is droplet coalescence, where drops merge together to reduce the total interfacial area present. • Observed after aging of an emulsion may be observed visually, or by measuring the volume of separated phase.

Particle size analysis	• **Particle size analysis gives useful information about the structure and stability of multiple emulsions, which are important characteristics of these systems.** • **It also enables the observation of the growth process of particles dispersed in multiple emulsions, accordingly, the evolution of their dimension in time.** • **Coulter counter or Malvern size analyzer is used to determine particle size.**