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PHYSICAL PHARMACEUTICS - II

UNIT 3

TOPIC :

- **Coarse dispersion :** Suspension, interfacial properties of suspended particles, settling in suspensions, formulation of flocculated and deflocculated suspensions. Emulsions and theories of emulsification, microemulsion and multiple emulsions; Stability of emulsions,
  preservation of emulsions, rheological properties of emulsions and emulsion formulation by HLB method.

Coarse Dispersion

- A coarse dispersion is a heterogeneous system in which the dispersed phase particles have a diameter greater than 0.5 µm (500 nm).
- These particles are large enough to be seen under an optical microscope and may even be visible to the naked eye.
- Because of their size, particles tend to settle under gravity and require agitation to redisperse.

Characteristics of Coarse Dispersion

Property	Description
Particle Size	> 0.5 µm (micrometers)
Visibility	Visible under a **light microscope**; sometimes even to the naked eye
Settling/Separation	Readily settles under gravity due to large particle size
Stability	**Thermodynamically unstable**, requires shaking or stabilizers (e.g., suspending agents, emulsifiers)
Redispersibility	Can be redispersed easily on shaking
Appearance	Often turbid or cloudy
Examples	Suspensions, emulsions, foams, aerosols (solid in gas), some dusts

Examples in Pharmacy

1. **Suspensions** → Oral suspensions (antacids, antibiotics).
2. **Emulsions** → Oil in water (O/W) or water in oil (W/O) emulsions used in creams, lotions.
3. **Foams** → Pharmaceutical foams (e.g., shaving foam, rectal foams).
4. **Aerosols** → Solid particles dispersed in gas (e.g., inhalers, dusting powders).

Pharmaceutical Importance

- **Drug Delivery:** Used for poorly soluble drugs to enhance bioavailability.
- **Topical Applications:** Creams, lotions, ointments rely on coarse dispersion for proper consistency.
- **Parenteral Suspensions:** Provide sustained drug release (e.g., depot injections).

Emulsions

- An emulsion is a thermodynamically unstable heterogeneous system consisting of two immiscible liquids, where one liquid (the dispersed phase) is dispersed as fine droplets within the other (the continuous phase) with the aid of an emulsifying agent.

Components of Emulsions

1. **Dispersed Phase (Internal Phase)**
   - Present as small droplets.
   - Also called the dispersed medium.
2. **Continuous Phase (External Phase)**
   - The medium in which the droplets are dispersed.
3. **Emulsifying Agent (Emulsifier / Surfactant)**
   - Surface active agent.
   - Reduces interfacial tension between oil and water.
   - Forms a protective film around dispersed droplets, preventing coalescence.

Classification of Emulsions

1. Oil-in-Water (O/W) Emulsion

- **Dispersed Phase:** Oil droplets
- **Continuous Phase:** Water
- **Emulsifier:** Hydrophilic (HLB > 10) e.g. Tween 80
- **Properties:**
  - Dilutable with water
  - Conducts electricity
  - Non-greasy, washable
- **Examples:**
  - Milk (natural O/W emulsion)
  - Oral emulsions (e.g., castor oil emulsion)
  - Moisturizing lotions

2. Water-in-Oil (W/O) Emulsion

- **Dispersed Phase:** Water droplets
- **Continuous Phase:** Oil
- **Emulsifier:** Lipophilic (HLB < 10) e.g. **Span 80**
- **Properties:**
  - Can be diluted with oil
  - Does not conduct electricity
  - Greasy, occlusive, moisturizing effect
- **Examples:**
  - Cold creams
  - Water-resistant sunscreens
  - Ointments for dry skin

3. Multiple Emulsions

- "Emulsion of emulsions" → droplets within droplets.
- **Types:**
  - **W/O/W** → water droplets inside oil globules, dispersed in water.
  - **O/W/O** → oil droplets inside water globules, dispersed in oil.
- **Purpose:**
  - Controlled/sustained drug release
  - Protection of active ingredients (e.g., vitamins, proteins)
  - Taste masking
- **Emulsifiers:** Requires a combination of hydrophilic and lipophilic surfactants.
- **Applications:**
  - Advanced topical drug delivery
  - Cosmetic formulations for prolonged action

4. Microemulsions

- Clear, thermodynamically stable emulsions with nanometer-sized droplets.
- **Droplet Size:** 10 – 100 nm
- **Appearance:** Transparent or translucent
- **Stability:** Thermodynamically stable (unlike normal emulsions)
- **Types:** O/W microemulsion, W/O microemulsion
- **Uses:**
  - Enhanced bioavailability of poorly soluble drugs
  - Transdermal and oral drug delivery
  - Cosmetic serums and perfumes
- **Examples:**
  - Cyclosporine ophthalmic emulsion (Restasis®)

Emulsifying Agents

- Emulsifying agents (emulsifiers) are chemical compounds that reduce interfacial tension between two immiscible liquids (oil and water), making them miscible to form a stable emulsion.

Classification of Emulsifying Agents

1. **Natural Emulsifiers**
   - **From Vegetable Sources:**
     - Gum Acacia
     - Agar
     - Tragacanth
     - Starch
   - **From Animal Sources:**
     - Egg yolk (contains lecithin)
     - Gelatin
2. **Semi-Synthetic Emulsifiers**
   - Methyl cellulose
   - Sodium carboxymethyl cellulose
3. **Synthetic Emulsifiers**
   - **Anionic surfactants**: Sodium lauryl sulfate, soaps
   - **Cationic surfactants**: Cetyl trimethyl ammonium bromide (CTAB)
   - **Non-ionic surfactants**: Tween 80, Span 80
4. **Inorganic Emulsifiers**
   - Milk of magnesia
   - Finely divided solids: Bentonite, kaolin
5. **Alcohols & Sterols**
   - Cholesterol
   - Lecithin

Properties of a Good Emulsifying Agent

- Chemically stable.
- Compatible with other ingredients.
- Non-toxic and safe for use.
- Effectively reduces interfacial tension.
- Provides a protective film around dispersed droplets.

Preparation of Emulsions

Emulsions are usually prepared by three main methods:

1. Dry Gum Method (Continental Method)

- **Ratio:** Oil : Water : Gum = **4 : 2 : 1**
- **Procedure:**
    1. In a mortar, gum is triturated with oil.
    2. Water is added all at once.
    3. Triturate rapidly until a clicking sound is heard and a thick creamy primary emulsion is formed.
    4. Remaining water is added in portions to make the final emulsion.

2. Wet Gum Method (English Method)

- **Ratio:** Oil : Water : Gum = **4 : 2 : 1**
- **Procedure:**
    1. Gum is first triturated with water in a mortar.
    2. Oil is added slowly in portions with continuous trituration.
    3. A primary emulsion is formed.
    4. Remaining water is added to form the final emulsion.

3. Bottle Method (For Volatile / Non-viscous Oils)

- **Ratio:** Oil : Water : Gum = **2 : 2 : 1**
- **Procedure:**
    1. Oil is placed in a bottle, gum is added and shaken vigorously.
    2. Water is then added and shaking is continued until a primary emulsion is formed.
    3. Remaining water is added gradually to form the final emulsion.

Stability of Emulsions

Emulsions are **thermodynamically unstable systems**. Over time, various physical instabilities may occur, leading to separation of phases or changes in properties.

Instabilities in Emulsions

1. Cracking (Breaking)

- Complete separation of dispersed phase and continuous phase into two distinct layers.
- **Causes:**
  - Use of wrong emulsifying agent
  - Microbial growth in the system
  - Temperature changes (freezing or overheating)
- **Result:** The emulsion cannot be redispersed by shaking.
- **Diagram:** Two separate layers (oil & water).

2. Creaming

- Upward or downward movement of dispersed droplets forming a concentrated layer.
- **Causes:** Difference in density between oil and water phases.
- **Types:**
  - **Upward creaming** → In **O/W emulsions** (oil rises due to being lighter).
  - **Downward creaming** → In **W/O emulsions** (water droplets settle down).
- **Note:** Creaming is reversible (can be redispersed by shaking).

3. Phase Inversion

- **Definition:** Conversion of an O/W emulsion into W/O, or vice versa.
- **Causes:**
  - Addition of electrolytes

    - Change in phase ratio (increase in dispersed phase concentration)
    - Temperature changes (affecting surfactant HLB value)
- **Example:** O/W lotion changing into greasy W/O type.

4. Coalescence

- **Definition:** Fusion of small dispersed droplets into larger droplets, leading to breaking of the emulsion.
- **Cause:** Weak or insufficient emulsifier film around droplets.
- **Result:** Leads to irreversible cracking.

Methods to Improve Stability

1. **Selection of proper emulsifying agent** (correct HLB value).
2. **Increase viscosity** of the continuous phase (using viscosity enhancers like tragacanth, methylcellulose).
3. **Proper storage conditions** – avoid excessive heat, light, or freezing.
4. **Maintain appropriate temperature** during storage.
5. **Reduce density difference** between oil and water phases.
6. **Reduce droplet size** by homogenization to prevent coalescence.

Theories of Emulsification

Emulsification is the process of stabilizing two immiscible liquids (oil & water) with the help of **emulsifying agents**. Several theories explain how emulsifiers stabilize emulsions.

1. Monomolecular Film Theory

- **Concept:**
    - Surfactant molecules (emulsifiers) form a single-molecule thick layer (monolayer) around dispersed droplets.
    - This film prevents droplets from merging (coalescence).
- **Mechanism:**
    - Surfactants contain:
        - **Hydrophilic head** → oriented towards water.
        - **Lipophilic tail** → oriented towards oil.
    - They align at the oil–water interface forming a protective monolayer.
    - This reduces interfacial tension and stabilizes droplets.
- **Examples of Emulsifiers:**
    - Tween 80 (Polysorbate 80)
    - Span 20
    - Sodium Lauryl Sulphate (SLS)
- **Key Points:**
    - Film = single molecule thick.
    - Works well with small-molecule surfactants.
    - Stabilization mainly by reducing surface tension.

2. Multimolecular Film Theory

- **Concept:**
  - Some emulsifiers (mainly natural colloids/polymers) form a thick, multi-layered film around droplets.
  - This film provides a mechanical and viscous barrier to prevent droplet fusion.
- **Mechanism:**
  - Emulsifiers like gum acacia, gelatin, casein adsorb at the oil–water interface.
  - They form a strong, thick coating of many molecules.
  - They also increase viscosity, slowing down droplet movement.
- **Examples of Emulsifiers:**
  - Gum acacia
  - Gelatin
  - Tragacanth
  - Sodium alginate
- **Key Points:**
  - Film = thick, viscous, multi-layered.
  - Provides good long-term stability.
  - Common in natural emulsifying agents.

3. Solid Particle Adsorption Theory

- **Concept:**
  - Very fine solid particles adsorb at the oil–water interface to form a rigid protective film around droplets.
- **Mechanism:**
  - Solid particles collect at the interface.
  - They form a mechanical barrier preventing coalescence.
  - Stability depends on particle wettability:
    - More wettable by water → **O/W emulsion**.
    - More wettable by oil → **W/O emulsion**.
- **Examples of Solid Emulsifiers:**
  - Bentonite
  - Kaolin
  - Magnesium hydroxide
  - Aluminium hydroxide
- **Key Points:**
  - No chemical surfactant required.
  - Film = rigid and strong.
  - Provides long-term physical stability.

Preservation of Emulsions

Emulsions contain water, oil, and emulsifiers, all of which can support:

1. Microbial growth (mainly in aqueous phase)
2. Oxidation (mainly in oil phase)

To prevent spoilage, rancidity, odor, discoloration, and loss of drug potency, appropriate preservatives and antioxidants are added.

1. Prevention from Microorganisms

- **Problem:**
  - Microbes (bacteria, molds, fungi) can grow in emulsions, especially in the water phase.
  - Leads to contamination, odor, degradation, and possible infection in pharmaceutical products.
- **Solution:** Add preservatives (antimicrobial agents).
- **Ideal Properties of Preservatives:**
  1. Effective at low concentrations
  2. Non-toxic and non-irritant
  3. Broad-spectrum activity (bacteria, fungi, yeast)
  4. Chemically stable in emulsion
  5. Soluble in the phase where microbial growth occurs (usually water)
- **Common Preservatives:**
  - Methylparaben
  - Phenol
  - Benzoic acid / Sodium benzoate

2. Prevention from Oxidation

- **Problem:**
  - Oils in emulsions (especially unsaturated fatty acids) are prone to oxidation.
  - Oxidation leads to:
    - Rancidity
    - Off-smell
    - Discoloration
    - Loss of drug potency
- **Solution:** Add antioxidants.
- **Ideal Properties of Antioxidants:**
  1. Chemically stable
  2. Non-toxic
  3. Effective at low concentrations
  4. Soluble in the oil phase
  5. Should not affect emulsion stability
- **Common Antioxidants:**
  - Butylated hydroxyanisole (BHA)
  - Butylated hydroxytoluene (BHT)
  - Tocopherols (Vitamin E)
  - Ascorbyl palmitate

Rheological Properties of Emulsions

Rheology is the study of flow and deformation of matter under applied force. For emulsions, it describes:

- Viscosity (thickness)
- Flow type (Newtonian or Non-Newtonian)
- How the emulsion pours, spreads, or applies on the skin

Types of Flow in Emulsions

A. Newtonian Flow

- Flow is directly proportional **to applied force;** viscosity remains constant**.**
- **Characteristics:**
  - Observed in dilute emulsions **(**low dispersed phase content)
  - Flow is linear with shear rate
- **Examples:** Simple liquid emulsions with low oil content

B. Non-Newtonian Flow

- Flow does not follow a linear relationsh**ip** with applied force; viscosity changes with shear rate**.**
- **Characteristics:**
  - Seen in concentrated emulsions
  - Optimum viscosity is desirable for stability
- **Examples:** Lotions, creams, ointments

Factors Affecting Rheological Properties

Factor	Effect
Type of emulsion	O/W and W/O emulsions behave differently
Phase ratio	Higher dispersed phase → higher viscosity
Droplet size	Smaller droplets → smoother, thicker emulsion
Emulsifier used	Certain emulsifiers increase viscosity
Temperature	Higher temperature → lower viscosity
Additives	Thickeners/polymers modify flow

Importance of Rheological Properties

1. **Physical Stability:**
    - High viscosity reduces creaming and sedimentation
2. **Spreadability:**
    - Proper flow ensures patient compliance
3. **Packaging & Dispensing:**
    - Flow must be compatible with container (tube, bottle, pump)
4. **Product Performance:**
    - Controls drug release and uniformity of application

Emulsion Formulation by HLB Method

HLB (Hydrophilic-Lipophilic Balance) System:

- Developed to select appropriate emulsifiers for stable emulsions.
- HLB number (1–20) represents the relative proportion of hydrophilic and lipophilic parts of an emulsifier molecule.

HLB Concept

HLB Value	Nature of Emulsifier	Type of Emulsion Produced
1–6	Lipophilic (oil-loving)	W/O (Water-in-Oil)
8–18	Hydrophilic (water-loving)	O/W (Oil-in-Water)
7–9	Intermediate	Can stabilize either type

- Oils and waxy materials have a required HLB number.
- Goal: Use an emulsifier with an HLB value close to the required HLB of the oil to produce a stable emulsion.

Example:

- Liquid paraffin → required HLB = 4 → produces W/O emulsion

HLB Values of Selected Emulsifiers

Chemical Designation	HLB Value
Ethylene Glycol Distearate	16
Sorbitan Sesquioleate	3–7
Diethylene Glycol Mono Stearate	4–7
Polyoxyethylene (10) Lauryl Ether	9.5
Polyoxyethylene (20) Sorbitan Monolaurate (Tween 20)	16.7
Polysorbate 80	15
Span 80 (Sorbitan Monooleate)	4.3
Poloxamer 188	29 (High HLB, highly hydrophilic)

Note: HLB values may slightly vary in literature depending on source and method of determination.

Steps for Formulating Emulsion Using HLB Method

1. Determine required HLB of the oil phase.
2. Select emulsifier(s) whose HLB value matches the required HLB.
3. Mix oil and emulsifier, then add aqueous phase gradually.
4. Homogenize to form a stable emulsion.

SUSPENSIONS

A suspension is a biphasic liquid dosage form in which finely divided solid particles are dispersed in a liquid.

- Dispersed phase: Solid particles
- Continuous phase: Liquid
- Particle size: 0.5–5 µm

Classification of Suspensions

Suspensions can be classified based on:

1. **General Classes**
2. **Proportion of Solid Particles**
3. **Electrokinetic Nature of Particles**

1. Based on General Classes

Type	Route / Use	Example	Notes
Oral Suspensions	By mouth	Paracetamol suspension	Standard particle size for oral use
Topical Suspensions	Applied on skin	Calamine lotion	External use; no systemic absorption
Parenteral Suspensions	IV / IM injection	Iron dextran suspension	Very fine particles; must be sterile
Ophthalmic Suspensions	Eye drops	Prednisolone eye drops	Very fine, non-irritating, sterile, isotonic

2. Based on Proportion of Solid Particles

Type	Solid Content (% v/v)	Example
Dilute Suspensions	2–10%	Cortisone acetate suspension
Concentrated Suspensions	50–70%	Zinc oxide suspension

Advantages of Suspensions

1. **Masking taste:**
   - Bitter or unpleasant drugs can be better tolerated in suspension form.
2. **Ease of swallowing:**
   - Suitable for children, elderly, or patients with difficulty swallowing tablets.
3. **Flexible dosing:**
   - Dose can be easily adjusted by measuring a specific volume.
4. **Improved stability:**
   - Some drugs that are unstable in solution are more stable as suspensions.
5. **Faster onset (compared to solids):**
   - Drug is already in finely divided form, which can dissolve faster after administration.

Disadvantages of Suspensions

1. **Physical instability:**
   - Sedimentation and caking can occur, requiring shaking before use.
2. **Dosing inaccuracy:**
   - Improper shaking may result in uneven distribution of drug particles.
3. **Bulky and inconvenient to carry:**
   - Liquid form is less portable than tablets or capsules.
4. **Microbial growth:**
   - Aqueous suspensions can support microbial contamination; preservatives may be needed.
5. **Reduced shelf life:**
   - Prone to aggregation, sedimentation, and chemical degradation over time.

Flocculated and Deflocculated Suspensions

Flocculated Suspensions

A flocculated suspension is a suspension in which the dispersed solid particles aggregate loosely to form **floccules**.

Characteristics:

- Particles stick together as loose aggregates (floccules).
- Sedimentation occurs rapidly due to the larger size of floccules.
- Sediment formed is **loose** and easily redispersible.
- Often preferred in pharmaceutical suspensions to avoid caking.

Example:

- Alumina suspensions
- Some oral antacids

Deflocculated Suspensions

A deflocculated suspension is a suspension in which no flocculation occurs, and the solid particles remain individual and separate.

Characteristics:

- Particles exist as single entities.
- Sedimentation is slow due to smaller particle size.
- Sediment formed is compact and may cake, making redispersion difficult.
- Not preferred for pharmaceutical suspensions due to poor redispersibility.

Example:

- Zinc oxide in water (without stabilizers)

Sedimentation in Suspensions

Sedimentation is the settling down of solid particles of a suspension to the bottom of the liquid due to gravity.

Difference between Flocculated and Deflocculated Suspensions

Feature	Flocculated Suspension	Deflocculated Suspension
Particle Arrangement	Particles form **loose aggregates (floccules)**	Particles exist as **separate entities**
Rate of Sedimentation	High	Low
Sediment Formation	Forms rapidly	Forms slowly
Sediment Type	Loose, does **not form hard cake**	Hard cake may form
Redispersibility	Easily redispersed	Difficult to redisperse
Appearance	Often **unpleasant** due to visible floccules	More **pleasant** appearance
Stability	More stable for pharmaceutical use	Less stable for pharmaceutical use

Suspension Additives

Type	Examples
Colouring Agents	Tartrazine, Erythrosine
Flavouring Agents	Vanilla, Strawberry, Orange
Sweetening Agents	Sucrose, Saccharin

Method of Preparation of Suspensions

1. Convert solid particles into fine powder.
2. Take the insoluble powder in a mortar.
3. Add sufficient liquid/vehicle to produce a smooth paste.
4. Add non-volatile solid ingredients, if required.
5. Add volatile ingredients, if required.
6. Add other ingredients and mix well.
7. Transfer to a measuring cylinder and make up to the required volume with vehicle.

Packaging and Storage

- **Packaging:** Thick container with a wide mouth.
- **Storage:** Cool, dry place away from light.

Stability Problems in Suspensions

1. **Caking**
    - Formation of hard sediment, especially in deflocculated suspensions. Small particles come close together forming a hard cake.
    - **Prevention:** Add flocculating agents to form loose floccules.
2. **Cap Locking**
    - Particles spread over the surface of the bottle mouth, sticking the cap.
    - **Prevention:** Use vehicles containing sucrose, glucose, sorbitol, etc.
3. **Colour Change**
    - Light-sensitive colours may degrade or change.
    - **Prevention:** Store the bottle in dark place.
4. **pH Change**
    - Acidity or alkalinity may change during storage.
    - **Prevention:** Add buffering agents to maintain stable pH.
5. **Rapid Settling of Particles**
    - Large particles of flocculated suspension settle quickly at the bottom.
    - **Prevention:** Add viscosity-enhancing agents to slow down sedimentation.