Manufacture of Pharmaceutical preparations a) Sterile formulations – large and small volume parenterals b) Manufacture of Ointments, Liquids, and creams c) Manufacturing of Tablets, granules, capsules, and powders d) Total parenteral nutrition

PARENTERAL PREPARATIONS

DEFINITION

- Parenteral preparations are **pyrogen-free preparations** that are intended to be administered by routes **other than the oral route**.
- The term *parenteral* is derived from two Greek words:
    - **Para** = outside
    - **Enteron** = intestine

CLASSIFICATION

Based on volume, parenteral preparations are classified into two main types:

1. **Small Volume Parenterals (SVPs)**
2. **Large Volume Parenterals (LVPs)**

SMALL VOLUME PARENTERALS (SVPs)

- The volume is generally **less than or equal to 100 mL**.
- They are supplied in **single-dose or multiple-dose containers**.
- They are mainly used to dispense most of the drugs.

LARGE VOLUME PARENTERALS (LVPs)

- These are supplied in **single-dose containers** with a volume **greater than 100 mL**.
- They are usually delivered through the **intravenous (IV) route**.
- They are commonly used to provide **electrolytes and nutrition** to the body.

FORMULATION ASPECTS

1. Therapeutic Agents

Examples include:

- Insulin
- Antibiotics
- Vaccines

- Antipyretics
- Analgesics
- Dextrose
- Sodium chloride (NaCl)
- Electrolytes

2. Vehicles

- **Water-based vehicles**: Water for Injection (WFI), Bacteriostatic Water for Injection (BWFI), Sterile Water for Injection (SWFI).
- **Aqueous vehicles**: Ethyl alcohol, Polyethylene glycol (PEG), Propylene glycol (PG).
- **Non-aqueous vehicles**: Fixed oils such as corn oil, peanut oil, cottonseed oil.

3. Added Substances (Additives)

1. **Antimicrobials**:
   - Phenyl mercuric acetate – 0.01%
   - Thiomersal – 0.01%
   - Benzothenium chloride – 0.01%
   - Phenol and Cresol – 0.5%
2. **Antioxidants**:
   - Sodium bisulfite
   - Ascorbic acid – 0.02 to 0.1%
   - Thiourea – 0.005%
3. **Buffers**:
   - Acetic acid
   - Adipic acid
   - Benzoic acid
4. **Bulking Agents**:
   - Lactose – 0.14 to 0.5%
   - Mannitol – 0.4 to 2.5%
5. **Chelating Agents**:
   - Disodium edetate – 0.003 to 0.05%
   - Tetrasodium edetate – 0.01%
6. **Protectants**:
   - Sucrose
   - Lactose (2–5%)
7. **Solubilizing Agents**:
   - PEG 300
   - Propylene glycol
8. **Tonicity Adjusting Agents**:
   - Sodium sulfate – 1.1%
   - Sorbitol – 2%
9. **Surfactants**:
   - Polyethylene – 0.1 to 0.5%
   - Sorbitan monooleate – 0.05 to 0.25%

VEHICLES

Water for Injection (WFI)

- Used in the manufacture of parenteral drugs where the solvent is water.
- As per the **USP (United States Pharmacopeia)**, it is highly purified water containing less than 10 CFU/100 mL of aerobic bacteria.

Sterile Water for Injection (SWFI)

- Sterile, non-pyrogenic, distilled water supplied in a **single-dose container**.
- Used for IV administration **after addition of a suitable solute**.
- May also serve as a **diluent**.
- No antimicrobial or other substance is added.
- pH is maintained at **5.5 (range 5.0–7.0)**.

Bacteriostatic Water for Injection (BWFI)

- Sterile water containing **0.9% benzyl alcohol**.
- Used for **diluting or dissolving medications**.
- The container can be re-entered multiple times (by sterile needle).
- Benzyl alcohol prevents growth of contaminants.

PRETREATMENT OF WATER

- Water for Injection is the most commonly used solvent, prepared by **reverse osmosis or distillation**, without added substances.
- Pretreatment ensures **uniformity, constant quality, and efficiency**.

Steps in Pretreatment:

- Chlorination or ozone treatment – suppress microbial growth.
- Prefiltration through depth filters – remove iron and suspended matter.
- Flocculating agents – remove suspended impurities.
- Water softening by ion exchange – remove calcium and magnesium to prevent scale deposits.
- pH adjustment to 6.0–6.5 – reduces scale formation.
- Deionization by ion exchange resins – removes ions from feed water.
- Activated carbon beds – remove chlorine and organics.
- UV radiation – suppress microbial growth.

REVERSE OSMOSIS (RO)

- Separation of solutes from water by applying pressure on a concentrated solution across a **semipermeable membrane**.
- Produces a less concentrated solution.

- Removes both **charged (ions)** and **neutral (organics)** solutes.

Mechanisms of Exclusion:

- Charged particles – repelled due to interfacial tension at water–membrane interface.
- Organics – excluded by sieve mechanism (depends on size and molecular weight).

Key Points:

- Viruses, bacteria, and pyrogens are effectively removed.
- Performance depends on feed water composition and required water quality.
- Often used with additional systems: chlorinators, flocculating agents, filters, water softeners, carbon beds, deionizers, etc.

DISTILLATION

- Purification process involving **heating and cooling**.
- Removes impurities by **phase change** (liquid → vapor → liquid).
- Kills microorganisms.
- Source water for WFI should be **pretreated** before distillation.
- Vapor condensation yields pure water.
- Final water is stored in **stainless steel tanks** at:
    - ~5 °C (cold) OR
    - 65–85 °C (hot) → to inhibit microbial growth and pyrogen formation.

CONTAINERS

1. **Glass Containers**
    - Type I, Type II, Type III, NP.
    - Commonly used for **vials and ampoules**.
2. **Plastic Containers**
    - Commonly used for **large-volume parenterals** (e.g., saline bags).

CLOSURES

- **Rubber closures** are commonly used.
- Rubber and its extractives can influence preservative loss and antimicrobial activity.
- Types of rubber used: **natural rubber, neoprene rubber, butyl rubber**.
- Butyl rubber minimizes preservative loss (e.g., chlorobutanol, methyl paraben, benzyl alcohol).

TERMINAL STERILIZATION

- Sterilization of product in its **final container**.
- Ensures **quantifiable microbial lethality**.
- Sterility Assurance Level (SAL) should be **less than 10^{-6}**.

- Product must withstand steam sterilization cycle for **15 minutes**.

BLOW-FILL-SEAL (BFS) TECHNOLOGY

- Widely accepted by **USFDA**.
- Process:
    1. Polypropylene granules heated at **200 °C** → tube-shaped parison formed.
    2. Parison reaches mould → container formed with sterile compressed air.
    3. Fill nozzle (mandrel) fills the liquid.
    4. Neck is sealed and container released.
- Each container is produced in **10–15 seconds**.
- Contamination rate is maintained **below 0.1%**.
- Example: *Rommelag's BFS bottle-pack 321 machine* forms **3000 bottles (1000 mL each) per hour with 6 moulds**.

PRODUCTION FACILITIES

1. Clean-up area
2. Preparation area
3. Aseptic area
4. Quarantine area
5. Finishing and packaging area

Liquid Dosage Forms

Liquid dosage forms are pharmaceutical preparations in which active ingredients are present in a liquid state, either dissolved or dispersed in a suitable vehicle. They are intended for internal or external administration and can be broadly classified as:

- **Monophasic liquid dosage forms**
    - Solutions
    - Aqueous solutions
    - Non-aqueous solutions
- **Polyphasic liquid dosage forms**
    - Suspensions
    - Emulsions
    - Colloids
- **Other liquid preparations**
    - Extracts
    - Tinctures

Solutions

A solution is a homogeneous liquid preparation in which one or more chemical substances (solutes) are completely dissolved in a suitable solvent or mixture of solvents.

Characteristics:

- Clear and transparent.
- Provide uniform dose per administration.
- Easy to prepare and administer.

Classification of Solutions

1. **According to the route of administration:**
    - **Oral solutions** – administered orally.
    - **Otic solutions** – instilled in ears.
    - **Ophthalmic solutions** – instilled in eyes.
    - **Topical solutions** – applied on skin.
2. **According to composition and uses:**
    - **Syrups** – aqueous solutions containing sugar.
    - **Elixirs** – sweetened hydroalcoholic solutions.
    - **Spirits** – alcoholic solutions of aromatic substances.
    - **Aromatic waters** – aqueous solutions of volatile substances.
    - **Tinctures/Fluid extracts** – alcoholic or hydroalcoholic preparations from crude drugs.
    - **Injections** – sterile and pyrogen-free solutions for parenteral use.
3. **According to vehicle used:**
    - **Aqueous solutions** – solvent is water.
    - **Non-aqueous solutions** – solvents like alcohol, ether, glycerol, oils.
4. **According to solute concentration:**
    - **Concentrated solutions** – high solute proportion.
    - **Dilute solutions** – lower solute proportion.
5. **According to saturation level:**
    - **Saturated solutions** – contain maximum solute at a given temperature.
    - **Unsaturated solutions** – can dissolve more solute.

Suspensions

Suspensions are biphasic liquid preparations containing insoluble solid drug particles dispersed in a liquid medium. They are coarse dispersions with particle size usually above 1 µm.

Important Features:

- Thermodynamically unstable but stabilized with suspending agents.
- Need to be shaken before use.

Formulation Components:

- **Active ingredient (API)** – insoluble drug.
- **Wetting agents** – facilitate dispersion (e.g., surfactants, glycerin).
- **Flocculating agents** – prevent caking.

- **Thickeners/viscosity enhancers** – increase stability.
- **Buffers/pH adjusters** – maintain stability.
- **Preservatives** – prevent microbial growth.
- **Coloring and flavoring agents** – improve acceptability.
- **Vehicle** – water or other base.

Evaluation of Suspensions:

- Sedimentation volume.
- Particle size and zeta potential.
- Redispersibility.
- Appearance, color, odor, taste.
- Rheological properties (flow behavior).
- Freeze–thaw stability.
- pH monitoring.
- Centrifugation tests.

Emulsions

Emulsions are biphasic systems of two immiscible liquids, where one liquid is dispersed as small droplets in the other, stabilized by emulsifying agents.

Types of Emulsions:

- **Oil-in-water (O/W):** oil dispersed in water; generally for internal use.
- **Water-in-oil (W/O):** water dispersed in oil; mostly for topical use.
- **Multiple emulsions:** O/W/O or W/O/W.
- **Microemulsions and Nanoemulsions:** very fine droplet size, transparent, thermodynamically more stable.

Methods of Preparation:

1. **Dry Gum (Continental) Method** – oil mixed with gum, water added at once.
2. **Wet Gum (English) Method** – gum mixed with water first, oil added gradually.
3. **Bottle Method** – oil shaken with gum in a bottle, water added.

Equipment Used:

- Mortar and pestle
- Mechanical stirrers
- Homogenizers
- Ultrasonifiers
- Colloid mills

Evaluation of Emulsions:

- Creaming and sedimentation.
- Coalescence and phase separation.
- Viscosity measurements.
- Particle size analysis.
- Accelerated stability testing (centrifugation, temperature).

Colloids

Colloids are liquid dispersions in which very fine particles (1 nm – 1 µm) are uniformly distributed in a continuous phase. They do not settle rapidly and cannot be easily filtered.

- Examples: colloidal sulfur, colloidal silver.
- Applications: sustained drug delivery, improved absorption, parenteral nutrition.

Extracts

Extracts are concentrated preparations obtained by extracting active constituents from plant or animal materials using suitable solvents.

- Solvents used: alcohol, water, hydroalcoholic mixtures.
- Methods: maceration, percolation, Soxhlet extraction.
- Example: Belladonna extract, Ginger extract.

Tinctures

Tinctures are alcoholic or hydroalcoholic solutions prepared from crude drugs or chemical substances.

- Ethanol concentration: usually 40–60%.
- Examples: Tincture of Iodine, Tincture of Opium, Tincture of Benzoin.

Additives in Liquid Dosage Forms

1. **Preservatives** – to prevent microbial growth (e.g., parabens, benzoates).
2. **Antioxidants** – prevent oxidation (e.g., ascorbic acid, sodium bisulfite).
3. **Buffers** – maintain pH.
4. **Sweetening agents** – improve taste (e.g., sucrose, sorbitol, saccharin).
5. **Flavoring agents** – mask unpleasant taste.
6. **Coloring agents** – improve appearance.
7. **Viscosity enhancers** – improve stability and palatability (e.g., glycerin, tragacanth, CMC).

Manufacturing Steps of Liquid Dosage Forms

1. **Selection of raw materials** – drug, solvent, and additives of pharmaceutical grade.
2. **Compounding** – dissolving, mixing, suspending, or emulsifying ingredients.
3. **Filtration** – removal of particulate matter.
4. **Sterilization (if required)** – by autoclaving, filtration, or aseptic processing.
5. **Filling and Packaging** – into bottles, ampoules, vials with appropriate closures.
6. **Labeling** – with instructions for storage, usage, and expiry.
7. **Quality control testing** – assay of drug content, pH, viscosity, sterility, stability.

Evaluation of Liquid Dosage Forms

- **Physical properties:** appearance, color, clarity, odor, taste.
- **Chemical properties:** pH, assay, preservative content.
- **Microbial tests:** sterility, preservative efficacy.
- **Stability studies:** short-term and long-term stability under various conditions.
- **Patient acceptability:** taste, palatability, convenience.

Powders

Definition

Powders are uniform mixtures of dry, finely divided drugs or chemicals intended for internal or external use. They can also be defined as solid dosage forms of medicaments meant for therapeutic purposes.

Introduction

Powders are available in **amorphous or crystalline form**. Many drugs are prepared in powder form for use in different dosage forms. Powders may be:

1. Derived from naturally occurring vegetable drugs.
2. Prepared by physically mixing two or more powdered chemical agents in definite proportions.
3. Composed entirely of solids or may contain small proportions of liquids uniformly dispersed over the solid mixture.

Particle Size and Its Importance

Significance of Particle Size

- **Dissolution rate:** Smaller particles dissolve faster, increasing bioavailability.
- **Suspendability:** Finer particles remain uniformly dispersed in liquids.
- **Distribution:** Ensures uniform dose-to-dose distribution in mixtures.
- **Non-grittiness:** Essential for dermal, ophthalmic, and other topical preparations.

Particle Size Ranges (USP Standards)

- **Very coarse (No.8):** All particles pass through sieve No.8; ≤20% through sieve No.60.
- **Coarse (No.20):** All particles pass through sieve No.20; ≤40% through sieve No.60.
- **Moderately coarse (No.40):** All particles pass sieve No.40; ≤40% through sieve No.80.
- **Fine (No.60):** All particles pass sieve No.60; ≤40% through sieve No.100.
- **Very fine (No.80):** All particles pass sieve No.80; no limit for finer particles.

Methods to Determine Particle Size

- **Sieving:** Successive sieves of decreasing size.
- **Light energy diffraction:** Measures light reduction as particles pass a sensor.
- **Microscopy:** Size determination using a grid.
- **Sedimentation rate:** Measures terminal settling velocity in a liquid.
- **Cascade impaction:** Separation by air stream velocity.
- **Laser holography:** Pulsed laser images aerosolized particles in 3D.

Advantages of Powders

- More stable than liquid dosage forms (less risk of chemical reactions).
- Rapid dissolution, leading to faster absorption and higher blood levels.
- Easy to swallow when mixed with food or drink.
- Useful as dry lubricants, drying agents, and adsorbents of toxins, gases, or bacteria.
- Cost-effective with minimal wastage.

Disadvantages of Powders

- Not suitable for drugs sensitive to moisture or air.
- Bitter, corrosive, or nauseating drugs are difficult to administer.
- Preparation is time-consuming, making them costlier than tablets or capsules.
- Dose accuracy can be a concern in bulk powders.
- Packaging can be challenging and expensive.

Classification of Powders

According to Number of Active Ingredients

1. **Simple powders:** Contain one active ingredient with an inert substance (e.g., lactose, starch).
    - Example: Hyoscine hydrobromide powder (anti-emetic).
2. **Compound powders:** Contain more than one active ingredient.
    - Examples: Compound bismuth powder, Compound effervescent powder, Compound kaolin powder.

According to Mode of Dispensing

1. **Bulk powders:** Not divided into individual doses; usually less potent drugs.
    - Examples: Boric acid, ZnO powder (dusting powders), Rhubarb powder.
2. **Divided powders (Unit-dose powders):** Pre-measured single doses, often for potent drugs.
    - Each portion is wrapped in paper to enclose the medication.
    - Examples: Headache powders, Laxative powders, ORS.

Preparation of Powders

Methods of Mixing

1. **Spatulation:** Mixing small amounts of powder of similar particle size on a sheet of paper using a spatula.
2. **Trituration:** Grinding powders in a mortar to achieve lightness and diffusibility.
3. **Sifting:** Breaking up coarse particles by passing through a sieve, often used for vegetable powders.
4. **Tumbling:** Rotating wide-mouthed containers to mix powders of varying densities without altering particle size.

Packaging of Powders

Divided Powder Packaging (Unit Dose)

- Used for potent drugs or controlled dosage.
- Individual doses are wrapped in paper and packaged in envelopes or boxes.
- Hygroscopic or volatile powders require an inner parchment wrapper.

Bulk Packaging (Multi-dose)

- Recommended for less potent drugs.
- Packaged in wide-mouthed jars or bottles; may also be supplied as aerosols.

Granules

Introduction

The term *granules* is derived from the Latin word “Granulum,” meaning “little grain.” Granules are prepared from powdered substances, in which small particles are aggregated with the help of a solvent or binder.

Definition

- Granules are agglomerates of smaller particles.

- They are small particles gathered into a larger, permanent aggregate in which the original particles can still be identified.

Shape and Size

- Generally irregular in shape, granules behave as a single large particle.
- Typically fall in the 4–12 sieve size range, though granules of various sizes can be prepared depending on requirements.

Characteristics

- Granular materials differ from homogeneous fluids in flow and deformation behavior.
- They may become inhomogeneous when sheared or shaken.
- Granular materials can clog when forced through constrictions.
- Compacted granules must expand (dilate) before deformation.
- Turbulence is nearly impossible in granular materials.
- They can support small shear stresses indefinitely.
- Granular materials may exhibit avalanches and are often anisotropic.

Types of Granules

1. **Effervescent Granules:**
    - Contain acids and carbonates or bicarbonates that react in water to release carbon dioxide.
    - Intended to be dissolved or dispersed in water before administration.
2. **Coated Granules:**
    - Multi-dose preparations coated with layers of excipients.
3. **Gastro-Resistant Granules:**
    - Delayed-release granules resistant to gastric fluid, releasing active substances in intestinal fluid.
4. **Modified-Release Granules:**
    - Coated or uncoated granules designed to modify the rate, place, or time of drug release.
5. **Granules Resulting from Wet Granulation:**
    - **Crust Granules:** Formed by drying a partially dissolved mixture that leaves a crust.
    - **Binder Granules:** Made using gelatin, starch, or similar substances as binders.
    - **Sintered Granules:** Formed by applying heat to melt the substance during manufacturing.

Granules Coating

- **Purpose:** To improve flavor or modify drug release.
- **Procedure:**

- **Small drug dose:** Starch granules are coated with adhesive material and then with powdered drug; repeated until desired amount is achieved.
- **Large drug dose:** The drug itself can be the starting material; granules are coated with required material. Some granules may remain uncoated for immediate release, while others receive varying coats of lipid (e.g., beeswax, carnauba wax, glyceryl monostearate) or cellulosic materials (e.g., ethylcellulose). Coating can be colored to distinguish thickness.

Desired Release Characteristics

- Granules of different groups are blended in proper proportions to achieve desired release.
- **Gastro-resistant/enteric coatings:** Various materials can be used, from water-resistant films to pH-sensitive materials. Some swell slowly or are digested/emulsified in intestinal juices.
- **Examples of enteric coating materials:**
  - Cellulose Acetate Phthalate (dissolves above pH 6.0)
  - Acrylate Polymers (pH 6–7)
  - Hydroxypropyl Methylcellulose Phthalate (pH 5.0–5.5)
  - Polyvinyl Acetate Phthalate (pH 5.0–5.5)

Preparation of Granules

Methods

1. **Wet Method:**
   - **Simple Wet Method:** Powder is moistened, passed through a screen for desired size, and dried on trays while periodically moved.
   - **Fluid Bed Processing:** Particles are suspended in air, sprayed with liquid excipient, and dried to form granules of defined size.
2. **Dry Method:**
   - **Roll Compactor Method:** Powder is passed through a roll compactor and granulation machine to produce uniform granules.
   - **Slugging Method:** Powder is compressed into large slugs/tablets, then granulated to desired size. Fines (unagglomerated powder) are collected and reprocessed.

Advantages of Granules

- Easier to handle than powders.
- Suitable for large doses not feasible in tablets.
- More chemically and physically stable than powders.
- Do not cake or harden on standing.
- Smaller surface area than powders, reducing environmental degradation.
- Dissolve more easily in water.
- Better flow properties.
- Can be coated to mask undesirable taste.

Disadvantages of Granules

- Packaging requires special care and is less economical than tablets/capsules.
- Accurate dose measurement by patient is difficult.
- Damage to packaging exposes entire product.
- Drugs prone to hydrolysis may not be suitable for granule formulation.

Effervescent Granules

Definition

Coarse or very coarse powders containing a medicinal agent in a dry mixture with sodium bicarbonate, citric acid, and tartaric acid.

Mechanism

- React with water to release carbon dioxide, producing effervescence.
- Combination of citric and tartaric acid ensures granule firmness and prevents stickiness.

Preparation Methods

1. **Fusion Method:**
    - Citric acid (with water of crystallization) acts as a binding agent.
    - Mixed powders are heated at 34–40°C, forming a spongy mass that is sieved and dried.
2. **Wet Method:**
    - Water or alcohol acts as a moistening agent, forming a pliable dough-like mass.
    - Granules are produced by sieving the mass.

Significance

- Provides effective effervescence.
- Ensures stable granulation.
- Masks unpleasant taste.
- Produces efficacious medicinal products.

Tablet Dosage Form

Introduction

- Tablets are the most common **solid dosage form** administered orally (GIT).
- Safer than injectables; pills (older form) have largely been replaced by tablets and capsules.
- Pills were first prepared by Upjohn in the 1950s.

Definition:

Tablets are solid dosage pharmaceutical forms containing drug substances with or without suitable diluents, prepared by **compression** or **molding**.

Composition:

- Active substances + **excipients** (diluents, binders, glidants, lubricants, disintegrants, sweeteners/flavors, pigments).
- Polymer coatings may be applied for:
  - Easier swallowing
  - Controlled release
  - Protection from environmental factors
  - Enhanced appearance

Properties of Tablets

- Vary in **shape, size, weight, hardness, disintegration, dissolution**.
- Must be **mechanically strong**, chemically and physically stable.
- Can be **disk-shaped** or special shapes (oval, oblong, cylindrical, square, triangular).
- Weight typically **0.2–0.8 g** for oral tablets.

Ideal Tablet Characteristics:

1. Free of defects (chips, cracks, discoloration)
2. Physically stable
3. Chemically stable
4. Predictable release of medicinal agents
5. Strong enough to withstand shocks
6. Uniform color
7. Free from unwanted odor

Excipients

Properties:

- Inert, compatible with API, cheap, easy to handle, stable, pure

Selection Criteria:

- Proper **shape, weight, hardness, dissolution rate, disintegration, friability**

Types and Classes of Tablets

1. Tablets Ingested Orally

- **Compressed Tablets:** Swallowed intact; single compression
  - Methods: **Direct Compression** or **Wet Granulation**

- **Multiple Compressed Tablets:** More than one compression
  - **Layered Tablets:** Separate incompatible drugs in layers
  - **Compression-Coated Tablets:** Tablet within tablet (e.g., Norgesic)

Subclasses of Multiple Compressed Tablets:

- **Repeat-action tablets**: For repeated drug release
- **Delayed/Enteric-coated tablets**: Protect drug from stomach acid
- **Sugar/Chocolate-coated tablets**: Mask taste, protect drug
- **Film-coated tablets**: Durable, less bulky
- **Chewable tablets**: Designed for chewing, suitable for children

2. Tablets Used in Oral Cavity

- **Buccal & Sublingual Tablets:** Held in mouth; absorbed directly; protect drugs destroyed in GI
- **Troches & Lozenges:** Local effect in mouth/throat; dissolve slowly
- **Dental Cones:** Placed in tooth socket to prevent bacterial growth

3. Tablets Administered by Other Routes

- **Implantation Tablets (Depot):** Subcutaneous implants for prolonged drug action; sterile
- **Vaginal Tablets:** Ovoid/pear-shaped; release drugs slowly; may have protective PEG coating

4. Tablets Used to Prepare Solutions

- **Effervescent Tablets:** Release CO_2 for rapid action (e.g., Alka-Seltzer)
- **Dispensing Tablets:** Added to water to prepare solutions; less commonly used
- **Tablet Triturates:** Small, molded tablets for potent drugs; may be prepared automatically
- **Hypodermic Tablets:** For parenteral solutions; now rarely used

Methods to Prepare Tablets

1. **Direct Compression**
   - Suitable for free-flowing, cohesive powders
   - Excipients: fillers, disintegrants, lubricants, glidants, binders
   - **Advantages:** Simple, rapid
   - **Disadvantages:** Air entrapment → capping, lamination
2. **Wet Granulation**
   - Steps: weigh & blend → dampen → screen → dry → size → add lubricant → compress
   - Widely employed; improves compressibility
3. **Dry Granulation**
   - Suitable for moisture-sensitive drugs

    - **Slugging:** Powder compacted → broken → compressed
    - **Roller Compaction:** Powder pressed between rollers → broken → compressed
4. **Fluid Bed Granulation**
    - Continuous process using a fluid bed granulator; latest technology

Post-Preparation Processes

1. **Tablet Dedusting:** Remove loose powder
2. **Tablet Coating:** Protects drug, masks taste, modifies release, improves aesthetics
3. **Waterproofing & Sealing Coats**
4. **Sub-coating:** Sugar-based for rounding & adhesion
5. **Smoothing & Final Rounding**
6. **Finishing & Coloring**
7. **Imprinting:** Debossed, embossed, engraved, or printed
8. **Polishing:** Drum, wax, or spray
9. **Packing:** Automated packaging

Problems in Tablet Manufacturing

1. In-process Manufacturing Issues

- **Capping & Lamination**: Separation of tablet layers
- **Picking & Sticking**: Powder adheres to punches
- **Mottling**: Uneven color distribution
- **Punch Variation**: Volumetric fill inconsistency
- **Hardness Variation**
- **Double Impression**: Repeated imprinting

2. Post Manufacturing Issues

- **Friability:** Tablets break during transportation
- **Disintegration & Dissolution**: May affect bioavailability

Quality Control Tests

- **Official Tests:** Disintegration, dissolution, friability
- **Non-Official Tests:** Weight variation, thickness, hardness, diameter

Advantages of Tablets

- Easy to carry & swallow
- Attractive appearance; taste masking possible
- Accurate dose; blister/strip packaging
- Prolonged stability
- Easy handling; reduced microbial contamination
- Suitable for large-scale production

Disadvantages of Tablets

- GI irritation (e.g., aspirin)
- Bioavailability issues due to slow dissolution
- Difficulty swallowing for some patients
- Not suitable for drugs needing demulcent action
- Bitter or unstable drugs may require coating or capsulation

Tablet Dosage Form

Introduction

- Tablets are the most common **solid dosage form** administered by the **oral route (GIT)**.
- They are considered **safer than injectables**.
- Pills are small, round, solid dosage forms containing a medicinal agent intended for oral administration. In modern practice, **pills have largely been replaced by tablets and capsules**.
- **Friable pills** were first prepared by **Upjohn in the 1950s**, but later they were replaced by **compressed tablets**.

Definition

- Tablets may be defined as **solid dosage pharmaceutical forms containing drug substances, with or without suitable diluents, prepared either by compression or molding methods**.
- They are usually prepared with the aid of suitable **pharmaceutical excipients**.
- Tablets may vary in **size, shape, weight, hardness, thickness, disintegration, dissolution**, and other characteristics depending on their **intended use** and **method of manufacturing**.

Further Definition:

- A tablet is a **solid unit dosage form** of medicament or medicaments with or without suitable diluents, prepared either by **molding** or **compression**.
- Tablets are a mixture of **active substances** and **excipients**, usually in **powder form**, pressed or compacted into a solid.

Advantages of Tablets

- Easy to carry and swallow
- Attractive in appearance
- Mask unpleasant taste with coating
- Accurate dose, no need for measurement
- Blister or strip packing protects from air, moisture, light
- Can be divided into halves or quarters for fractional dosing
- Stable for prolonged periods

- Easy handling and reduced microbial contamination
- Suitable for large-scale production
- Coating can improve palatability or reduce gastric irritation

Disadvantages of Tablets

- GI irritation (e.g., aspirin)
- Bioavailability issues from slow dissolution
- Difficulty swallowing in children or ill patients
- Cannot achieve demulcent action like syrups
- Bitter or odor-sensitive drugs may require coating or capsulation
- Drugs with poor wetting, low dissolution, or high GI absorption site may be difficult to formulate

Properties of Tablets

1. Tablets vary in **shape, size, and weight** depending on the amount of medicament and mode of administration.
2. They should be an **elegant product** with a clear identity.
3. They should have the **strength** to withstand mechanical shocks during handling and transportation.
4. Tablets should maintain **chemical and physical stability** to preserve their properties.
5. They must be able to **release the medicinal agent** effectively in the body.
6. Tablets are usually **disk-shaped with convex surfaces**, but special shapes such as **round, oval, oblong, cylindrical, square, and triangular** are also available.
7. The **weight of oral tablets** generally ranges from 0.2 to 0.8 g including diluents. Tablets for non-oral routes may be lighter or heavier.
8. Tablets offer numerous **advantages** for patients, prescribers, manufacturers, and pharmacists.

Composition of Tablets

- Tablets consist of **active substances** and **excipients**, usually in **powder form**, compressed into a solid.

Excipients include:

- **Binders** – to hold the tablet together
- **Glidants (flow aids)** – to improve powder flow
- **Lubricants** – to prevent sticking during compression
- **Disintegrants** – to ensure tablets break up in the digestive tract
- **Sweeteners or flavors** – to mask unpleasant taste
- **Pigments** – to make uncoated tablets visually attractive

Characteristics of an Ideal Tablet

1. **Free of Defects:**
    - Should have its own identity
    - Free from contamination, chips, cracks, discoloration
2. **Physical Stability:**
    - Should maintain physical properties under environmental or stress conditions
3. **Chemical Stability:**
    - Should maintain chemical composition to prevent alteration of medicinal agents
4. **Release of Medicinal Agents:**
    - Should release drugs in a **predictable** and **reproducible** manner
5. **Strength:**
    - Should withstand mechanical shocks during production, packaging, shipping, and dispensing
6. **Colour:**
    - Must be uniform; non-uniform coloring affects aesthetics and perceived quality
7. **Odour:**
    - Any odour may indicate a stability problem (e.g., aspirin degradation)

Types and Classes of Tablets

Four major types:

1. Tablets ingested orally
2. Tablets used in the oral cavity
3. Tablets administered by other routes
4. Tablets used to prepare solutions

1. Tablets Ingested Orally

- Designed to be swallowed intact (except chewable tablets)

Subtypes:
I. Compressed Tablets:

- Swallowed with water or suitable liquid
- Disintegrate in stomach; absorption occurs from gastric fluids
- **Preparation:** Single compression using tablet machines
- Types:
    1. **Direct Compressed Tablets**
    2. **Wet Granulation Tablets**

II. Multiple Compressed Tablets:

- Prepared by **more than one compression**
- **Layered Tablets:** Incompatible drugs compressed into layers

- **Compression Coated Tablets (Tablet within Tablet):** Core tablet surrounded by coating; e.g., Norgesic
- **Advantages:** Separate drugs to prevent incompatibility; control release
- **Disadvantages:** Tedious, expensive, requires precise machinery

Subclasses of Multiple Compressed Tablets:

1. **Repeat-action tablets:** Uncontrolled gastric release; limitations exist
2. **Delayed-action & Enteric-coated tablets:** Release drugs after a delay; protect stomach and drugs
3. **Sugar and Chocolate-coated tablets:** Mask taste, protect drugs; increase size and shipping cost
4. **Film-coated tablets:** Durable, less bulky, faster to apply
5. **Chewable tablets:**
    - Meant to be chewed before swallowing
    - Suitable for children and patients without water
    - Common bases: Mannitol, sorbitol, lactose, chocolate powder, dextrose, glycine
    - Must have **acceptable taste**, disintegrate quickly, and avoid hard granules

2. Tablets Used in Oral Cavity

Subtypes:

1. **Buccal and Sublingual Tablets:**
    - Flat oval tablets; absorbed in mouth
    - Protect drugs destroyed in GI tract
    - Contain sweetening agents for taste
2. **Troches and Lozenges:**
    - Dissolve slowly for local effect in mouth/throat
    - Formulated by **molding or compression**
    - No disintegrants; slow dissolution via increased binding agent
    - Contain sweeteners and flavorings
3. **Dental Cones:**
    - Placed in empty socket after tooth extraction
    - Prevent bacterial growth

3. Tablets Administered by Other Routes

Subtypes:

1. **Implantation Tablets (Depot Tablets):**
    - Subcutaneous or intramuscular; prolonged drug release
    - Small, cylindrical or rosette-shaped, sterile
    - Used in veterinary medicine and human birth control (e.g., steroidal hormones)
2. **Vaginal Tablets:**
    - Ovoid or pear-shaped; slow drug release

- Treat vaginal infections
- Some laxatives also formulated as compressed tablets
- May contain disintegrating agents that swell or effervesce
- PEG layer may facilitate insertion and protection

4. Tablets Used to Prepare Solutions

Subtypes:

1. **Effervescent Tablets:** Release CO_2; rapid drug action (e.g., Alka-Seltzer)
2. **Dispensing Tablets:** Added to water for a solution; less common now
3. **Tablet Triturates:**
   - Small, molded or compressed tablets
   - Used for potent/toxic drugs
   - Prepared by moistening powders with alcohol, molding, drying
   - Automatic machines prepare up to 2500/min
4. **Hypodermic Tablets:**
   - Originally for extemporaneous preparation of injectable solutions
   - Soft, soluble tablets; free of insoluble particles
   - Rarely used today

2. Methods to Prepare Tablets

1) Direct Compression Method

- Some granular chemicals (e.g., potassium chloride) can be compressed directly due to their free-flowing and cohesive properties.
- Excipients used to aid direct compression:
  - **Fillers:** Spray-dried lactose, microcrystalline cellulose, sucrose-starch mixtures, dicalcium phosphate.
  - **Disintegrants:** Direct compression starch, sodium carboxymethyl starch, cross-linked polyvinylpyrrolidone.
  - **Lubricants:** Magnesium stearate, talc.
  - **Binders:** Carboxymethyl cellulose, agar, acacia gum, glucose.
- Lubricants improve flow, prevent sticking, reduce friction, and give sheen to tablets.
- Air entrapment can cause capping or splitting; forced feeders help reduce this problem.

2) Wet Granulation Method

- Widely used method for compressed tablets.
- Steps:
  1. Weighing and blending ingredients
  2. Preparing dampened powder/mass
  3. Screening into granules
  4. Drying granules
  5. Sizing by dry screening

6. Adding lubricant and blending
7. Compressing into tablets

3) Dry Granulation Method

- Powder mixture is compacted into large pieces and broken into granules.
- Used for moisture-sensitive or heat-sensitive materials.
- Processes:
  - **Slugging:** Powder compressed into large slugs, broken and screened.
  - **Roller Compaction:** Powder compacted between rollers, sized, lubricated, and compressed.
  - Binders: Methylcellulose, hydroxyl methylcellulose (6–12%).

4) Fluid Bed Granulation Method

- Entire granulation process completed continuously in a fluid bed granulator.
- Latest technological method for tablet preparation.

Quality Control Tests

- **Official Tests:** Disintegration, dissolution, friability
- **Non-official Tests:** Weight variation, thickness, hardness, diameter

Capsules Dosage Form

Definition

Capsules are **unit doses of drugs enclosed in a soluble shell** made of **gelatin, starch, or similar material**, intended to be swallowed whole **orally**.

Introduction

- Capsules are **as popular as tablets** and widely used in modern pharmacy.
- They are a **convenient means of dispensing** solids, semi-solids, and liquids.
- All capsules consist of a **soluble shell**, generally made of gelatin.
- **Hard capsules** are used for **solid substances**, whereas **soft capsules** are preferred for **liquids and semi-solids**.
- Capsules are generally administered **orally** and swallowed as a whole.

Other Routes:

- Some capsules are administered **rectally or vaginally**, serving as substitutes for **suppositories**.
- Soft capsules can also be used for **eye ointments**, where the capsule is pricked and the ointment transferred to the eye.

- Capsules provide a **tasteless and odorless enclosure**, making it convenient to administer otherwise difficult drugs.
- **Limitation:** Aqueous or hydro-alcoholic liquids **cannot be filled** in capsules as they dissolve gelatin.

Precautions/Danger

- Capsules should **not** be used for **highly water-soluble materials** like ammonium chloride, potassium bromide, potassium chloride, etc., because **rapid release can cause irritation**.
- Capsules should **not** contain **deliquescent substances** (which absorb moisture) or **efflorescent substances** (which lose water), as these can **soften or damage the shell**.

Advantages

1. Can dispense **solids, semi-solids, liquids**.
2. Avoid unpleasant taste or odor.
3. Easy to swallow.
4. Satisfactory and reliable disintegration.
5. Attractive dosage form.
6. Colored shells protect from light.
7. Shells are **inert** and digested easily.
8. Less adjuncts than tablets.
9. Flexibility and resistance to mechanical stress (12–15% moisture).

Disadvantages

1. More expensive than tablets.
2. Cannot use **aqueous or alcoholic solutions**.
3. Highly soluble salts can cause **irritation**.
4. Deliquescent or hygroscopic substances unsuitable.
5. Insoluble substances (e.g., some bismuth salts) may cause **enteroliths**.

Types of Capsules

There are **two main types of capsules**:

1. **Hard Gelatin Capsules**
2. **Soft Gelatin Capsules**

1. Hard Gelatin Capsules

- Also called **dry-filled capsules**.
- Consist of **two parts**:
  - **Capsule body**
  - **Shorter cap**

- The **cap slips over the body**, fully enclosing the drug.
- Made from **gelatin, sugar, and water**.

Types of Hard Capsules:

- **Snap Fit** – simple, but may slit or dent
- **Coni Snap**
- **Coni Snap Supro**
- All have **locking grooves** (usually two) for better closure.

Capsule Shell Composition

- **Gelatin:** Forms the main structure, derived from **pork skin and bones**.
  - Skin gelatin → plasticity
  - Bone gelatin → firmness (watch calcium phosphate content to avoid haziness)
- **Plasticizers:** Glycerin, sorbitol – make the shell flexible.
- **Water:** For gel formation
- **Other additives:** Preservatives (methyl-paraben, propyl-paraben), colors, flavors, sugars, acids, enteric materials.

Important notes:

- Gelatin solubility allows **disintegration in stomach fluids**.
- Average gelatin molecular weight: 20,000–200,000.
- Typical preservatives: 0.2% mixture of methylparaben: propylparaben (4:1)
- Flavors ≤ 2% (ethyl-vanillin, essential oils)
- Sugar ≤ 5% for chewable characteristics

Manufacturing Summary

1. **Dipping:** Pins corresponding to capsule bodies and caps are dipped in heated gelatin solution.
2. **Rotation:** Pins rotated to evenly coat with gelatin.
3. **Drying:** Pins passed through controlled kilns.
4. **Removal & Trimming:** Capsule bodies and caps removed and trimmed.
5. **Assembly:** Caps placed on bodies.

Storage:

- Controlled **temperature and humidity**.
- Normal moisture content: 10–15%.
- Low humidity → brittle shells; high humidity → tacky or bloated capsules.

Sizing:

- Sizes 000, 00, 0E, 0, 1, 2, 3, 4 (capacity 200–1370 µl)

- Approximate drug capacities for aspirin:
    1. 000 → 1000 mg
    2. 00 → 650 mg
    3. 0 → 520 mg
    4. 1 → 320 mg
    5. 2 → 260 mg
    6. 3 → 195 mg
    7. 4 → 160 mg
    8. 5 → 97 mg

Special Manufacturing Techniques

1. **Imprinting:** Printing words or logos.
2. **Sealing/Banding:** Tamper-proofing.
3. **Two-phase filling:** Separates incompatible drugs in same capsule.
4. **Coating:** Protects shell or drug.

Hard Gelatin Capsule Manufacturing Steps

1. Quality control of raw materials and equipment validation.
2. **Gelatin solution preparation:** 25–30% gelatin in hot demineralized water under vacuum.
3. Aging in stainless steel tanks.
4. Addition of dyes, opacifiers, preservatives.
5. **Dipping:** Pins dipped in gelatin at 45–55°C.
6. **Spinning:** Even coating formation on pins.
7. **Drying:** Controlled kiln drying.
8. **Cutting & Joining:** Capsules trimmed and caps placed.
9. **Output:** ~1 million capsules/day (size-dependent).
10. **Assembling:** Pre-locked capsules for filling.

Materials to be Filled

Additives may include:

1. **Diluents:** Lactose, mannitol, sorbitol, starch – to achieve desired bulk.
2. **Protective sorbents:** Magnesium/calcium oxides or carbonates – separate incompatible or hygroscopic materials.
3. **Glidants:** Talc, stearates – improve powder flow in automated filling.
4. **Anti-dusting compounds:** Edible oils – prevent inhalation hazards.

Limitations:

- Highly water-soluble substances (e.g., citric acid, sodium chloride) may damage gelatin.
- Some poorly soluble drugs (e.g., benzocaine) can migrate into shell.

Filling Techniques:

- **Manual:** Spreading powder on tile, filling by hand.
- **Industrial:** Semi-automatic or fully automatic machines, filling 15,000–20,000 capsules/hour.

Finishing

1. **Salt Polishing:** Removes adhering material; done before imprinting.
2. **Cloth Dusting:** Rub capsules with cloth (sometimes oiled) for gloss.
3. **Brushing:** Soft rotating brush removes remaining dust.
4. **Inspection:** Detect damaged or imperfect capsules.
5. **Sealing & Locking:** Prevents cap separation and tampering.

Modern Uses of Hard Gelatin Capsules

- Enclose **powders, granules, pellets, pastes, and oils**.
- Prevent leakage with **thixotropic agents** or banding.
- Supply **incompatible drugs** separately in one capsule.
- Drug delivery in **bronchial tract** (punctured capsule releases powder mist).

2. Soft Gelatin Capsules

- Soft, globular gelatin shell, **plasticized with glycerin or sorbitol**.
- **Elastic and pliable** compared to hard gelatin capsules.
- Used for **liquids, semi-solids, and powders**, as well as **suppository substitutes**, **ear, eye, nose, and throat formulations**, cosmetics, and foods.

Composition:

- Similar to hard gelatin capsules but with **higher plasticizer content** for elasticity.

Shapes:

- Spherical, round, oval, oblong, elliptical, tube-shaped
- Capacity: 0.1 ml – 30 ml

Manufacturing

- Requires **specialized large-scale equipment**.
  Processes:

1. **Plate process:** Warm gelatin sheet with liquid fill sandwiched between another sheet; pressure seals capsules.
2. **Rotary die process (Scherer, 1933):**
   - Gelatin ribbons form pockets, fill material injected, sealed, and cut.
   - Bi-colored capsules possible.
3. **Reciprocating die process:**
   - Vertical dies form pockets in gelatin ribbons; capsules filled, sealed, shaped, and cut; fall into refrigerated tanks.

Materials to be Filled

- Liquids, suspensions, pasty materials, dry powders.
- **Liquids:** Vegetable/aromatic oils, hydrocarbons, ethers, esters, alcohols, PEGs, non-ionic surfactants.
- **Conditions:**
  - Flow by gravity at ≤ 35°C
  - Viscosity 0.2–3000 cps at 25°C
  - Avoid water (>5%), alcohols, ketones, acids, amines, and extremes of pH (<2.5 or >7.5)

Suspensions:

- Suspended solids must remain uniformly distributed; liquid bases carefully selected (vegetable oils, non-ionic surfactants, carbowax 400).

Applications

- Contain medication elegantly and **easy to swallow**.
- Examples: **Vitamins, Digoxin, Demecycline HCl**

Physical Stability

- **Hard capsules:** Avoid high/low humidity – softening or brittleness.
- **Soft capsules:** Equilibrate with environment; extreme conditions can cause bloating, sticking, fusion.
- **Accelerated tests:** 80% RH at room temperature or 104°F for 15 days to evaluate stability.
- Store capsules in containers **preventing moisture exposure**, and within advised temperature ranges.

Total Parenteral Nutrition (TPN)

1. Introduction

Total Parenteral Nutrition (TPN) is a **life-saving therapeutic approach** used to provide **complete nutritional support** to patients **intravenously**, when oral or enteral feeding is not possible or adequate.

- It bypasses the gastrointestinal tract entirely.
- Administered through **central venous catheters** (preferred) or peripheral veins (short-term).
- Supplies **macronutrients (carbohydrates, proteins, fats)** and **micronutrients (vitamins, trace elements, electrolytes)** in sterile, balanced form.

2. Indications for TPN

TPN is used when a patient:

- **Cannot eat** (coma, unconsciousness, severe anorexia nervosa).
- **Should not eat** (GI obstruction, perforation, severe pancreatitis, fistulas).
- **Will not absorb nutrients adequately** (short bowel syndrome, malabsorption, severe diarrhea, Crohn's disease flare-ups).
- **Severe hypercatabolic states** (major burns, trauma, sepsis, post-major surgery).

3. Composition of TPN Solution

Component	Purpose	Examples
Carbohydrates	Main energy source (70% of calories)	Dextrose (25–70% solutions)
Proteins (Amino acids)	Maintain nitrogen balance, tissue repair	Essential & non-essential amino acids
Fats (Lipids)	Energy + essential fatty acids	Intralipid (soybean oil, MCTs, egg phospholipids)
Electrolytes	Maintain acid-base & water balance	Na^+, K^+, Mg^{2+}, Ca^{2+}, Cl^-, HCO_3^-, PO_4^{3-}
Vitamins	Cofactors for metabolic pathways	Vit. A, D, E, K, B-complex, C
Trace Elements	Enzyme activity & immune function	Zn, Cu, Mn, Cr, Se
Water	Solvent & hydration	Sterile water for injection

4. Routes of Administration

A. Central Parenteral Nutrition (CPN)

- **Preferred method for long-term use.**
- Delivered via central vein (subclavian, jugular) → rapid dilution in blood.
- Can use **highly concentrated solutions** (hyperosmolar).

B. Peripheral Parenteral Nutrition (PPN)

- Short-term (≤ 2 weeks) use.
- Lower osmolarity (<900 mOsm/L) to prevent phlebitis.
- Requires larger fluid volumes.

5. Compounding of TPN

- Done in **hospital pharmacy clean room** under **laminar airflow hood**.
- Steps:
    1. **Calculate daily requirements** for energy, protein, fluids, electrolytes.
    2. **Aseptically transfer components** into large parenteral bag (3-in-1 admixture or 2-in-1 with separate lipids).
    3. Mix thoroughly and visually inspect for particulate matter, precipitation.
    4. Label with patient name, composition, rate of infusion, expiry.

6. Administration

- Infused **continuously over 24 hours** via infusion pump.
- Strict aseptic technique to prevent **catheter-related infections**.
- Blood glucose monitored every 4–6 hrs initially (risk of hyperglycemia).

7. Complications of TPN

Type	Examples
Metabolic	Hyperglycemia, hypoglycemia (if abruptly stopped), electrolyte imbalance, liver dysfunction
Mechanical	Catheter occlusion, pneumothorax during insertion
Infectious	Catheter-related bloodstream infection (CRBSI)
Nutritional	Deficiency/excess of micronutrients, refeeding syndrome

8. Monitoring Parameters

- **Daily:** Weight, fluid balance, blood glucose.
- **Twice weekly:** Electrolytes, liver function, renal function.
- **Weekly:** Triglycerides, albumin, pre-albumin.

9. Advantages of TPN

- Provides complete nutrition when enteral route is not possible.
- Can be tailored to patient's needs (individualized formulation).
- Maintains positive nitrogen balance and supports wound healing.

10. Disadvantages / Limitations

- Expensive and labor-intensive.
- Risk of serious infection.
- Metabolic complications if not carefully monitored.
- Requires skilled healthcare team (pharmacist, nutritionist, physician, nurse).