# Unit-3

# Industrial Pharmacy-1

## B.Pharma 5th Sem Notes

### Unit: 3

**Capsules:**

- **Hard gelatin capsules:** Introduction, Production of hard gelatin capsule shells. size of capsules, Filling, finishing and special techniques of formulation of hard gelatin capsules, manufacturing defects. In process and final product quality control tests for capsules.
- **Soft gelatin capsules:** Nature of shell and capsule content, size of capsules,importance of base adsorption and minim/gram factors, production, in process and final product quality control tests. Packing, storage and stability testing of soft gelatin capsules and their applications.

**Pellets:**

- Introduction, formulation requirements, pelletization process, equipments for manufacture of pellets

# Introduction

Capsules are **solid unit dosage forms** in which the drug substance is enclosed within a **hard or soft soluble shell**. The shell is generally made of **gelatin**, but modern capsules may also use **hydroxypropyl methylcellulose (HPMC)** or other polymers for vegetarian formulations.

Capsules are used in pharmaceutical preparations because they **mask unpleasant taste and odor, improve patient compliance, and protect the drug from environmental factors such as light and air**.

**Or**

Capsules are solid dosage forms in which the drug substance is enclosed in a shell or container. The capsule shell consists of a hard or soft gelatin coating that contains and protects the active ingredient.

**Types of Capsules:**

- Hard Gelatin Capsules (HGCL)
- Soft Gelatin Capsules (SGCL)

# Components of Capsules

Capsules mainly consist of two parts:

## 1. Capsule Shell

The shell encloses the drug and is usually prepared from:

- **Gelatin** (derived from collagen of animal origin)
- **Plasticizers** – e.g., glycerin, sorbitol (mainly in soft capsules)
- **Water** – provides flexibility
- **Coloring agents** – for identification
- **Opacifying agents** – e.g., titanium dioxide
- **Preservatives** – e.g., methyl paraben

## 2. Fill Material

The material placed inside the capsule shell may include:

- Powders
- Granules
- Pellets
- Tablets (capsules containing mini-tablets)
- Liquids or semi-solids (mainly in soft gelatin capsules)

**Advantages of Capsules:**

- Masks unpleasant taste and odor
- Provides protection to sensitive ingredients
- Easy to swallow for patients
- Allows for accurate dosing
- Aesthetically pleasing with colored shells
- Can provide modified release formulations

**Disadvantages of Capsules:**

- **Hygroscopic Issues:** Gelatin contains water; if the environment is too dry, they become brittle. If too humid, they become sticky.
- **Dietary Restrictions:** Standard gelatin is animal-derived (bovine or porcine), which may not suit vegan or certain religious diets (though HPMC "veggie" caps are an alternative).
- **Cost:** Generally more expensive to manufacture than standard tablets.

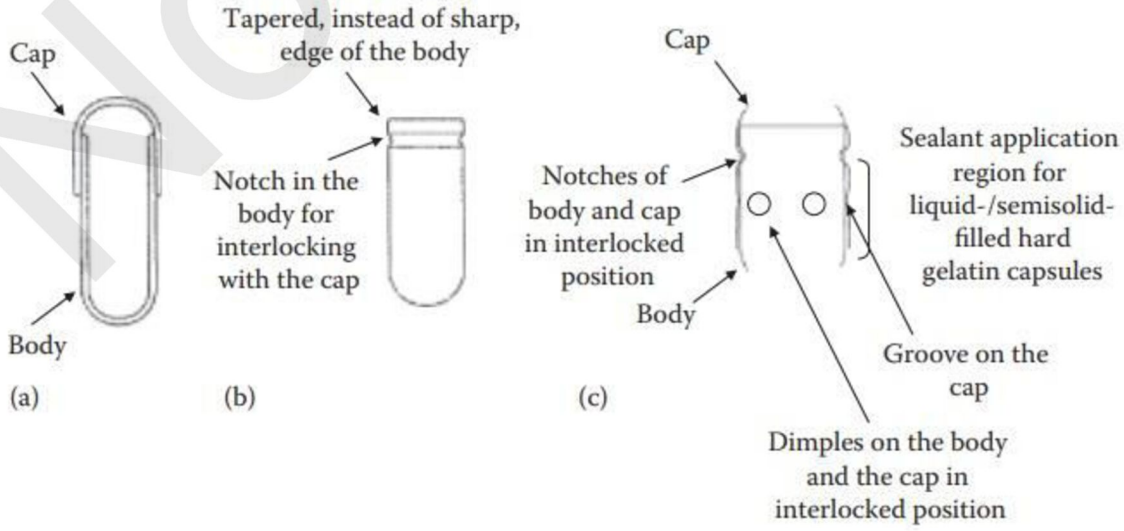
## 1. Hard Gelatin Capsules (HGCL):

**Introduction:**

Hard Gelatin Capsules are solid dosage forms consisting of two interlocking cylindrical shells (body and cap) made from gelatin, which enclose powdered or granulated drug substances. They are designed for oral administration.

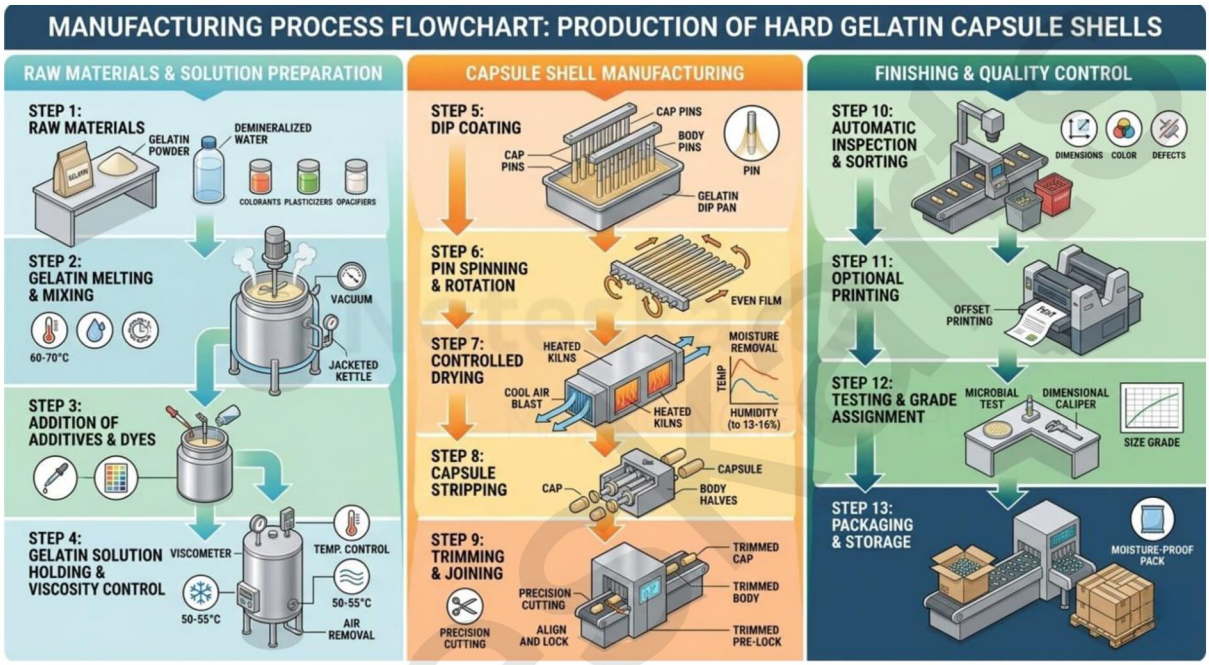
Hard gelatin capsules are **two-piece capsules** consisting of:

- **Body** – longer portion that holds the drug
- **Cap** – shorter portion that fits over the body



**Characteristics:**

- Size: 000 to 5 (0 being the largest)
- Usually filled with dry powders or granules
- Shell is rigid and brittle
- Moisture content: 12-16%
- Dissolution: 30-60 minutes



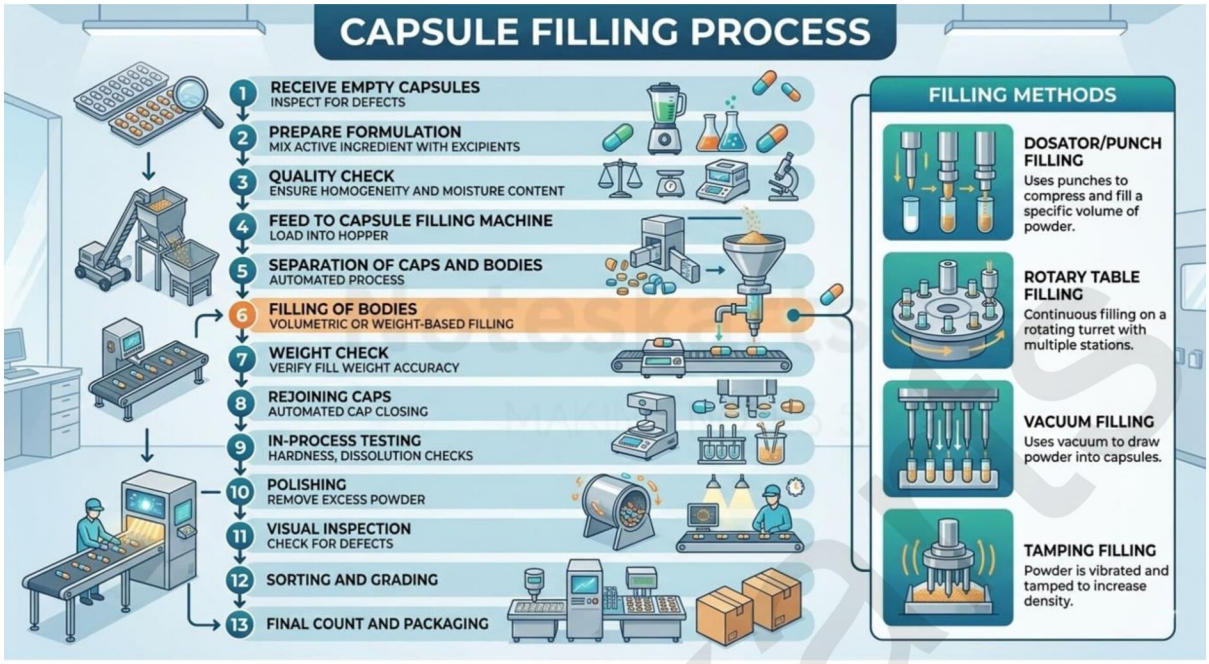

## Capsule Sizes and Classification

Hard gelatin capsules are manufactured in standard sizes ranging from 000 (largest) to 5 (smallest). Each size accommodates different quantities of fill material.

### Capsule Size Chart

| Size | Body Length (mm) | Diameter (mm) | Fill Volume (mg) | Fill Volume (mL) |
|---|---|---|---|---|
| **000** | 26.1 | 9.91 | 500-700 | 0.68 |
| **00** | 23.3 | 8.53 | 400-500 | 0.50 |
| **0** | 20.4 | 7.64 | 325-400 | 0.37 |
| **1** | 19.4 | 6.91 | 270-320 | 0.30 |
| **2** | 18.0 | 6.35 | 200-250 | 0.23 |
| **3** | 15.9 | 5.59 | 130-170 | 0.15 |
| **4** | 14.3 | 5.19 | 100-120 | 0.10 |
| **5** | 11.6 | 4.91 | 65-85 | 0.08 |

## Capsule Filling Process:




The process of filling capsules can be broken down into three main phases: preparation, filling, and finishing.

- **Phase 1: Preparation & Quality Control (Steps 1-3)** The process begins by inspecting empty capsules for defects. Simultaneously, the formulation is prepared by mixing the active ingredients with excipients, followed by quality checks to ensure the mixture is uniform and has the correct moisture content.
- **Phase 2: Automated Filling Operation (Steps 4-8)** Empty capsules and the prepared powder are loaded into the filling machine. The machine automatically separates the capsule caps from the bodies, fills the bodies using precise volumetric or weight-based measurements, verifies the weight accuracy, and then mechanically rejoins the caps to seal the capsules.
- **Phase 3: Finishing, Inspection & Packaging (Steps 9-13)** Once sealed, the capsules undergo in-process testing (like hardness and dissolution). They are then polished to remove residual powder, visually inspected for any final defects, sorted, graded, and finally counted for packaging.

### Finishing Operations

After filling, capsules undergo several finishing steps to improve appearance, functionality, and ensure quality standards.

| Operation | Purpose | Method | Parameters |
|---|---|---|---|
| **Polishing** | Remove excess powder and dust | Tumbling in polishing drum | 5-10 minutes at 40-50 rpm |
| **Banding** | Seal bodies and caps | Gelatin or HPMC band application | Band solution at 40-50°C |
| **Printing** | Add identification marks | Inkjet or Offset printing | Non-toxic food-grade inks |
| **Capsule Cleaning** | Remove foreign particles | Air classification or tumbling | Remove particles >10 µm |
| **Moisture Conditioning** | Adjust moisture content | Climate chambers | 12-16% final moisture |

**Special Formulation Techniques for Hard Gelatin Capsules**

**Enteric-Coated Capsules**

Enteric coating prevents dissolution in the stomach, allowing release in the small intestine.

- Applications: Acid-labile drugs, NSAIDs
- Coating Materials: Cellulose acetate phthalate (CAP), HPMCP
- Coating Process: Pan coating or spray coating

**Sustained/Extended Release Capsules**

Drug is released gradually over an extended period.

- Technology:

1. Microencapsulation of active ingredient
2. Use of hydrophobic and hydrophilic polymers
3. Matrix systems

**Immediate Release Capsules**

Standard capsules designed for rapid dissolution and absorption.

- Typical dissolution time: 30-60 minutes

**Sprinkle Capsules**

Can be opened and contents sprinkled on food for patients who cannot swallow.

- Contains beads or granules
- Used for pediatric and geriatric patients

### Capsules with Liquid Fills

Powders mixed with liquid vehicles or suspended in oils.

- Requires special processing to prevent leakage

### Manufacturing Defects in Hard Gelatin Capsules

| Defect | Cause | Impact | Prevention |
|---|---|---|---|
| **Cracks/Splits** | Low humidity, brittleness | Leakage, instability | Proper humidity control |
| **Sticking** | High moisture, improper drying | Jamming, breakage | Optimize drying profile |
| **Discoloration** | Oxidation, contamination | Reduced shelf life | Use antioxidants |
| **Microbial contamination** | Improper sterilization | Loss of potency | GMP compliance |
| **Misalignment** | Machine calibration issues | Poor seal | Regular maintenance |
| **Weak seals** | Poor banding technique | Powder leakage | QC of banding process |
| **Incomplete filling** | Machine malfunction | Underdosing | Weight variation checks |
| **Over-filling** | Calibration error | Capsule damage | Dosator calibration |

### Quality Control Tests for Hard Gelatin Capsules

#### In-Process Quality Control Tests

These tests are performed during manufacturing to ensure compliance with specifications:

| Test | Specification | Method | Frequency |
|---|---|---|---|
| **Capsule Weight** | ±5% of target | Electronic balance | Every batch, min 20 units |
| **Moisture Content** | 12-16% | Karl Fischer titration | Every batch |

| | | | |
|---|---|---|---|
| **Bulk Density** | As per specification | Bulk density apparatus | Each batch |
| **Appearance** | No cracks, discoloration | Visual inspection | Continuous during filling |
| **Hardness** | 6-12 kP | Capsule hardness tester | Every 30 min during filling |
| **Friability** | <1% loss | Roche friability apparatus | Every batch |
| **Powder Blend Uniformity** | RSD <5% | Content uniformity assay | Before filling |

**Final Product Quality Control Tests**

| Test Parameter | Specification | USP/BP Method | Acceptance Criteria |
|---|---|---|---|
| **Description** | Color, shape, size | Visual | As per approved standard |
| **Identification** | Confirm active ingredient | HPLC/TLC | >95% active ingredient |
| **Assay (Potency)** | 95-105% of labeled amount | HPLC | 95-105% |
| **Dissolution** | 80% at 45 minutes | USP II Apparatus (Paddle) | As per monograph |
| **Hardness** | 6-12 kP | Monsanto hardness tester | 6-12 kP |
| **Friability** | <1% loss | Roche apparatus (1.6 m, 4 min) | <1% |
| **Moisture Content** | 12-16% | Karl Fischer | 12-16% |
| **Microbial Contamination** | Total aerobic count | USP <2021> | <100 CFU/g |
| **Uniformity of Content** | RSD <5% | HPLC assay | RSD <5% |
| **Disintegration** | <30 minutes | USP apparatus | <30 min (in water at 37°C) |
| **Related Substances** | <0.05% impurity | HPLC | <0.05% any single impurity |

## 2. Soft Gelatin Capsules (SGCL)

**Introduction:**

Soft Gelatin Capsules are single-piece, sealed capsule shells made from gelatin containing a liquid, semi-solid, or oily core material. They are designed to be easy to swallow and provide rapid absorption of contents.

**Characteristics:**

- Moisture content: 4-8% (lower than hard capsules)
- Contains plasticizers (sorbitol, glycerin, water)
- Single-piece construction
- Flexible shell
- Various shapes available (oval, round, square)
- Ideal for oils, liquids, and lipophilic drugs

**Nature of Shell and Capsule Content**

**Shell Composition**

| Component | Percentage | Function | Specification |
|---|---|---|---|
| **Gelatin (Grade A)** | 40-45% | Film former | Type A or Type B |
| **Glycerin** | 30-35% | Plasticizer | Humectant, flexibility |
| **Water** | 15-20% | Solvent | Humectant |
| **Sorbitol** | 0-5% | Alternative plasticizer | Flexibility enhancement |
| **Preservatives** | <0.1% | Prevent microbial growth | Sodium bisulfite, parabens |
| **Colorants** | <0.05% | Visual identification | FDA-approved dyes |

**Capsule Content Types**

- Oil-based liquids: Fatty acids, essential oils
- Semi-solid matrices: Lipophilic or hydrophilic gels
- Powders/Granules: Suspended in lipid vehicles
- Emulsions: Oil-in-water or water-in-oil

**Properties of Soft Capsule Content**

- Viscosity: 50-10,000 cps
- Miscibility: Must be compatible with gelatin and plasticizers
- Hydrophobicity: Prevents moisture transfer
- Stability: Chemical and thermal stability required

**Soft Gelatin Capsule Sizes**

Soft capsules are available in various sizes and shapes, typically larger than hard capsules due to the nature of fill materials.

| Size Code | Length (mm) | Width (mm) | Fill Volume (mL) | Common Uses |
|---|---|---|---|---|
| **00** | 26-27 | 13-14 | 0.8-1.0 | Vitamins, fish oil (regular strength) |
| **0** | 23-24 | 11.5-12 | 0.5-0.7 | Supplements, herbal extracts |
| **1** | 20-21 | 10-11 | 0.3-0.5 | Pharmaceutical liquids |
| **2** | 18-19 | 9-10 | 0.25-0.35 | Specialty pharmaceutical |
| **3** | 15-16 | 7.5-8.5 | 0.15-0.25 | High-dose active ingredients |
| **Custom** | Variable | Variable | Variable | Specialized formulations |

**Base Absorption and Minim/Gram Factors**

Base absorption refers to the amount of fill material (base) that the capsule shell can accommodate. The Minim/Gram factor is used to calculate the exact fill volume needed for accurate dosing.

**Important Calculations**

**Minim Factor:**

The volume in minims (16.23 µL) of one unit of fill material at the same relative density as water (1.0 g/mL).

**Gram Factor:**

The weight in grams of one minim (16.23 µL) of the fill material.

**Formula:**

Fill Weight = Fill Volume × Specific Gravity of Fill Material

**Example Calculation**

If a soft capsule size 00 holds approximately 0.9 mL:

1. And the fill material is fish oil (specific gravity ≈ 0.92):
2. Fill Weight = 0.9 mL × 0.92 = 0.828 g = 828 mg

**Base Absorption Standards**

| Capsule Size | Maximum Fill Volume | Optimal Fill Volume | Minimum Shell Weight |
|---|---|---|---|
| **00** | 1.0-1.2 mL | 0.9-1.0 mL | 300-350 mg |
| **0** | 0.7-0.8 mL | 0.65-0.70 mL | 250-280 mg |
| **1** | 0.5-0.6 mL | 0.45-0.50 mL | 200-220 mg |
| **2** | 0.35-0.4 mL | 0.30-0.35 mL | 150-170 mg |
| **3** | 0.25-0.3 mL | 0.20-0.25 mL | 120-140 mg |

**Soft Gelatin Capsule Production Process**

**Overall Manufacturing Flowchart**

Step 1: Raw Material Selection & Testing
Step 2: Gelatin Solution Preparation (50-55°C)
Step 3: Addition of Plasticizers (Glycerin, Sorbitol)
Step 4: Filtration & Degassing
Step 5: Filling Concentrate Preparation
Step 6: Encapsulation by Rotary Die Process

↓ Cap and Body Formation Simultaneously ↓

Step 8: Softening/Conditioning (Moisture adjustment)
Step 9: Separation of Capsules
Step 10: Individual Capsule Processing
Step 11: In-Process Quality Tests
Step 12: Drying (Controlled humidity chambers)
Step 13: Final Inspection & Sorting
Step 14: Stability/Compatibility Testing
Step 15: Packaging & Labeling

**Detailed Process Stages**

**Stage 1: Gelatin Solution Preparation**

- Gelatin + Water heating to 50-55°C
- Addition of glycerin (30-35% w/w)
- Addition of sorbitol (5-10% w/w)
- Filtration to remove impurities
- Degassing under vacuum

**Stage 2: Encapsulation (Rotary Die Process)**

The rotary die process is the most common method for soft gelatin capsule manufacturing.

| Process Parameter | Typical Range | Unit | Importance |
|---|---|---|---|
| **Gelatin Temperature** | 45-55 | °C | Maintains viscosity for proper sealing |
| **Fill Temperature** | 30-45 | °C | Prevents premature setting |
| **Die Pressure** | 20-40 | PSI | Controls seal strength |
| **Machine Speed** | 3-15 | Capsules/sec | Production rate |
| **Humidity** | 40-55 | %RH | Prevents brittleness/stickiness |
| **Ambient Temperature** | 18-22 | °C | Optimal processing conditions |

**Stage 3: Soft Gelatin Encapsulation Steps**

1. Gelatin ribbon forms on rotating die surface
2. Fill material injected into pocket formed by upper/lower ribbons
3. Pressure applied to seal capsule
4. Sharp cutters separate capsule from ribbon
5. Warm gelatin residue falls away
6. Completed capsule exits the machine

**Stage 4: Post-Encapsulation Processing**

7. Softening: Capsules exposed to controlled humidity (50-55% RH) for 2-4 hours
8. Conditioning: Temperature and humidity adjustment
9. Separation: Manual or mechanical separation of joined capsules
10. Drying: Gradual moisture reduction to 4-8%

**Drying Protocol for Soft Gelatin Capsules**

| Phase | Temperature (°C) | Humidity (%RH) | Duration | Moisture Target (%) |
|---|---|---|---|---|
| **Initial Conditioning** | 20-22 | 55-65 | 4-8 hours | 25-30% |
| **Phase 1 Drying** | 25-30 | 40-50 | 6-12 hours | 15-20% |
| **Phase 2 Drying** | 30-35 | 30-40 | 12-18 hours | 10-15% |
| **Phase 3 Drying** | 35-40 | 20-30 | 18-24 hours | 4-8% |

| | | | | |
|---|---|---|---|---|
| **Final Equilibration** | 20-22 | 40-50 | 4-8 hours | 4-8% |

## Quality Control Tests for Soft Gelatin Capsules

### In-Process Quality Control

| Test | Parameter | Specification | Frequency |
|---|---|---|---|
| **Weight Check** | Individual & Average Weight | ±10% of target | Every 15-30 min |
| **Size Inspection** | Capsule Dimensions | Within ±0.5 mm | Every batch |
| **Seal Integrity** | Capsule Sealing | No leakage | Every 30 min (burst test) |
| **Visual Inspection** | Cracks, discoloration, defects | Zero defects | Continuous |
| **Fill Distribution** | Uniformity of fill | Homogeneous | Visual every 10 min |
| **Moisture Content** | Water activity | 4-8% | Every batch |

### Final Product Quality Control Tests

| Test | Specification | Method | Acceptance Criteria |
|---|---|---|---|
| **Description** | Appearance & Color | Visual inspection | Matches approved standard |
| **Identification** | Confirm active ingredient | HPLC/GC-FID | >95% active ingredient |
| **Assay/Potency** | 95-105% of labeled amount | HPLC analysis | 95-105% |
| **Weight Variation** | Fill weight uniformity | Individual weighing | ±10% of target |
| **Moisture Content** | 4-8% water content | Karl Fischer titration | 4-8% |
| **Burst Strength** | Capsule rupture resistance | Burst test apparatus | >5 psi |

| | | | |
|---|---|---|---|
| **Seal Integrity** | No leakage from seal | Visual + burst test | No defects observed |
| **Friability** | Shell integrity during handling | Roche friability | <2% loss |
| **Dissolution** | Drug release rate | USP II (Paddle) | As per monograph |
| **Microbial Limits** | Contamination test | USP <2021> | <100 CFU/g, <1 CFU/10 units |
| **Related Substances** | Impurity levels | HPLC | <0.05% any single impurity |
| **Peroxide Value** | Oxidation indicator (for oils) | Titration method | <5 mEq/kg |

## Packing, Storage and Stability Testing of Soft Gelatin Capsules

### Packing Materials and Methods

| Packaging Type | Material | Advantages | Disadvantages | Use Case |
|---|---|---|---|---|
| **Blister Pack** | PVC/PVDC + Aluminum | Good protection, portable | Moisture ingress possible | Single dose, retail |
| **HDPE Bottle** | High-density polyethylene | Cost-effective, lightweight | Moisture permeability | Bulk packaging |
| **Glass Bottle** | Amber/Clear glass | Excellent barrier, reusable | Heavy, breakable | Premium products |
| **Foil Pouch** | Aluminum foil laminate | Superior moisture barrier | Not eco-friendly | Moisture-sensitive |
| **Strip Pack** | Individual capsule packs | Convenient, fresh | Higher cost | Travel, compliance |

### Packing Recommendations

- Use desiccants (silica gel, calcium carbonate) in all packages
- Include moisture-indicator cards for monitoring
- Use child-resistant closures as required by law
- Include Package Insert with storage instructions

**Storage Conditions**

| Storage Condition | Temperature Range | Humidity Range | Light Exposure | Shelf Life |
|---|---|---|---|---|
| **Room Temperature** | 15-25°C | 40-60% RH | Protected from light | 2-3 years |
| **Cool** | 8-15°C | 40-60% RH | Protected from light | 3-5 years |
| **Refrigerated** | 2-8°C | 30-50% RH | Protected from light | 5+ years |
| **Frozen** | -20°C or below | <20% RH | Protected from light | 10+ years |

**Storage Instructions for Consumers**

- Store in cool, dry place away from direct sunlight
- Keep container tightly closed
- Do not refrigerate unless specified
- Protect from heat, moisture, and humidity
- Do not mix with other medications in same container

## Stability Testing Protocol

Stability testing follows ICH Q1A(R2) guidelines to predict shelf life and storage conditions.

**Long-term Stability Testing**

| Testing Condition | Temperature | Humidity | Duration | Sampling Points |
|---|---|---|---|---|
| **Long-term** | 25°C ±2°C | 60% ±5% RH | 36 months | 0, 3, 6, 9, 12, 18, 24, 36 months |
| **Intermediate** | 30°C ±2°C | 75% ±5% RH | 12 months | 0, 3, 6, 9, 12 months |
| **Accelerated** | 40°C ±2°C | 75% ±5% RH | 6 months | 0, 3, 6 months |

**Parameters Monitored During Stability Testing**

- Appearance: Color, clarity, separation
- Assay/Potency: HPLC analysis

- Moisture Content: Karl Fischer titration
- Dissolution Profile: USP apparatus testing
- Peroxide Value: For lipophilic content
- Microbial Limits: Bacterial & fungal counts
- Water Activity: Aw measurement
- pH: If applicable

**Applications and Uses of Soft Gelatin Capsules**

| Category | Examples | Advantages | Dosage Range |
|---|---|---|---|
| **Vitamins & Minerals** | Vitamin E, Fish Oil, CoQ10 | Improved absorption, easy to take | 100-1000 mg/capsule |
| **Herbal Extracts** | Ginseng, Ginger, Turmeric | Liquid extract stability, bioavailability | 200-800 mg/capsule |
| **Pharmaceuticals** | Ibuprofen, Acetaminophen | Liquid fill for rapid dissolution | 200-500 mg/capsule |
| **Essential Oils** | Oregano, Tea Tree, Garlic | Odor masking, easy dosing | 100-500 mg/capsule |
| **Probiotics** | Lactobacillus, Bifidobacterium | Protected from moisture & light | 1-10 billion CFU/capsule |
| **Hormones** | Melatonin, DHEA | Stable liquid matrix | 1-10 mg/capsule |
| **Anti-inflammatory** | Omega-3 fatty acids | High lipid solubility benefits | 300-1000 mg/capsule |
| **Nutraceuticals** | Krill oil, Astaxanthin | Bioavailability enhancement | 100-500 mg/capsule |

# Pellets:

- Introduction, formulation requirements, pelletization process, equipments for manufacture of pellets

## Pellets:

## Introduction to Pellets:

**Pellets** are small, free-flowing, spherical or semi-spherical solid units used as a **multiparticulate dosage form** in pharmaceutical formulations. Their diameter generally ranges from **0.5 mm to 1.5 mm**.

Pellets contain **active pharmaceutical ingredients (API)** along with excipients and are usually filled into **hard gelatin capsules** or compressed into **tablets**.

Unlike single-unit dosage forms (tablets), pellets distribute uniformly in the **gastrointestinal tract**, resulting in improved drug absorption and reduced side effects.

**Examples:** Omeprazole pellets, Diclofenac pellets, Proton pump inhibitor capsules.

## Advantages of Pellets

- Uniform distribution in GI tract.
- Reduced dose dumping.
- Improved **bioavailability**.
- Lower irritation of GI mucosa.
- Flexibility in formulation (immediate or controlled release).
- Better flow properties during capsule filling.

### Disadvantages of Pellets

- **Process complexity:** Pelletization requires specialized equipment, expertise, and tightly controlled process parameters.
- **Scale-up challenges:** Moving from laboratory to production scale may alter pellet size distribution, morphology, and release characteristics.
- **Higher coating material consumption:** The large surface area of pellet populations demands significantly more coating material than equivalent tablets.
- **Higher manufacturing cost:** Capital and operational expenditure for fluid bed processors, extruders, and spheronizers is substantially greater than for conventional dosage forms.
- **Risk of agglomeration:** Pellets may aggregate during coating or storage if process parameters (spray rate, bed temperature, inlet air humidity) are not carefully controlled.

**Characteristics of Ideal Pellets**

| Parameter | Ideal Specification |
|---|---|
| Size range | 0.5 – 2.0 mm (commonly 0.7 – 1.4 mm) |
| Shape | Spherical; shape factor (SF) ≥ 0.90 |
| Surface texture | Smooth, non-porous surface for uniform coating |
| Bulk density | High and consistent (for reproducible capsule filling) |
| Drug content uniformity | RSD < 2.0% (per USP/ICH Q6A) |
| Friability | < 0.5% weight loss |
| Moisture content | < 2.0% (drug-dependent) |

**Classification of Pellets**

Pellets may be classified on different bases:

**A. Based on Drug Loading**

- **Drug-layered pellets:** Non-pareil (starter) seeds coated with successive drug layers.
- **Matrix pellets:** Drug uniformly distributed throughout the pellet matrix.
- **Reservoir pellets:** Drug core enclosed within a functional polymeric coat that controls release.

**B. Based on Release Pattern**

- **Immediate-release (IR) pellets**
- **Enteric-coated (EC) pellets**
- **Sustained/extended-release (SR/ER) pellets**
- **Pulsatile-release pellets**
- **Targeted-release pellets (colonic, gastric-retentive)**

## FORMULATION REQUIREMENTS

- A successful pellet formulation demands a thorough understanding of drug physicochemical properties and the strategic selection of excipients. Each component serves a defined functional role in shaping the pellet's physical integrity, drug release, and stability.

### Drug-Related Considerations

#### Solubility and Dissolution

- The aqueous solubility of a drug governs the choice of excipients and processing method. BCS Class I/III (high-solubility) drugs may require release-retarding polymers to sustain therapeutic concentrations.
- BCS Class II/IV (low-solubility) drugs necessitate solubility-enhancing strategies such as solid dispersions, surfactant addition, or particle size reduction before pelletization.

#### Particle Size of Drug Substance

- Micronised or finely milled drug particles (D90 < 50 µm) are preferable as they distribute uniformly in the pellet matrix, ensuring content uniformity and consistent drug release. Coarse particles can cause non-homogeneous distribution and affect spheronization quality.

#### Drug Load

- High drug-load formulations (> 50% w/w) are challenging because insufficient excipient is available to confer plasticity and cohesion. Extrusion–spheronization accommodates higher drug loads (up to 80%) than other techniques, but requires careful optimization of MCC content and liquid addition.

#### Moisture Sensitivity and Thermal Sensitivity

- Hygroscopic drugs require selection of anhydrous or low-moisture excipients and minimum use of aqueous granulating liquids.
- Thermolabile drugs preclude high-temperature processes (melt pelletization, hot melt extrusion), favouring aqueous extrusion–spheronization or solution/suspension drug layering instead.

#### Compatibility

- Drug–excipient compatibility must be established by differential scanning calorimetry (DSC), Fourier-transform infrared spectroscopy (FTIR), and accelerated stability studies before finalising the formulation matrix.

**Excipients Used in Pellet Formulation**

**Diluents / Fillers**

Diluents constitute the primary matrix when drug dose is low. They must be inert, non-hygroscopic, and compatible with the drug and binder system.

| Key Diluents and Their Roles |
|---|
| Microcrystalline Cellulose (MCC, Avicel PH 101/102) – The most critical excipient in extrusion–spheronization; acts as a molecular sponge, absorbing water into its fibrous structure to create a plastic, cohesive wet mass ideal for forming smooth spherical pellets. |
| Lactose (monohydrate / anhydrous) – Water-soluble diluent; modifies drug release by increasing hydrophilicity of the pellet matrix. Unsuitable for reducing-sugar sensitive drugs. |
| Dicalcium Phosphate Dihydrate – Insoluble, imparts high density and hardness; used for pellets requiring sustained or slow release. |
| Mannitol – Preferred for moisture-sensitive drugs (low hygroscopicity); also provides a pleasant mouthfeel for chewable pellet formulations. |
| Starch and Pregelatinised Starch – Provides cohesiveness and acts as a disintegrant when low drug loading pellets are desired. |

**Binders**

Binders promote inter-particulate cohesion, controlling pellet hardness, porosity, and drug release. Binder concentration and molecular weight significantly influence these properties.

- **Hydroxypropyl Methylcellulose (HPMC, Methocel):** Excellent binder and film former; concentration affects pellet hardness and drug release rate.
- **Polyvinylpyrrolidone (PVP / Povidone K25–K90):** Highly soluble; promotes rapid dissolution when used as binder; also used as a matrix former for solid dispersions in HME pellets.
- **Hydroxypropyl Cellulose (HPC, Klucel):** Thermoplastic binder used in hot melt extrusion at temperatures above its glass transition temperature (~105°C).
- **Gelatin:** Traditional binder for sugar-starter pellets; provides strong cohesion but may cause extended dissolution in older capsule shells.
- **Ethylcellulose:** Hydrophobic binder contributing to sustained release; used both as a matrix binder and as a functional coating polymer.

### Lubricants and Glidants

These excipients are added in small quantities to reduce friction, prevent sticking to equipment surfaces, and improve powder flow during processing.

- **Magnesium Stearate (0.1–1.0%):** Reduces die-wall friction; hydrophobic in nature, so excess may retard drug release.
- **Talc (1–5%):** Anti-adherent; prevents pellet-to-pellet sticking during coating operations.
- **Colloidal Silicon Dioxide (Aerosil):** Glidant that improves flowability of pellets during capsule filling.
- **Glyceryl Monostearate:** Lipid-based lubricant used in melt pelletization.

### Release-Modifying Polymers

The release-modifying polymer is arguably the most critical formulation decision in controlled-release pellet development. It determines the mechanism (diffusion, erosion, osmotic), rate, and location of drug release.

| Polymer | Type / Solubility | Application |
|---|---|---|
| Ethylcellulose (EC, Surelease, Aquacoat) | Hydrophobic, water-insoluble | SR film coat; diffusion-controlled release |
| Eudragit RS / RL | Quaternary ammonium, pH-independent | SR coat; RL more permeable than RS |
| Eudragit L100 / S100 | Anionic, pH 6.0 / pH 7.0 soluble | Enteric coating; intestinal/colonic targeting |
| HPMCAS (Aqoat) | Anionic, pH-dependent | Enteric coat; amorphous solid dispersions |
| HPMC (Methocel) | Hydrophilic, non-ionic | Hydrophilic matrix; erosion/diffusion SR |
| Carnauba Wax / Beeswax | Hydrophobic lipid | Melt pellet matrix; slow drug release |
| Poloxamers (Lutrol F68) | Non-ionic surfactant | Enhances wettability in SR matrices |

### Spheronization Aids

These excipients are essential in extrusion–spheronization to confer plasticity to the wet mass and enable rounding of extrudates into spheres.

- **MCC (primary):** The predominant spheronization enhancer. Typical concentration: 30–80% of formulation.
- **Kappa-Carrageenan:** Alternative to MCC; used for modified-release pellets; confers unique gel-like plasticity.
- **Sodium CMC (low viscosity):** Increases plasticity of the wet mass; used alongside MCC for highly hydrophobic drugs.
- **Chitosan:** Biopolymer with mucoadhesive properties; used in targeted delivery pellet systems.

### Surfactants and Solubilisers

- **Sodium Lauryl Sulphate (SLS, 0.1–2%):** Anionic surfactant; improves wettability and promotes dissolution of BCS Class II drugs.
- **Polysorbate 80 (Tween 80):** Non-ionic; enhances drug solubilisation and binder spreading.
- **Docusate Sodium (DOSS):** Combined surfactant and lubricant for poorly wettable drugs.

### Granulating Solvents

Water is the most commonly used granulating liquid due to its safety, low cost, and compatibility with most excipients. Non-aqueous solvents (ethanol, isopropanol, acetone) are used for moisture-sensitive or water-insoluble drugs. Mixed solvent systems (water–ethanol) control dissolution rate of the granulating liquid, affecting extrudate plasticity.

### Critical Quality Attributes (CQAs) Linked to Formulation

| Formulation-CQA Relationships |
|---|
| MCC concentration → Plasticity of wet mass → Sphericity and roundness of final pellets |
| Binder type/concentration → Inter-particulate cohesion → Pellet hardness and friability |
| Release polymer type/coat weight → Membrane permeability → Drug release rate and mechanism |

| |
|---|
| Drug particle size → Uniformity of distribution in matrix → Content uniformity (RSD) |
| Granulating liquid volume → Plasticity and extrudability → Pellet shape, size, and porosity |
| Surfactant concentration → Wettability of matrix → Drug dissolution rate |

## Pelletization Process:

**Pelletization** is the process of converting powders or granules into small spherical pellets.

**General Steps in Pelletization**

**Step 1: Mixing of Ingredients**

- API and excipients are blended to obtain a homogeneous mixture.

**Step 2: Wet Massing**

- Binder solution is added to produce a **plastic mass** suitable for extrusion.

**Step 3: Extrusion**

- Wet mass is forced through an **extruder** to produce cylindrical extrudates.

**Step 4: Spheronization**

- Extrudates are broken and rounded into spherical pellets using a **spheronizer**.

**Step 5: Drying**

- Pellets are dried using **fluidized bed dryers or tray dryers**.

**Step 6: Screening**

- Pellets are passed through sieves to obtain uniform size.

**Step 7: Coating (Optional)**

- Functional coating is applied for **modified or controlled drug release**.

## Pelletization Techniques

1. **Extrusion – Spheronization**
    - Most common method.
    - Produces highly spherical pellets.
2. **Layering Techniques**
    - Drug solution or powder layered onto inert cores.
    - Types:
        - Solution/Suspension layering
        - Powder layering

3. **Cryopelletization**
    - Droplets of drug solution are solidified using liquid nitrogen.
4. **Balling / Agitation**
    - Powders rolled into pellets in a rotating drum or pan.

## EQUIPMENT FOR MANUFACTURE OF PELLETS

The manufacture of pharmaceutical pellets employs a range of specialized equipment, each designed for a specific unit operation. The choice of equipment depends on the pelletization method, batch size, drug–excipient properties, regulatory requirements, and scale of production.

### Extruders

Extruders are the primary equipment in the extrusion–spheronization process. They force the wet mass through a die plate to produce cylindrical extrudates of defined diameter.

### Screw Extruder (Single and Twin Screw)

The most widely used extruder type. One or two Archimedean screws rotate inside a cylindrical barrel, conveying and pressurizing the wet mass toward the die plate. Single-screw extruders (co-rotating) are simpler; twin-screw extruders provide better mixing, distributive flow, and self-wiping action, producing more uniform extrudates. Twin-screw extruders are also the standard for hot melt extrusion.

- **Components:** Feed hopper, barrel (optionally jacketed), single/twin screws, breaker plate, die screen (0.5–2.0 mm holes), drive motor with variable speed.
- **Advantages:** Continuous operation, scalable, high throughput, suitable for a wide range of wet mass consistencies.
- **Limitations:** Frictional heat generation; not ideal for thermolabile drugs at high screw speeds.
- **Commercial examples:** Caleva, Alexanderwerk, Leistritz ZSE 18 HP-PH (HME).

### Sieve / Basket Extruder

The wet mass is pressed through a cylindrical screen or basket by rotating blades, paddles, or rollers. Extrusion force is relatively low, making it suitable for soft, fragile formulations or those prone to heat degradation.

- **Advantages:** Gentle processing, minimal heat generation, simple equipment.
- **Limitations:** Lower throughput compared to screw extruders; unsuitable for very stiff wet masses.

### Ram / Piston Extruder

A hydraulic or mechanical piston compresses the wet mass and forces it through a die in a batch-wise manner. Primarily used at laboratory scale for formulation development.

- **Advantages:** Very precise and controllable extrusion pressure; ideal for characterizing wet mass rheology.
- **Limitations:** Slow batch process; not scalable to production.

**Gear / Roll Extruder**

Two counter-rotating perforated rolls (gear wheels) compress wet mass into extrudates at high production rates. Each depression in the gear produces a discrete extrudate cylinder.

- **Advantages:** High production capacity; compact design.
- **Limitations:** Less suitable for sticky or very cohesive masses; cleaning and changeover are complex.

**Spheronizer (Marumerizer)**

The spheronizer is the definitive equipment for converting cylindrical extrudates into spherical pellets. It consists of a stationary cylindrical chamber and a rotating friction plate at the base.

**Design and Working Principle**

The friction plate carries a crosshatched (waffle-type) or knurled pattern and rotates at 600–2000 rpm. Extrudates fed into the chamber experience:

- Centrifugal force: propels particles toward the wall
- Friction with plate: imparts rotational motion to each particle
- Wall collision and gravity: create the toroidal (rope-like) flow

The combination of these forces breaks extrudates into uniform lengths, rounds the ends, and progressively shapes them into smooth spheres within 2–10 minutes.

**Key Parameters**

- **Plate rotation speed:** Higher speed → better sphericity but risk of fracture and fines generation.
- **Spheronization time:** Optimised to achieve desired sphericity without over-working (which causes thermal softening or moisture loss).
- **Batch load:** Correct mass load ensures sufficient inter-particle collisions without overloading.
- **Commercial examples:** Caleva Spheronizer, Glatt GPCG Spheronizer, LCI Marumerizer.

**High-Shear Mixer–Granulator**

Used for wet massing in extrusion–spheronization and for melt pelletization. Consists of a stainless-steel mixing bowl with a bottom-driven main impeller and a side-mounted chopper blade.

- **Impeller:** Generates intensive shear and distributive mixing; ensures uniform hydration and binder distribution.
- **Chopper:** High-speed secondary blade breaks large agglomerates and controls granule size.
- **Jacketed bowl:** Circulating hot or cold water enables controlled heating (for melt pelletization) or cooling (for solidification).
- **Process monitoring:** Motor current/torque curves, power consumption, and acoustic emission sensors can detect wet mass endpoint.
- **Commercial examples:** Diosna P-series, Collette Gral, Fielder PMA, Bohle BM.

**Fluid Bed Processor (FBP)**

The fluid bed processor is the most versatile equipment platform in pellet manufacture, performing drying, direct pelletization, drug layering, and functional coating within a single closed system.

**General Design**

Heated, filtered air is forced upward through a perforated distributor plate (product bowl screen) at a velocity sufficient to fluidize and suspend pellet particles. A liquid spray system (two-fluid or peristaltic pump-driven nozzle) deposits liquid droplets onto fluidized particles. A bag filter or cyclone at the outlet retains fine particles.

**Fluid Bed Dryer (FBD)**

After spheronization, wet pellets are loaded into the FBD product bowl. Hot air (inlet temperature 40–80°C, product temperature typically 30–50°C) gently and uniformly dries the pellet bed to < 2% moisture in 15–60 minutes, far faster and more uniform than tray drying. Inlet air temperature, volume flow, and product temperature are closely controlled to prevent pellet deformation or melting.

**Wurster Coater (Bottom-Spray FBP)**

The Wurster configuration is the pharmaceutical industry gold standard for pellet coating. A cylindrical partition tube (Wurster insert) sits centrally above the air distributor plate. The air velocity beneath the insert is higher than in the surrounding annular region, propelling pellets upward through the spray zone for coating and then downward in the annulus for drying and recirculation.

- **Advantages:** Highly uniform coat thickness; minimal aggregation; suitable for all functional coating types.

- **Scale range:** Laboratory (0.5 L) to production (1200 L).
- **Commercial examples:** Glatt GPCG, Aeromatic Fielder Strea-1, Vector FLM.

**Rotary Fluid Bed Granulator (Tangential-Spray)**

A motorised rotating disc at the bottom of the processing chamber creates a combined rotational, centrifugal, and upward fluidization motion (helicoidal path). This maximises particle–particle and particle–wall collisions, producing very dense, smooth, spherical pellets ideal for powder layering and direct pelletization.

- **Particularly effective for:** High drug-load powder layering; producing high-density pellets for capsule filling.
- **Commercial examples:** Glatt Rotor Insert (GPCG-Rotor), Freund CF Granulator, Vector FL-M.

**Pan Coater / Perforated Pan Coater**

Rotating pan coaters (conventional or perforated) are used for large-scale film coating and sugar coating of pellets. Pellets tumble in the rotating drum while spray guns apply coating solution and drying air is blown directly through the perforated drum wall (in perforated pan designs) or across the pellet bed (conventional pan).

- **Advantages:** Low equipment cost; very high batch capacity (up to several hundred kg).
- **Limitations:** Poorer coating uniformity than Wurster; risk of pellet attrition from mechanical tumbling forces; not suitable for fragile pellets or thin sustained-release coatings.
- **Commercial examples:** O'Hara Labcoat M, Thomas Engineering Accela-Cota, Manesty Spansule coater.

**Hot Melt Extruder (HME System)**

The HME system consists of a gravimetric powder feeder, heated twin-screw extruder barrel (multiple independently controlled heating zones), die head, and downstream pelletizing unit.

**Downstream Pelletizing Options**

- **Strand pelletizer:** Extrudate is cooled on a conveyor belt and cut into segments by rotating blades; produces cylindrical pellets that may require downstream spheronization.
- **Underwater pelletizer:** Die face is submerged; rotating blades cut extrudates as they emerge; water-quenched pellets are spherical and smooth.
- **Hot-face pelletizer:** Blades cut at the die face in open air; pellets are air-cooled; fastest method.

- **Commercial examples:** Thermo Fisher Process 11, Leistritz ZSE 18/27, Berstorff ZE 25, Coperion ZSK.

### Cryogenic Pelletization System

The cryogenic pelletization unit comprises a precision metering pump, a spray/droplet-generation nozzle, a liquid nitrogen cryogenic bath, a conveyor belt or rotating drum submerged in (or passing over) the liquid nitrogen, and a freeze-dryer (lyophilizer) for final product drying.

- **Applications:** Biopharmaceuticals (proteins, vaccines, mRNA formulations), thermolabile small molecules.
- **Advantages:** Extremely gentle processing; preserves biological activity; excellent sphericity.

**Limitations:** High equipment and operational cost; limited batch size; specialized infrastructure required.

## QUALITY EVALUATION OF PELLETS

Comprehensive quality evaluation is essential to ensure that pellets meet pharmacopoeial standards and product-specific specifications across physical, chemical, and functional dimensions.

| Test / Parameter | Method / Acceptance Criteria |
|---|---|
| Particle Size Distribution | Sieve analysis or laser diffraction; D50, D90; Span = (D90−D10)/D50 < 0.5 |
| Shape / Sphericity | Image analysis; Shape Factor ≥ 0.90; Aspect Ratio ≈ 1.0 |
| Surface Morphology | Scanning Electron Microscopy (SEM) |
| Bulk & Tapped Density | USP <616>; Carr's Index < 15%; Hausner Ratio < 1.25 |
| Friability | Roche friabilator, 100 rotations; weight loss < 0.5% |
| Mechanical Strength | Texture Analyser; crushing force (product-specific) |
| Drug Content Assay | HPLC or UV spectrophotometry; 95–105% of label claim |

| | |
|---|---|
| Content Uniformity | RSD < 2.0% across ≥ 10 pellet samples |
| Moisture Content | Karl Fischer Titration or Loss on Drying (LOD); < 2.0% |
| Porosity / Internal Structure | Mercury intrusion porosimetry; Micro-CT imaging |
| In Vitro Drug Release | USP Apparatus I/II or IV; profile at specified pH media; f2 ≥ 50 |
| Coat Weight Gain | Gravimetric measurement; typically 5–25% for SR/EC coats |







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