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B.Pharm
Sem-1

Subject Name: Pharmaceutics
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3.1 MONOPHASIC LIQUIDS

The compounding of solution retains an important place in therapeutics owing to the simplicity of preparation and rapid absorption of soluble medicinal products. Solutions are of particular value for paediatrics, geriatrics and psychiatric patients who have difficulty in swallowing solid dosage forms and in cases where individualized dosages are required. 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 consist of either true or colloidal solutions or solubilised system. All these consist of only a single phase and may have either aqueous or non-aqueous solvents as the base.

3.1.1 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 brought into intimate contact with mucous membrane of throat and allowed to remain in contact with it for few seconds, before they are thrown out of mouth. 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, and stimulation the flow of saliva, which released drugs. 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.

(3.1)

Storage: Gargles should be dispensed in clear, fluted glass bottles. Coloured bottles are required to be used if gargles need protection from sunlight.

Labeling: For EXTERNAL USE ONLY.

NOT TO BE SWALLOWED.

Formula: Phenol gargle

R_x

Phenol glycerin – 5 ml

Amaranth solution - 1 ml

Purified water - q.s. to 100 ml

This gargle may be prepared by mixing amaranth solution (1% w/v in chloroform water) with a small quantity of water and adding Phenol glycerin (16% w/w phenol and 84% w/w glycerin) to it. The solution is stirred and 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.

Packaging: Pack in flip flop bottles, water proof packing.

3.1.2 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. They may be either acidic or basic in their reaction and in some instances are fairly effective in reducing bacterial concentration and odours in the mouth for short periods of time.

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

Storage: Keep in cool and dry place, Dispense in clear, fluted bottles.

Labeling: FOR EXTERNAL USE ONLY

- Not to be swallowed in large amount
- Pack in narrow mouth bottle

Formula: R_x

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

Zinc sulphate – 20 g

Zinc chloride – 10 g

Oilute hydrochloride acid – 10 ml

Compound tartarzine solution – 10 ml

Chloroform water to produce – 1000 ml

The preparation may be 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 and the final volume is made up with water.

Zinc sulphate and Zinc chloride included in the preparation acts as astringents. Chloroform water acts as the flavouring agent and preservative while tartrazine serves as the colour. Zinc sulphate usually contains a small quantity of oxychloride which may make the solution turbid. This however disappears on addition of dilute hydrochloric acid.

3.1.3 Throat Paint

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.

Storage: Throat paint should be stored in airtight container and in cool place.

Labeling: For EXTERNAL USE ONLY.

Not to be swallowed.

Formula: R_x

Potassium iodide - 2.5 gm

Iodine - 1.25 gm

Alcohol – 4 ml

Water - 2.5 ml

Peppermint oil - 0.4 ml

Glycerin – 100 ml

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 and make up the volume to q.s.

- Paint are applied with soft brush.

Packing: A wide mouth, fluted, light resistant, screw car glass bottle is used and dispensed in amber coloured bottle.

3.1.4 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.

Ear drops are generally used for their cleansing, pain relieving and antiseptic actions. The main classes of drugs include analgesics like benzocaine, 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 - 5 g

Propylene glycol q.s to 100 ml

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

3.1.5 Nasal Drops

Nasal drops are liquid preparations intended for instillation into the nostrils usually with the help of a dropper. Nasal drops are mostly based on aqueous vehicles although oily drops (containing liquid paraffin of suitable viscosity) are not uncommon. Oily vehicles are generally not preferred since the oil may retard the ciliary action of the mucosa and may even cause lipoid pneumonia if drops of the oil enter the lungs. Nasal drops are generally formulated to resemble the nasal secretions as closely as possible. Thus, these are usually isotonic and slightly buffered to maintain a pH of 5.5 to 7.5. Additionally, the preparation is made slightly viscous with the help of thickening agents like methyl cellulose to match its viscosity with that of the nasal secretions.

Commercial nasal preparations usually contain decongestants, antibiotics, antihistamines and drugs for asthma prophylaxis. Examples include Ephedrine Nasal drops, Phenylephrine Nasal drops, etc.

Nasal drops are usually supplied in amber coloured fluted bottles with rubber teat and dropper closure.

Example : Ephedrine Nasal Drops

Ephedrine Hydrochloride - 0.5 g

Chlorbutol - 0.5 g

Sodium Chloride - 0.5 g

Purified water q.s to 100 ml

The drops may be prepared by first dissolving Chlorobutol in small quantity of hot water followed by cooling the solution to room temperature. Other ingredients are then dissolved in the solution, which is filtered and the final volume is made up with water. These drops are used as decongestant with Ephedrine acting as the active medicament. Chlorobutol acts as the preservative while Sodium chloride is added to make the solution iso-osmotic with nasal secretions.

3.1.6 Nasal Sprays

Nasal sprays are suspensions or solution of drugs intended for spraying in to the nostrils. The chief uses of nasal sprays are to relieve nasal congestion and inflammation and to treat infections. They are intended to be retained in the nasal tract, they are usually viscous and coarse since fine droplets tend to penetrate further in to the respiratory tract. These preparations are usually supplied in pressurized containers or plastic squeeze bottles.

3.1.7 Enemas

Enemas are liquid preparations meant to be introduced into the rectum for cleansing, therapeutic or diagnostic purposes. Evacuation enemas are rectal injections employed to evacuate the bowel in constipation or before an operation. e.g., Enema of soap, Sodium phosphate enema, Olive and arachis oil enema, etc. Retention enemas are usually employed to influence the general system by absorption or to affect locally the seat of disease. They may possess anthelmintic (quassia), nutritive, sedative (chloral hydrate), or anti-inflammatory (corticosteroids) properties, or they may contain radio-opaque substances (barium sulphate) for X-ray examination.

Large volume enemas are administered from a douche can and should be warmed to body temperature before use. Small volume enemas are available in polythene or polyvinyl chloride bags sealed to a rectal nozzle and these are more convenient for personal administration since the patient has simply to insert the nozzle and squeeze the bag.

3.1.8 Syrups

Syrups are sweet viscous concentrated aqueous solution of sucrose in purified water.

Simple syrup I.P contains 66.7%w/w sucrose in purified water (100 ml)

Simple syrup USP contains 85%w/v sucrose in purified water (100 m.)

Medicated Syrup: Contains a therapeutic or medicinal agent e.g. Cough syrup.

Flavoured Syrup: Contains flavouring agent but no medicinal substances e.g. Cherry syrup.

Advantages

1. Syrup retards oxidation because it is partly hydrolyzed into its reducing sugar such as laevulose and dextrose.
2. It prevents decomposition of vegetable substances. Syrup has high concentration of sugar having high osmotic pressure which prevents the growth of bacteria, fungi, microbes. It acts as a self preservative.
3. They are palatable due to the sweetness of sugar. It is a valuable vehicle for the administration of nauseous and bitter substances.
4. Syrups are good demulcents and soothing agents and hence they are of special value in cough syrup.
5. Syrups have good patient compliance.

Concentration of sucrose in sugar based syrup is very important. A dilute solution may lead to growth of micro-organisms whereas saturated solution may lead to crystallization of same part of sucrose. Both syrup concentrations as per IP and USP gives stable syrup. Syrup containing various concentrations of sucrose needs antimicrobial preservative.

Fig. 3.1

Method of Preparation

The choice of particular method depends on the physical and chemical characteristics of the substance being used.

1. Hot Process

This method is used when active constituents is neither volatile nor heat labile.

Procedure

- Weighed sucrose is taken in beaker.
- Purified water is added.
- Heated on water bath (less than 70°C) till a solution is obtained.
- Product is filtered.
- Volume is made upto q.s.

Excessive heat may leads to inversion of sucrose.

2. Percolation

- Sucrose is placed in percolator.
- Water is passed through sucrose slowly.
- Neck of percolator is packed with cotton.
- Rate of percolation regulates rate of dissolution.
- After complete dissolution final volume is made upto q.s.

3. Agitation Without Heat

Procedure for heat labile constituents

- 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 upto q.s.

4. Addition of Medicating or Flavouring Liquid to Syrup

This method is used when fluid extracts, tinctures or the other liquids are to be added to syrup.

- Alcohol is added to dissolve the resinous or oily substances.
- Alcohol acts as a preservative also.

Formulation of Syrup

1. **Vehicle:** Syrups are prepared by using purified water.
2. **Adjuncts:** The following adjuncts are generally added to improve the formulation of syrup.

- **Chemical Stabilizer:** Glycerin, sorbitol, propylene glycol is added in small quantity to syrup to prevent the crystallization.
- **Colouring agent:** Many syrup are attractively coloured with coal tar dyes such as amaranth, compound tartarazine and Green S.
- **Flavouring agents**
  (i) Tinctures: Lemon and ginger tincture
  (ii) Fruit juice: Cherry, Raspberry
  (iii) Essence: Vanilla, orange

Preservatives: Syrups are self preservative. Generally, Benzoic acid, Sodium benzoate, Methyl paraben etc.

Storage: Stored in well dried, completely filled and well stoppered bottle in a cool dark place. Store at a temperature not exceeding 25°C.

3.1.9 Elixir

Elixirs are defined as clear, aromatic, sweetened, hydroalcolohic liquids intended for oral us

- They provide a palatable means of administering potent or nauseous drugs.
- Elixirs are less sweet and less viscous then syrup may contain less or no sucrose.
- Elixirs are more stable than syrups and hence preferred over syrup.
- Elixirs contain 4-40% of alcohol (ethanol).
- They may contain glycerin and syrup for increasing the solubility of medicaments or for sweetening purpose.
- Elixirs may also contain suitable flavouring and colouring agents.
- Preservatives are not needed in elixirs as alcohol content is sufficient to act as preservative.

Types

Non-medicated: Not contain medicament and used as flavoring agent.

For example: Aromatic elixir.

Medicated: Which contain a potent drug such as antibiotics, antihistamines, sedatives.

Fig. 3.2 : Paracetamol Elixir

Method of Preparation

- Elixirs are prepared by simple dissolution with agitation or by mixing two or more liquids.
- Ingredients are dissolved in their respective solvents. For example alcohol soluble ingredients in alcohol and water soluble in water.
- Alcoholic strength is maintained by adding the aqueous solution to the alcoholic solution.
- The mixture is then made upto the desired volume (q.s.).
- At this stage the product may not be clear due to separation of some of the flavouring agent because the alcoholic strength is reduced.
- Then elixir allowed to stand for some time here the oil globules starts precipitating.
- Then elixir is filtered.
- Talc can be added to absorb the excess of oils.
- Filtration gives clear product.

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.

Container: Elixirs are dispense in well filled, well closed air tight or glass bottles having screw caps.

Storage: Store in cool and dry place, protected from sunlight.

Formula:

R_x

Lemon oil	-	0.025 ml
Syrup	-	375 ml
Talc	-	30 gm
Purified water	-	q.s. to 1000 ml

3.1.10 Liniment

- Liquid or semi-liquid preparation meant for application to the skin.
- The liniments are usually applied to the skin with friction and rubbing of skin (on the affected area).
- The liniment may be alcoholic or oily solution or emulsion.
- In alcoholic preparation, alcohol helps in the penetration of medicament to the skin and also increases its counter irritant effect and rubefacient action.
- In oily liniments, arachis oil is commonly used which spreads more easily on the skin.
- Some lubricants may contain soap which helps in easy application of liniment on skin.
- Liniment should not be applied on broken skin because it may cause excessive irritation.
- Liniment contain medicament possessing analgesic action, rubefacient, counter irritant properties and applied in joint pain, muscle pain etc.

Should be dispensed in colored fluted bottle.

Labelling: FOR EXTERNAL USE ONLY

Storage: Stored in tightly closed container.

Formulation: Turpentine liniment

Soft soap – 9 gm

Camphor – 5 gm

Turpentine oil – 65 ml

Purified water - q.s. to 100 ml

Note: Rubefacient: Dilates blood vessels.

Counter irritant: Causes superficial inflammation to cure deep inflammation.

3.1.11 Lotions

- Lotions are liquid preparations meant for external use without friction.
- They are applied direct to the skin with the help of some absorbent material, such as cotton wool, gauze soaked in it.
- Lotions are not applied to broken skin it may cause excessive irritation. The insoluble matter should be divided very finely for preparing lotions. Bentonite as a suspending agent is added to it.
- Lotions are applied for antiseptic action, astringent action, germicidal action e.g. Calamine lotion.
- Alcohol is sometimes included in aqueous lotions for its cooling and soothing effect e.g. salicylic acid lotion.

Fig. 3.3

Preparation: Lotions are prepared by triturating the ingredients to a smooth paste and then adding the remaining liquid phase with trituration.

Storage: Lotions should be stored in well closed and in air tight container.

Lebelling: FOR EXTERNAL USE ONLY

Formula: Calamine lotion

R_x

Calamine – 15 gm

Zinc oxide – 5 gm

Bentonite – 3 gm

Sodium citrate - 0.5 gm

Glycerin – 5 ml

Liquid phenol - 0.5 ml

Rose water - q.s. to 100 ml

3.2 BIPHASIC LIQUIDS

3.2.1 Emulsion

- An emulsion is liquid preparation containing two immiscible liquids, one of which is dispersed as globules (dispersed phase = internal phase) in the other liquid (continuous phase = external phase).
- Droplets ranging in diameter (0.1-100 um).
- Emulsion is thermo dynamically unstable and is stabilized by presence of emulsifying agent (emulgent or emulsifier).
- Emulsion no more official in I.P.
- Emulsion protect the drug which are susceptible to hydrolysis and oxidation. It also provide prolonged action of medication.
- In the form of an o/w emulsion, ephedrine has more prolonged effect when applied to nasal mucosa , than when used in an oily solution.

3.2.2 Types of Emulsion

Primary emulsion containing one internal phase, for example,

- oil-in-water emulsion (o/w)
- water-in-oil emulsion (w/o).

Secondary emulsion also called multiple-emulsion contains two internal phases, for instance,

- o/w/o
- w/o/w.

It can be used to delay release or to increase the stability of the active compounds.

3.2.3 Test for Emulsion

Dilution test: Addition of water to a w/o emulsion and oil to o/w emulsion would crack the emulsion and lead to separation of the phases.

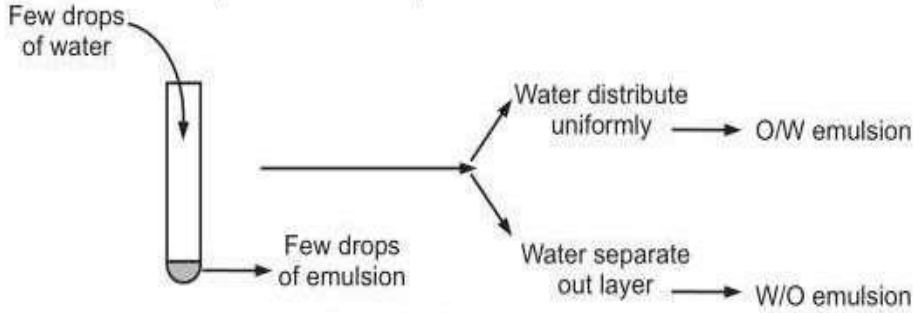


Fig. 3.4: Dilution test

Conductivity test: When current is passed to an emulsion which is connected to a voltage bulb, the bulbs glows if it is o/w emulsion since water is good conductor of electricity and when the bulb does not glow it is w/o emulsion because oil is non-conductor of electricity.

i.e. o/w = current flow

w/o = current do not flow

o/w = current not flow (when purified water instead of portable water is taken)

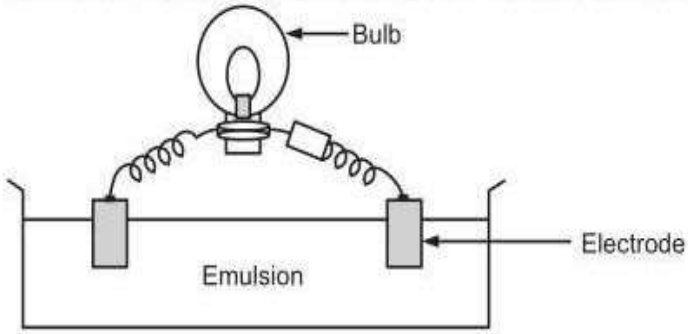


Fig. 3.5: Conductivity test

Dye test: Water-soluble dye will dissolve in the aqueous phase whereas oil-soluble dye will dissolve in the oil phase. For example: Amaranth (o/w Emulsion), Scarlet/Sudan (w/o Emulsion).

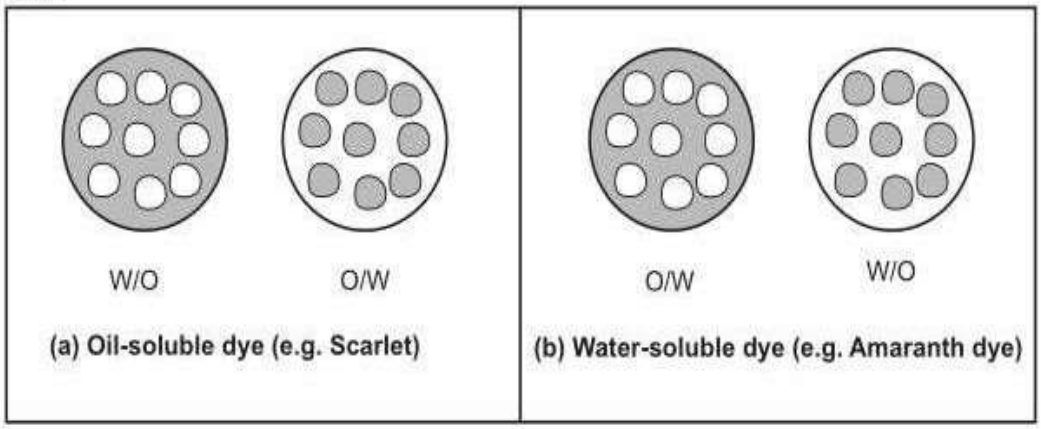


Fig. 3.6: Dye test

Fluorescent test: Oils give fluorescence under UV light, while water does not. Therefore, O/W emulsion shows spotty pattern while W/O emulsion fluorescence.

Filter paper test: o/w emulsion should spread out rapidly when dropped on to filter paper, in contrast w/o will migrate slowly.

Cobalt chloride test: filter paper soaked in cobalt chloride ($COCl_2$) solution and allowed to dry, turn blue to pink on evaporation to o/w emulsion.

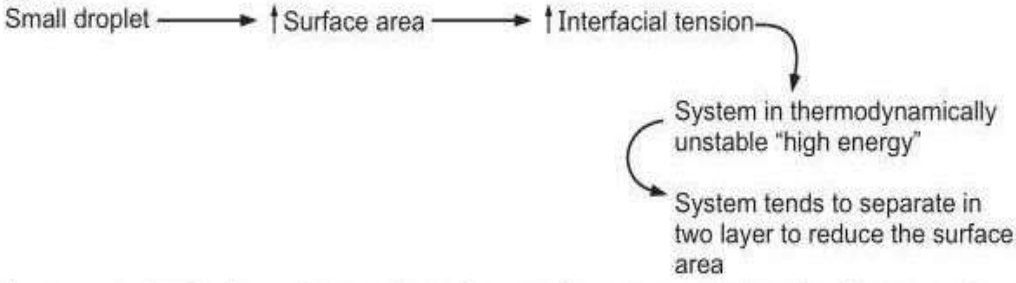
Pharmaceutical applications of emulsions

- To mask the bitter taste of the drugs.
- o/w emulsion is convenient means of orally administration of water-insoluble liquids.
- o/w emulsion facilitates the absorption of water-insoluble compounds comparing to their oily solution preparations (e.g. vitamins).
- Oil-soluble drugs can be given pareneterally in form of oil-in water emulsion. (e.g. Taxol)
- Emulsion can be used for external application in cosmetic and therapeutic uses.

3.2.4 Theories of Emulsification

- In case of two immiscible liquids, cohesive force between the molecules of each separate liquid exceeds adhesive force between two liquids. This is manifested as interfacial energy or tension at boundary between the liquids.

  Therefore, to prevent the coalescence and separation, emulsifying agents have been used.

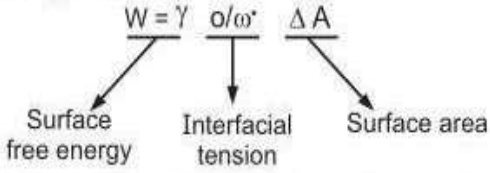


Surfactant: Adsorbed at oil/water interface to form monomolecular film to reduce the interfacial tension. e.g., Tween and Spans.

Hydrophillic colloids: Forming a multimolecular film around the dispersed droplet. e.g., Acacia.

Finely divided solids: They are adsorbed at the interface between two immiscible liquid phases to form particulate film. e.g., Bentonite and veegum.

(a) Monomolecular adsorption:



Surface active agent (SAA) is molecule which have two parts, one is hydrophilic and the other is hydrophobic. Upon the addition of SAA, they tend to form monolayer film at the oil/water interface.

The functions of surface active agents to provide stability to dispersed droplets are as follows:

- Reduction of the interfacial tension.
- Form coherent monolayer to prevent the coalescence of two droplet when they approach each other.
- Provide surface charge which cause repulsion between adjust particles.

Bancroft rule

As per bancroft rule, the emulsifying agent being used in an emulsion should be favourable to the external phase of the emulsion.

So even though there may be a formula that is 60% oil and 40% water, if the emulsifier chosen is more soluble in water, it will create an oil-in-water system.

The Hydrophilic-Lipophilic Balance (HLB) of a surfactant can be used in order to determine whether it is a good choice for the desired emulsion or not.

In Oil in Water emulsions, use emulsifying agents that are more soluble in water than in oil (High HLB surfactants).

In Water in Oil emulsions, use emulsifying agents that are more soluble in oil than in water (Low HLB surfactants).

(b) Multimolecular adsorption

	Polysaccharides	Amphoterics	Synthetic or semi-synthetic polymers
Colloids	Acacia Agar Alginic acid Carrageenan Guar gum Karraya gum Tragacanth	Gelatin	Carbomer resins Cellulose ethers Carboxymethyl chitin PEG-n (ethylene oxide polymer)

Hydrophilic colloids form multimolecular adsorption at the oil/water interface. They have low effect on the surface tension.

- Their main function as emulsion stabilizers is by making coherent multi-molecular film. This film is strong and resists the coalescence. They have, also, an auxiliary effect by increasing the viscosity of dispersion medium.

(c) Solid particle adsorption

Finely divided solid particles are adsorbed at the surface of emulsion droplet to stabilize them. Those particles are wetted by both oil and water (but not dissolved) and the concentration of these particles form a particulate film that prevent the coalescence.

Finely divided soilds	Bentonite Hectorite Kaolin Magnesium aluminium silicate Montorillonite Aluminium hydroxide Magnesium hydroxide Silica

Emulsion Stability

The process by which an emulsion completely breaks is generally considered to be governed by four different droplet loss mechanisms, i.e.

- Brownian flocculation,
- Creaming,
- Sedimentation flocculation and disproportionation.

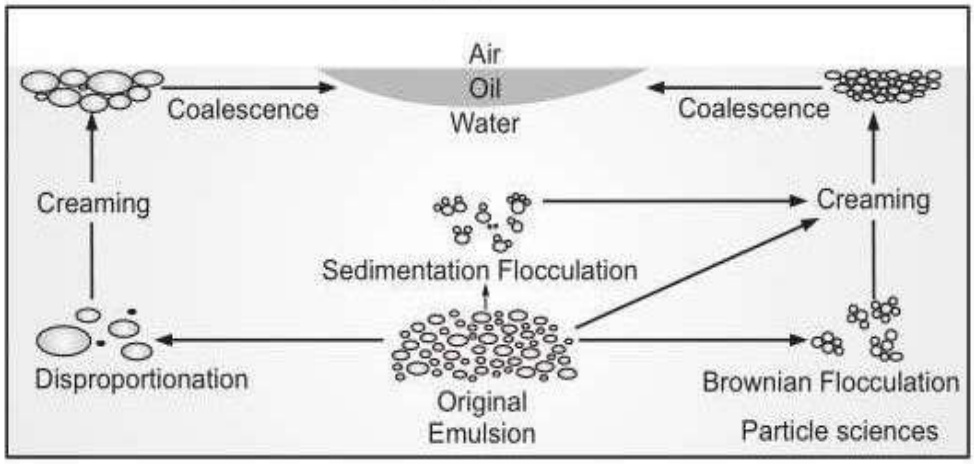


Fig. 3.7: Mechanism leading to coalescence of an oil in water emulsion

Creaming – upward and downward

- Creaming derives its name from the most commonly known example of a de-emulsification process.
- The separation of milk into its cream and skim milk components. Creaming is not an actual breaking but a separation of the emulsion into two emulsions, one of which (the cream) is richer in the disperse phase than the other. Creaming is the principal process by which the disperse phase separates from an emulsion and is typically the precursor to coalescence.
- The creaming rate (or settling rate for disperse phases more dense than the continuous phase) can be estimated from the Stoke's equation:

$$\upsilon = 2r^2 (\rho - \rho_0)\, g/9\eta$$

where, υ is the creaming (settling) rate, r is the droplet radius, ρ is the density of the droplet, ρo is the density of the dispersion medium, η is the viscosity of the dispersion medium (continuous phase) and g is the local acceleration due to gravity.

Flocculation

- The aggregation of droplets to give 3-D clusters without coalescence occurring. Importantly, all droplets maintain their own integrity and remain as totally separate entities. It results when there is a weak, net attraction between droplets and arises through various mechanism.

- Flocculation may be subdivided for convenience into two general categories: that resulting from sedimentation aggregation and that from Brownian motion aggregation of the droplets.

Disproportionation or Ostwald ripening

- It is dependent on the diffusion of disperse phase molecules from smaller to larger droplets through the continuous phase.
- The pressure of dispersed material is greater for smaller droplets than larger droplets as per the Laplace equation.

Coalescence

- A few globules tend to fuse with each other and form bigger globules.
- In this process, emulsifier film around the globules is destroyed to some extent.

Breaking

- Complete separation of phases, irreversible process.

  Phase Inversion

  In phase inversion o/w type emulsion changes into w/o type and vice versa. It is a physical instability.
- It may be brought about by the addition of an electrolyte, by changing the phase volume ratio or by temperature changes, by changing chemical nature of emulsifier

  Phase inversion can be minimized by using the proper emulsifying agent in adequate concentration, and by storing the emulsion in a cool place.

3.2.5 Preparation of Emulsions

Preparation of emulsions depends on the scale at which it is produced.

- **On small scale** mortar and pestle can be used but its efficiency is limited. To overcome this drawback small electric mixers can be used although care must be exercised to avoid excessive entrapment of air.
- **For large scale** production mechanical stirrers are used to provide controlled agitation and shearing stress to produce stable emulsions.
- The methods commonly used to prepare emulsions can be divided into two categories:

(A) Trituration Method

This method consists of dry gum method and wet gum method.

(1) Dry Gum Method

In this method, the oil is first triturated with gum with a little amount of water to form the primary emulsion. The trituration is continued till a characteristic 'clicking' sound is heard and a thick white cream is formed. Once the primary emulsion is formed, the remaining quantity of water is slowly added to form the final emulsion.

(2) Wet Gum Method

As the name implies, in this method first gum and water are triturated together to form a mucilage. The required quantity of oil is then added gradually in small proportions with thorough trituration to form the primary emulsion.

Once the primary emulsion has been formed remaining quantity of water is added to make the final emulsion.

(B) Bottle Method

This method is employed for preparing emulsions containing volatile and other non-viscous oils. Both dry gum and wet gum methods can be employed for the preparation.

As volatile oils have a low viscosity as compared to fixed oils, they require comparatively large quantity of gum for emulsification.

In this method, oil or water is first shaken thoroughly and vigorously with the calculated amount of gum. Once this has emulsified completely, the second liquid (either oil or water) is then added all at once and the bottle is again shaken vigorously to form the primary emulsion. More of water is added in small portions with constant agitation after each addition to produce the final volume.

Formulae for Primary Emulsion

Dry gum method or continental method

	Oil	Gum	Water
For fixed oil	4	1	2
For volatile	2	1	2
Oleo resins	1	1	2

3.2.6 Evaluation of Emulsion

Stability testing of emulsions involves determining stability at long term storage conditions, accelerated storage conditions, freezing and thawing conditions. Stress conditions are applied in order to speed up the stability testing.

1. The stress conditions used for speeding up instability of emulsions include:
   - Centrifugal force, Agitational force, Aging and temperature.
2. Physical parameters are evaluated to assess the effect of any of the above stress conditions:
   (a) Phase separation
   (b) Viscosity
   (c) Electrophoretic properties
   (d) Particle size and particle count

1. Determination of particle size and particle count: Determination of changes in the average particle size or the size distribution of droplets is an important parameter used for the evaluation of emulsions. It is performed by optical microscopy, sedimentation by using Andreasen apparatus and Coulter counter apparatus.

2. Determination of viscosity: Determination of viscosity is done to assess the changes that might take place during aging. Emulsions exhibit non-newtonian type of flow characteristics.

The viscometers which should be used include cone and plate viscometers.

3. Determination of phase separation: This is another parameter used for assessing the stability of the formulation.

Phase separation may be observed visually or by measuring the volume of the separated phases.

4. Determination of electrophoretic properties: Determination of electrophoretic properties like zeta potential is useful for assessing flocculation since electrical charges on particles influence the rate of flocculation.

Types of Surfactants

- Anionic
- Cationic
- Non-ionic
- Ampholytic

(a) Anionic: Monovalent, polyvalent and inorganic soaps sulphates and sulphanotes, alkali soaps includes sodium, potassium and ammonium salts are lauric, myristric, palmitic, stearic and oleic acid are water soluble which forms o/w emulsion.

Metallic soaps like calcium or magnesium salts are fatty acid are water insoluble and tend to form w/o emulsion. Organic soaps forms o/w emulsion. Sulphated alcohols such as sodium lauryl sulphate form o/w emulsion.

Sodium dioctyl sulphosuccinate is frequently used sulphonates di-(2-ethyl hexyl) sodium sulphosuccinate called Aerosol OT.

(b) Cationic emulgent: They are commonly used in lotion and cream due to their remarkable bactericidal property. For example: domiphen bromide, cetyl pyridium bromide, benzalkonium chloride, cetyl trimethyl ammonium bromide.

(c) Non-ionic emulgents: For example: Glyceryl ester, fatty acid esters of sorbitol, and their poly oxyethylene derivative, polyoxyethene glycol esters and Sorbitan fatty acid esters e.g. Sorbitan mono palmitate (span-40) are non-ionic and oil soluble promoting w/o emulsion.

Polyoxyethylene sorbitan monopalmitate (tween 40) are hydrophilic, water soluble derivative promotes o/w emulsion.

(d) Amphoteric: N-dodecyl, N, N- dimethyl betaine, lecithin.

PEG esters such as polyoxy ethylene glycol 400 monostearate are widely used to prepare emulsified lotion and creams.

Natural emulgents: Most commonly used is acacia. Others are Gelatin which is amphoteric in nature, Lecithin (phospholipid) and Cholesterol.

Acacia and gelatin: Form interfacial monolayer.

Lecithin and cholesterol: Form interfacial mono molecular layer.

Lecithin is a phospholipids and form o/w emulsion, Darken on storage.

Cholesterol form: w/o emulsion.

Finely dispersed solids: Colloidal clays such as bentonite, veegum, oxide, silica gel, aluminium hydroxide, Magnesium oxide. Magnesium hydroxides are most commonly used finely dispersed solids which act by forming particular particulate film around dispersed globules.

- **Bentonite** produce both o/w and w/o type of emulsion depending on order of mixing.
- **Veegum** is also as an emulgent for o/w emulsion but it is chiefly used as an stabilizer in cosmetic creams and lotion.
- **Auxilairy emulgents** are incapable of forming stable emulsion. Have thickening property. Thus, consistency of an o/w emulsion prepared by using acacia. It can be increased by tragacanth or agar which act as auxiliary emulsion.

List of antioxidants (0.001-0.1%)

- Gallic acid
- Propyl Gallate
- Ascorbic acid
- Sulphites
- alpha -Tocopherol
- Butylated hydroxyl toluene
- Butylated hydroxyl anisole
- Ascorbyl palmitate

3.2.7 Preservative used in Emulsion

Type	Example	Characteristic
Acid and acid derivatives	Benzoic acid Sorbic acid Propionic acid Dehydroacetic acid	Antifungal
Alcohols	Chlorobutanol Phenoxy- 2-ethanol	Eye prep. Synergism
Aldehydes	Formaldehyde, Glutaraldehyde	Broad spectrum
Formaldehyde Derivatives	Hexamethylene tetramine Mono and de- methyl ol dimethyl hydantoin	Broad spectrum
Phenolic	Phenol,Cresol,chlorothymol p-phenyl phenol p-chlorometaxylenol Methyl-p-hydroxybenzoate Propyl-p-hydroxybenzoate Benzyl-p-hydroxybenzoate Butyl -p-hydroxybenzoate	Broad spectrum
Quaternaries	Chlorhexidine Benzethonium chloride Benzalkonium chloride Cetyl pyridinium chloride Cetyl Methyl ammonium bromide	Broad spectrum
Mercurials	Phenyl mercuric acetate Sodium Ethyl mercuric Thiosalicylate	Broad spectrum

3.3 SUSPENSIONS

- Suspensions are biphasic, heterogeneous system in which finely divided insoluble solid particles (disperse phase) are dispersed or suspended in a vehicle (dispersion medium).

- The diameter of disperse phase may range from 0.5 µm to 100 µm.
- Systems in which particle size is below than this range are called colloidal (1 nm – 0.5 µm diameter).
- Suspension can be used as oral dosage form, applied topically to skin or given parenterally.

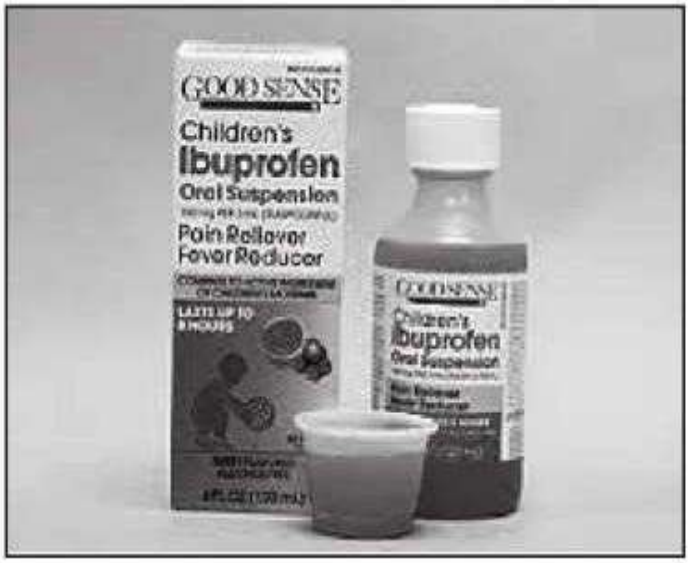


Fig. 3.8

3.3.1 Properties of Good Suspensions

1. The dispersed particles should settle slowly and should redisperse immediately on shaking.
2. The product should remain sufficiently homogeneous for atleast the period between shaking the container and removing the required dose.
3. The viscosity of suspension should be such that it can be easily removed from container and transferred to site of application without any difficulty.
4. The sediment produced on standing should not form a hard cake.
5. Suspension particles should be small and uniformly sized in order to give a smooth, elegant product free from grittiness.
6. The suspension should be physically and chemically stable during handling and storage conditions.
7. It should have good syringibility in case of parenteral suspension.
8. It should produce thixotropic property, gel to sol upon shaking and sol to gel on storage.

Advantages of Suspensions

1. Insoluble drug may be made more palatable (masking bitter taste).
   For example: Chloramphenicol.
2. Insoluble drug can be prepared in a more stable manner. For example: Procaine penicillin G.

3. Suspensions results in more bioavailability compared to any other dosage form.

   Solution > Suspension > Capsule > Compressed tablet > Coated tablet.

4. Duration and onset of action can be controlled. For example: Protamine Zinc-insulin injection.
5. Lotion leaves a cooling layer of medicament on skin.
6. It can be prepared for both immediate and sustained drug release preparations.

Disadvantages of Suspensions

1. Suspensions require shaking before use, to ensure uniformity of dose.
2. If suspension is not shaken well, accuracy of dose gets affected.
3. Improper storage condition can affect the disperse system.
4. Sufficient care must be taken during handling and transport.

3.3.2 Classification

1. **Based on general classes:**
   - **Oral Suspensions –**

   e.g. Paracetamol suspension

   Antacid suspension

   Antibiotic suspension

   Anthelminitics suspension

   Laxative suspension

   - **Topical suspensions –** (Externally applied)

     E.g.- Calamine lotion.

   - **Parenteral suspension –** e.g. Cholera vaccine, insulin, Zinc suspension.

2. **Based on proportion of solid:**
   - **Dilute suspension –** (2 to 10% w/v solid)

     E.g. Cortisone acetate, Prednisolone acetate.

   - **Concentrated suspension –** (50% w/v)

     E.g. Zinc oxide suspension.

3. **Based on deteriorate nature of solid particles**
   1. Flocculated
   2. Deflocculated

Flocculated suspension	Deflocculated suspension
1. Particles exist as loose aggregates.	1. Particles exist as separate entity.
2. Rate of sedimentation is high.	2. Rate of sedimentation is low.
3. Sediment formed rapidly.	3. Sediment formed slowly.
4. Consist of loosely packed particles possessing a Scaffolding like structure a hard dense cake does not form and the sedimentation can easily redispersed.	4. Sediment becomes very closely packed as the repulsive forces between the particles are overcome a hard cake is formed which is difficult to redisperse.
5. Elegant preparation are obtained due to uniform distribution of loosely bonded flocs.	5. Unsightly preparation result due to the formation of sedimentation.

4. Based on size of solid particles

1. Colloidal suspension – (< 1 micron)
2. Coarse suspension – (> 1 micron)
3. Nano suspension – (10 ng less than 1 mm)

3.3.3 Applications of Suspensions

1. Suspension is usually applicable for drug which is insoluble or poorly soluble e.g. Prednisolone syrup.
2. To prevent degradation of drug or to remove stability of drug e.g. Oxytetracycline suspension.
3. To mask the bitter drug. e.g. Chloramphenicol palmitate.
4. Topical application e.g. Calamine lotion is used.
5. Parenteral applications for control rate of drug absorption e.g. Penicillin procaine.
6. Vaccine as immunizing agent e.g. Cholera vaccines.
7. X-Ray contrast agent e.g. Barium Sulfate for examining alimentary canal.

Theoretical consideration of suspensions

I. Particle size control
II. Wetting
III. Sedimentation
IV. Brownian movement
V. Electrokinetic
VI. Aggregation

1. **Particle size:** It should be in range. Too large and too small should be avoided. Large particles will settle fast at bottom of container. Too fine particles can form cake.

2. **Sedimentation:** Means settling of particles on floccules occur under gravitational force in liquid dosage form.

$$V_{sed} = \frac{d^2 (\rho_s - \rho_0) g}{18\eta_0}$$

d = Diameter of particle

ρ_s = Density of disperse phase

g = Acceleration due to gravity

η_0 = Viscosity of disperse medium in poise

V_{sed} = Sedimentation velocity in cm/sec

ρ_o = Density of disperse medium

Stoke's law only applies to:

1. Spherical particle in a very dilute suspension (0.5 to 2 gm/100 ml).
2. Particles which freely settle.
3. Particles with no physical or chemical attraction.

Sedimentation volume for flocculated suspension

$$F = \frac{V_u}{V_o}$$

F = Sedimentation volume

V_u = Final volume

V_o = Original volume before settling

F is the ratio of ultimate volume of sediment to the original volume of sediment before settling.

When $F < 1 \rightarrow V_u < V_o$

$F = 1 \rightarrow V_u = V_o$

System is in flocculated equilibrium, no clear supernatant liquid on standing.

When $F > 1 \rightarrow V_u > V_o$

That means sediment volume is greater than original volume due to the network of flocs formed in suspension and so loose and fluffy sediment.

3. **Degree of flocculation:** It is the ratio of sedimentation volume of the flocculated suspension, F to the sedimentation volume of deflocculated suspension F_∞

$$\beta = \frac{F}{F_\infty}$$

$$\beta = \frac{(V_u/V_o) \text{ flocculated}}{(V_u/V_o) \text{ deflocculated}}$$

The minimum value of β is 1, when flocculated suspension sedimentation volume is equal to the sedimentation volume of deflocculated suspension.

4. Brownian movement

- Prevents sedimentation by keeping the dispersed material in random motion.
- Brownian movement depends upon density of dispersed phase, the density and viscosity of disperse medium.
- Kinetic bombardment of particles by the molecules of suspending medium will keep particles suspending provided that their size is below critical radius.
- Brownian movement can be observed if particles are of 2 to 5 mm and when density of particle and viscosity medium is favourable.

Brownian Movement is given by

$$D_i^2 = RTt/N_3\pi\eta r$$

R = Gas constant

T = Temperature

t = Time

N = Avogadro number

η = Viscosity of medium

r = Radius of particle

5. Electrokinetic parameter

(δ) Zeta potential: The zeta potential is defined as the difference in potential between the surface of tightly bound layer (shear plane) and electro neutral region of solution.

- The potential located at the shear plane is known as the zeta potential.
- It has a practical application in the stability of disperse systems since the potential governs the degree of repulsion between adjacent, similarly charged, dispersed particles.
- If zeta potential is reduced to a certain value, the attractive force exceed the repulsive force and the particles came together leading to flocculation. If zeta potential increased repulsion occurs.

6. Formulation of Suspension:

It involves the following ingredients:

1. **Medicament:** Drug with non-aqueous solubility.
2. **Flocculating agent:** The particle should be well dispersed in a vehicle. Dispersion can be improved by adding a surfactant, electrolyte or a polymer. It act as a deflocculating agent.
   - **(a) Electrolytes:** As flocculating agent by reducing the electric barrier between the particles due to a decrease in zeta potential
     - Forms a bridge between adjacent particles.
     - Particles links in loose manner

     E.g. Sodium salts of acetate, phosphates, citrates.

(b) Surfactant: Non-ionic surfactant acts by reducing surface tension or by forming bridges between particles.

Ionic surfactant also cause flocculation by neutralization of charge on each particle, thus resulting in flocculated system (also depends which type of charge is present on particles)

(c) Polymers: The linear branches chain molecules of polymer forms a gel network within the system, which becomes absorbed onto the surface of dispersed particles thus holding in flocculated state. E.g. Starch, alginates, cellulose derivative, carbamers, tragacanth.

3. **Deflocculating agent:** Prevent flocculation by reducing viscosity and is called as dispersant. An agent for thinning suspensions or slurries. They are low molecular weight anionic polymers. e.g.: polyphosphates, lignosulphonates, and water soluble synthetic polymers.
4. **Suspending agents:** They are hydrophilic colloids which forms colloidal dispersion with water and then acts by increasing viscosity of external phase.
   - Reducing rate of sedimentation of particles.
   - Particles remain suspended for long time.
   - Easier to withdraw accurate dose.

They are also known as Thickening agents.

E.g. Tragacanth BP – 0.2% conc.

BP compound tragacanth – 2.0%

Bentonite BP – 2-3%

3.3.4 Types of Suspending Agents

1. **Natural polysaccharides**

(a) Acacia: Protective colloid and suspending agent used in preparation containing resinous tincture that precipitates on addition of water.

(b) Tragacanth: Better than acacia, used to suspend heavy indiffusible substances.

(c) Alginates: 1-5% Viscous in nature immediately after preparation but the viscosity decreases within 24 hours.

Alginate mucilage must not be heated above 60°C due to polymerization its viscosity is lost.

2. **Semi-synthetic derivative**

(a) Methyl cellulose – 0.5 to 2% (sol to gel, gel to sol)

(b) SCMC – 0.25%-1% (oral, external, IV)

(c) Microcrystaline cellulose – insoluble in water, but show a good dispersion.

- Used in combination with MC, HPMC to flocculate dispersion.

3. **Inorganic agents**
   (a) Bentonite – 3% for external use.
   (b) Magnesium aluminiun silicate (veegum) – 5%.
4. **Synthetic compound**
   (a) Carbamers – 0.5% conc.
   (b) Colloidal silicon dioxide – 4% for external use.
5. **Wetting agents:** These substances reduces the surface tension between solid particles and liquid medium. This is achieved by the solid liquid interface in such a way that the affinity of the particles towards the surrounding medium is increased, there by helping in the penetration of liquid into the particles, thus resulting in good suspension (0.5%), for example: Spans and tweens etc.
6. Preservative substances which protect substance from bacterial growth. They should be stable and compatible. e.g. Benzoic acid, methyl and propyl paraben, EDTA.
7. **Organoleptic agent**
   (a) Flavouring agent – e.g. Vanilla, Strawberry, Banana.
   (b) Sweetening agent – Sucrose, Sodium saccharin, Aspartame.
   (c) Coloring agent – Sunset yellow, Tartrazine, Erythrosine.
   (d) Perfumes – Rose water and Lavender oil.
8. **Chemical stabilizers:** To maintain the stability of formulation. e.g. Citric acid, disodium diedetate, sodium citrate.

3.3.5 Manufacturing and Dispensing of Suspension

1. **Suspension containing diffusible solids**
   - Drug is finely powdered with other ingredients.
   - $3/4^{th}$ of vehicle is added to make cream.
   - Addition of rest of vehicle.
   - Volume is makeup.
   - Suspension is labelled properly and corked

   e.g. Light kaolin, light Magnesium carbonate, Sodium bicarbonate, Peppermint water.

   Labelling: Shake well before use.
2. **Suspension containing indiffusible solids:** Prepared by using compound tragacanth and Tragacanth mucilage (mixture of tragacanth, ethanol and chloroform water) e.g., Aspirin, Chalk, Phenobarbitone, Zinc oxide.

Note: Formulation method of suspension using

1. Tragacanth mucilage
2. Compound tragacanth powder

The procedure is same as that of diffusible solid additional point is step one where drug is also triturated with suspending agent with the addition of vehicle in small quantity and then reset procedure is same.

3. **Suspension containing precipitate forming liquid:** Liquid preparation containing resinous matter when mixed with water show precipitation of resin, which stick to the walls of container and tolu tincture. To prevent this compound tragacanth or Tragacanth mucilage is used e.g. Myrrh, Tolu, Lobelia.
4. **Suspensions containing poorly wettable solids:** Some substances like sulfur and Hydrocortisone are both insoluble in water and poorly wettable by it.

   In these type of suspension, a suitable wetting agent is added which is adsorbed at the solid liquid interface in such a way that the affinity of particles for surrounding medium is increased which interparticular forces are decreased.

   E.g. Sulfur lotion – quilliar tincture is used as suspending agent.
5. Suspension produced by chemical reaction – e.g. $MgSO_4 + (NaOH)_2 + Na_2SO_4$

   For preparing milk of magnesia suspension (antacid). Precipitate is produced by chemical reaction.

3.3.6 Evaluation of Suspension

(1) Sedimentation method

(2) Rheological method

(3) Electrokinetic method

(4) Micromeritic method

Sedimentation Volume

Sedimentation volume of the formulations was determined using the following formula.

$$F = \frac{V_u}{V_o}$$

F = Sedimentation volume,

V_u = Ultimate settled height of suspension,

V_o = Original height of the suspension before settling

Ease of Redispersibility

The suspension was allowed to settle in a measuring cylinder. The mouth of the cylinder was closed and was inverted through 180° and the number of inversions necessary to

restore a homogeneous suspension was determined. If the homogeneity of the suspension was attained in one inversion, then the suspension was considered 100% easily redispersible. Every additional inversion decreases the percentage of ease of redispersibility by 5%.

Viscosity determination (Rheological parameter)

The viscosity of all formulations was determined by using Brookfield digital viscometer. The measurements were carried out using spindle number-3 (disc type) rotating at 10, 20, and 100 rpm. The temperature was maintained at 30°C

Particle size distribution

Using optical microscope particle size distribution studies were carried out.

1. Eye piece micrometer was calibrated using stage micrometer,
2. Sample was uniformly suspended in paraffin oil.
3. A slide of above suspension was prepared, placed under microscope and measured the size of the particles.

Electro kinetic method

Measurement of Zeta-potential using Micro electrophoresis.

Apparatus and Zeta Plus (Brook haven Instruments Corporation, USA).

It shows the stability of a disperse system.

Zeta potential

The zeta potential of the formulated suspensions was determined using a Zeta Plus (Brookhaven Instruments Corporation, USA).

Approximately 1 mL of suspension was transferred into a plastic.

Cuvette using a pipette and diluted with distilled water.

The Brookhaven zeta potential software was used for the Parameters set to a temperature of 25°C and refractive index (1.33)

The zeta potential of the formulation is determined on day 0, 7, 14, 21 and day 28 post formulation.

Packaging of Suspensions

Pharmaceutical suspensions for oral use are generally packed in **wide mouth container** having adequate space above the liquid to ensure proper mixing.

Parenteral suspensions are packed in either glass ampoules or vials.

Ideal Requirements of Packaging Material

- It should be inert.
- It should effectively preserve the product from light, air, and other contamination through shelf life.
- It should be cheap.
- It should effectively deliver the product without any difficulty.

Materials Used For Packaging

Generally glass and various grades of plastics are used in packaging of suspension.

Glass

Generally soda lime and borosilicate glass are used in preparation of non-sterile suspensions.

Amber glass does not allow U.V. light to pass through. Amber characteristics can be developed in the glass by addition of various types of additives.

Disadvantages of Glass Materials

- They are fragile.
- They are very heavy as compared to plastic so handling and transport is difficult.
- Most important disadvantage of glass that glass constituents get extracted into the product.

Plastic

Due to the negative aspects of glass, plastic material significantly use of plastic as packaging material for sterile as well as non-sterile pharmaceutical suspension increased.

Advantages of Plastic Material

Materials used: Polyethylene, Poly Vinylene Chloride, Polystyrene, Polycarbonate etc.

Closure and Liners

With an exception of ampoules all containers required elastomeric closure.

Factors affecting in selecting closure

- Compatibility with product
- Seal integrity
- It should be stable throughout the shelf life

Factors affecting in selecting liner

- Chemical resistance
- Appearance
- Gas and vapour transmission
- Removal torque
- Heat resistance
- Shelf life
- Economical factors

STORAGE REQUIREMENTS & LABELLING

Labelling

- Shake well before use.
- Do not freeze.
- Protect from direct light (for light sensitive drugs).
- In case of dry suspensions powder the specified amount of vehicle to be mixed may indicated clearly on label.