Unit-5

Industrial Pharmacy-1

B.Pharma 5th Sem Notes

Unit: 5

Cosmetics:

- Formulation and preparation of the following cosmetic preparations: lipsticks, shampoos, cold cream and vanishing cream, tooth pastes, hair dyes and sunscreens.

Pharmaceutical Aerosols:

- Definition, propellants, containers, valves, types of aerosol systems; formulation and manufacture of aerosols; Evaluation of aerosols; Quality control and stability studies.

Packaging Materials Science:

- Materials used for packaging of pharmaceutical products, factors influencing choice of containers, legal and official requirements for containers, stability aspects of packaging materials, quality control tests.

Cosmetics:

Cosmetics are preparations applied externally to the human body (skin, hair, nails, lips, and external genital organs) for cleansing, beautifying, promoting attractiveness, or altering appearance without affecting body structure or functions.

Lipsticks:

Definition:

A lipstick is a cosmetic product applied to the lips to add colour, moisture, and protection. It contains a combination of waxes, oils, pigments, emollients, and preservatives moulded into a stick.

Composition / Formulation

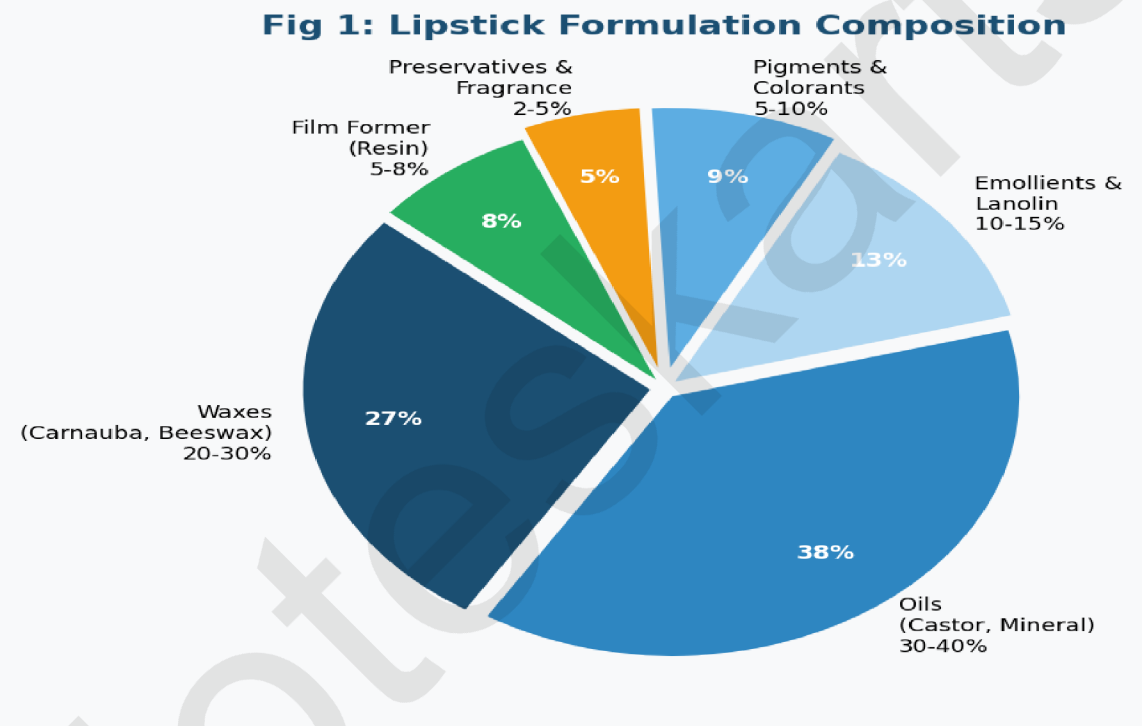

Fig 1: Typical Lipstick Formulation Composition

Ingredient	Examples	Function	% Range
Waxes	Carnauba wax, Beeswax, Candelilla wax	Structural rigidity, moulding	20–30%
Oils	Castor oil, Mineral oil, Lanolin oil	Gloss, spreadability	30–40%
Emollients	Isopropyl myristate, Lanolin	Moisturisation, feel	10–15%
Pigments & Dyes	D&C Red, Iron oxides, TiO2	Colour, opacity	5–10%
Film Formers	Polyvinylpyrrolidone (PVP)	Adhesion, gloss retention	5–8%

Preservatives	Methylparaben, BHA	Microbial protection	0.1–0.3%
Fragrance / Flavour	Rose, vanilla, mint	Masking odour, appeal	0.5–2%
Sunscreen agents	Octinoxate, Zinc oxide	UV protection (SPF variants)	0–8%

Manufacturing Process

1. Melt waxes (carnauba, beeswax) in a jacketed kettle at 80–85°C.
2. Add oils and emollients gradually with continuous stirring.
3. Incorporate pigments and colorants by passing through a three-roller mill.
4. Add preservatives, fragrance, and any active agents at 60–65°C.
5. Pour the molten mass into pre-cooled metal moulds (about 5–10°C).
6. De-mould, inspect for uniformity, and flame-pass the sticks for a glossy finish.
7. Assemble into the lipstick case, cap, and label.

Quality Control Tests

- Melting Point Test: 55–75°C (ensures stability during storage)
- Breaking Strength: Minimum load required to break the stick (≥ 300–500 g)
- Surface Texture & Bloom: Visual examination for smoothness
- Rub-out Test: Uniform colour deposition on skin
- Stability Testing: 45°C / 75% RH for 3 months; check for rancidity, color change
- Skin Irritation & Patch Test: Dermatological safety assessment

Shampoos

Definition

A shampoo is an aqueous cosmetic preparation used for cleaning the scalp and hair. It contains detergents (surfactants), conditioning agents, preservatives, and functional additives.

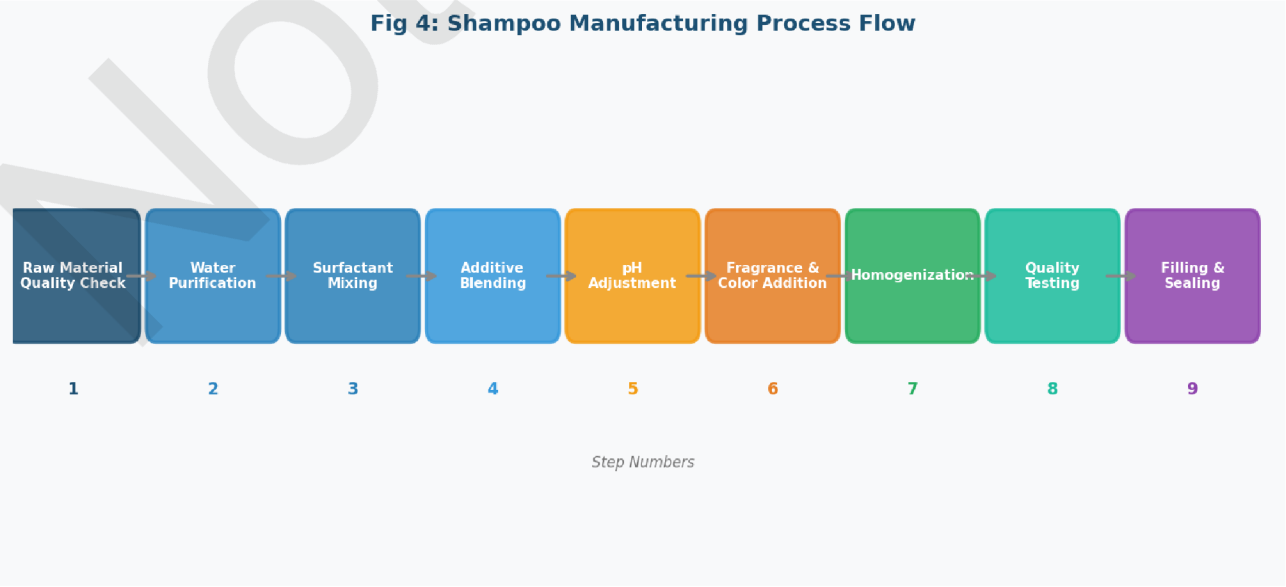

Fig 4: Shampoo Manufacturing Process Flow

Classification

Type	Key Feature	Suitable For
Clear/Transparent	High surfactant; no opacifier	Normal hair
Cream/Lotion	Emulsified with conditioning agents	Dry/damaged hair
Conditioning	Contains cationic polymers / silicones	Chemically treated hair
Medicated/Anti-dandruff	Zinc pyrithione, selenium sulfide, ketoconazole	Dandruff, seborrheic dermatitis
Dry Shampoo	Starch/talc aerosol base; no rinsing	Travel, convenience
Baby Shampoo	Amphoteric surfactants; tear-free, mild	Infants & sensitive scalp

Formulation Ingredients

- Primary Surfactant: Sodium Lauryl Sulphate (SLS), SLES — cleansing, foaming
- Secondary Surfactant: Cocamidopropyl Betaine — mildness, foam stability
- Conditioning Agents: Quaternary ammonium compounds, dimethicone, panthenol
- Thickeners: NaCl (2–4%), Carbomer, Hydroxyethylcellulose
- Preservatives: Methylparaben, Phenoxyethanol (0.1–0.3%)
- Opacifying Agents: Glycol distearate, TiO2 (for pearlescent effect)
- Active Ingredients: Zinc pyrithione (anti-dandruff), Biotin (hair growth)
- Chelating Agents: EDTA — prevents mineral buildup
- Fragrance & Colorants: Approved cosmetic grade

Manufacture

1. Heat deionised water to 60–70°C in the main mixing vessel.
2. Add SLES slowly with gentle mixing to avoid excess foam.
3. Incorporate secondary surfactants and conditioning polymers.
4. Add thickeners and opacifiers; allow to homogenise.
5. Cool to 40°C; add heat-sensitive ingredients (fragrance, preservatives, actives).
6. Adjust pH to 5.0–6.5 with citric acid or NaOH.
7. Quality check: viscosity, pH, foam, clarity; fill and seal.

Cold Cream and Vanishing Cream

Cold Cream

Cold cream is a W/O (water-in-oil) emulsion used for cleansing, moisturising, and protecting the skin. The name arises from the cooling sensation on application due to water evaporation.

Ingredient	Amount (g/100 g)	Role
White beeswax	12.0	Emulsifier, stiffening agent
Cetyl esters wax	2.5	Emollient, consistency
White mineral oil (heavy)	56.0	Emollient base
Sodium borate (Borax)	0.5	Emulsifier (reacts with beeswax)
Purified water	28.5	Aqueous phase
Fragrance	0.5	Perfuming
Preservative (methylparaben)	0.1–0.2	Antimicrobial

Preparation: Heat oil phase (wax + mineral oil) to 70°C. Dissolve borax in hot purified water. Add aqueous phase to oil phase slowly with stirring. Cool with continuous mixing to form stable W/O emulsion. Add fragrance at 40°C.

Vanishing Cream

Vanishing cream is an O/W (oil-in-water) emulsion with high water content. It is absorbed rapidly by the skin leaving no visible greasy film — hence 'vanishing'. Used as a moisturiser and as a base for medicated and colour cosmetics.

Ingredient	Amount (g/100 g)	Role
Stearic acid	15.0	Emulsifier + gives pearlescent body
Glycerol monostearate (GMS)	2.0	Co-emulsifier
Glycerin	5.0	Humectant
Potassium hydroxide (KOH)	0.7	Neutralises stearic acid → soap emulsifier
Purified water	76.5	Continuous aqueous phase
Preservative	0.2	Antimicrobial protection
Fragrance	0.3	Perfuming

Feature	Cold Cream (W/O)	Vanishing Cream (O/W)
Emulsion type	Water-in-Oil (W/O)	Oil-in-Water (O/W)
Feel on skin	Greasy, heavy	Light, non-greasy
Disappearance	Remains visible	'Vanishes' on application
Primary use	Cleansing, night cream	Day cream, make-up base
Moisture retention	Occlusive – high retention	Non-occlusive – breathable
Key emulsifier	Borax + beeswax	Potassium stearate (soap)

Toothpastes

Definition

A toothpaste (dental cream) is a gel or paste used with a toothbrush to clean teeth, promote oral hygiene, and prevent cavities, gingivitis, and plaque formation.

Formulation Composition

Ingredient Category	Example Ingredients	% Concentration	Function
Abrasives	Hydrated silica, CaCO3, DCPD	20–40%	Remove plaque & stains
Humectants	Glycerin, Sorbitol, PEG	20–35%	Prevent drying, maintain texture
Water	Purified water	20–40%	Solvent, consistency
Binders/Thickeners	Carrageenan, CMC, Carbomer	0.5–2%	Stability, prevent syneresis
Detergents	Sodium Lauryl Sulphate (SLS)	1–2%	Foaming, cleaning
Fluoride Compounds	Sodium fluoride, MFP	0.05–0.15% F	Anticaries activity
Antimicrobials	Triclosan, CPC, Zinc citrate	0.1–0.3%	Antibacterial, antigingivitis
Sweeteners	Sodium saccharin	0.1–0.3%	Taste improvement
Flavours	Peppermint, spearmint oil	1–1.5%	Freshness, palatability
Preservatives	Methylparaben, Na benzoate	0.05–0.1%	Microbial protection
Whitening Agents	H2O2, pyrophosphates	Varies	Stain removal

Manufacture of Toothpaste

1. Prepare the humectant blend (glycerin + sorbitol + water) with heating if needed.
2. Disperse thickeners/gums in the humectant blend under high shear to avoid lumps.
3. Add abrasives slowly to the paste under vacuum mixing.
4. Dissolve fluoride and antimicrobial agents separately in water; incorporate.
5. Add SLS as a pre-dissolved solution; avoid excessive aeration.
6. Incorporate flavours, sweeteners, colourants, and preservatives at low temperature.
7. De-aerate the paste under vacuum; adjust pH to 6.0–8.0.
8. Fill into aluminium/plastic tubes under controlled conditions; seal and label.

Quality Control Tests

- pH: 6.0–8.0 (protects enamel; too acidic is erosive)
- Viscosity / Consistency: Measured using a viscometer at 25°C
- Fluoride Content: Ion-selective electrode method (must meet BP/USP limit)
- Foaming Power: Shake test; foam volume measurement
- Abrasivity Index (RDA): Radioactive dentin abrasion — must be ≤ 250
- Microbial Tests: Total aerobic count, absence of pathogens
- Stability: 40°C/75% RH for 3 months — check syneresis, colour, odour

Hair Dyes

Classification of Hair Dyes

Type	Duration	Mechanism	Common Agents
Temporary	1–2 washes	Surface deposition; no penetration	Azo dyes, D&C dyes; rinse gels
Semi-permanent	6–8 washes	Partial penetration into cortex	Nitro dyes, low MW direct dyes
Quasi-permanent / Demi	10–15 washes	Slight oxidation; no ammonia	Low H_2O_2 + small oxidation dyes
Permanent	Until new growth	Oxidative coupling in cortex	p-Phenylenediamine (PPD) + H_2O_2
Natural / Herbal	Semi-permanent	Metallic/plant pigment binding	Henna (Lawsone), Indigo

Permanent Hair Dye – Formulation & Mechanism

Permanent hair colouration is a two-component system mixed just before use:

- Component A (Developer / Oxidation Base): Contains primary intermediate (e.g. PPD, PTD), couplers (resorcinol, naphthol), ammonia/alkalising agent, surfactants, conditioners.
- Component B (Oxidant / Developer): H_2O_2 (3–12%), stabilisers, acidic pH buffer.

Steps of Oxidation Colouration:

1. Ammonia swells and opens the hair cuticle.
2. Oxidation intermediates and H_2O_2 penetrate into the cortex.
3. H_2O_2 oxidises intermediates to reactive quinone-imine species.
4. Quinone-imines couple with coupler molecules to form large, coloured azo/indamine dye molecules — too large to diffuse out.
5. Excess H_2O_2 lightens natural melanin (simultaneous bleaching + colouring).

Safety Concern: PPD is a known sensitiser. Patch test 48 hours before use is mandatory. EU Cosmetics Regulation 1223/2009 regulates permissible concentrations.

Sunscreens

Definition & Importance

Sunscreens are topical preparations that absorb, reflect, or scatter ultraviolet (UV) radiation, protecting skin from UVA (320–400 nm) and UVB (280–320 nm) radiation. They prevent sunburn, photoaging, and skin cancer.

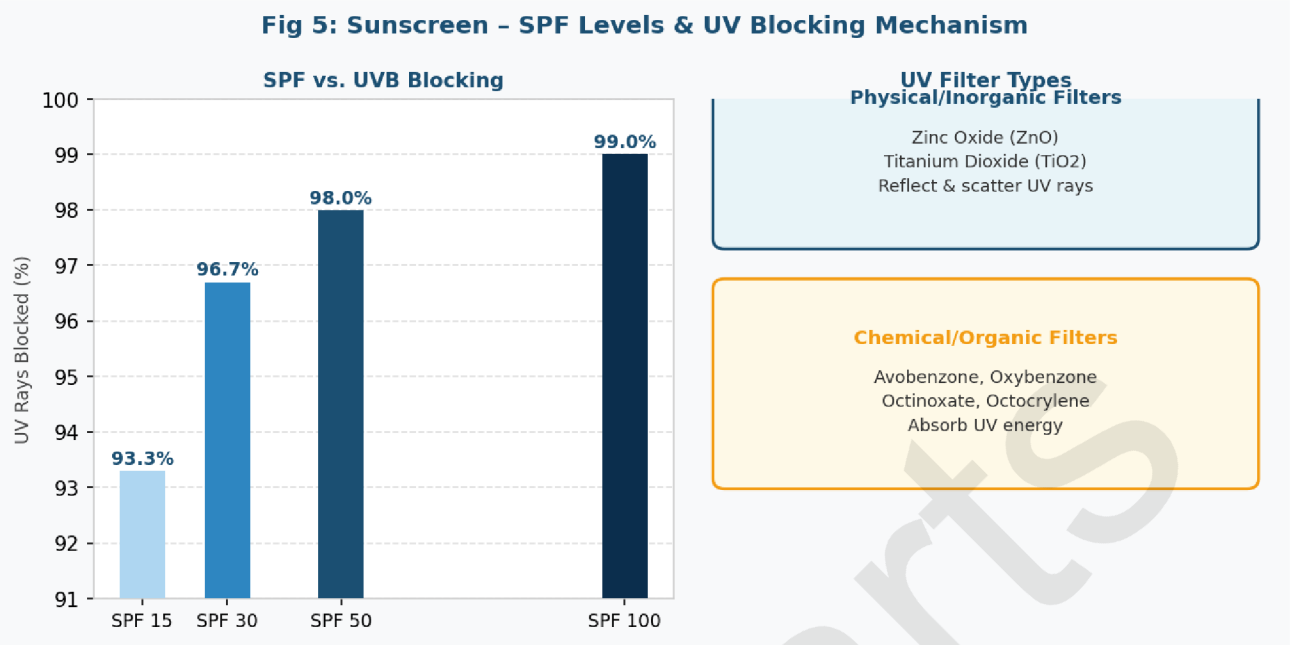

Fig 5: SPF Levels vs. UVB Blocking & UV Filter Types

Types of UV Filters

Filter Type	Examples	UV Range	Mechanism
Physical / Inorganic	Zinc oxide (ZnO), Titanium dioxide (TiO2)	UVA + UVB (broad spectrum)	Reflect and scatter UV photons
Chemical / Organic	Avobenzone, Oxybenzone, Octinoxate, Octocrylene	UVA and/or UVB (specific)	Absorb UV energy; undergoes photochemical reaction
Combination	ZnO + Avobenzone blend	Full UVA + UVB	Synergistic broad-spectrum protection

SPF – Sun Protection Factor

SPF measures UVB protection: SPF 30 blocks ~96.7%, SPF 50 blocks ~98%, SPF 100 blocks ~99% of UVB. For UVA, the PA (Protection Grade of UVA) or Critical Wavelength ≥ 370 nm is used.

Typical Sunscreen Formulation (SPF 50 Emulsion)

Ingredient	Concentration	Role
Zinc oxide (micro/nano)	10–15%	Physical UVA/UVB blocker
Octinoxate / Ethylhexyl methoxycinnamate	7.5%	Chemical UVB absorber
Avobenzone (Butyl methoxydibenzoylmethane)	3%	Chemical UVA absorber
Octocrylene	5–10%	Photostabiliser for Avobenzone
Emollient base (caprylic/capric triglyceride)	10–15%	Skin feel, dispersion

Emulsifiers (cetearyl alcohol, PEG-100 stearate)	2–5%	O/W emulsion stability
Humectant (glycerin)	3–5%	Skin hydration
Polymer film former	0.5–1%	Water resistance
Antioxidants (Vitamin E, C)	0.5–1%	Prevent oxidative degradation
Preservatives	0.2–0.5%	Microbial protection
Water	q.s. to 100%	Continuous phase

Evaluation of Sunscreens

- In vitro SPF: Spectrophotometric method (diffuse transmittance) — ISO 24443
- In vivo SPF: Human skin MED (minimal erythema dose) test — ISO 24444
- Broad Spectrum Test: Critical wavelength ≥ 370 nm; UVA/UVB ratio
- Water Resistance: Compare SPF before and after 40 min / 80 min water immersion
- Photostability: UV exposure; measure filter content by HPLC post-exposure
- Skin Safety: Dermatological testing, repeat insult patch test (RIPT)

Pharmaceutical Aerosols

Definition

A pharmaceutical aerosol is a pressurised dosage form that upon activation delivers a fine dispersion of liquid, solid, or semisolid material in a gaseous medium. The system relies on a propellant contained in a sealed pressurised container to generate the energy needed for product discharge.

Characteristics:

- Self-contained, one-step patient administration
- Delivers medication to target sites (lungs, skin, nasal mucosa)
- Reproducible metered doses
- Protection of active ingredient from contamination and degradation

Propellants

Propellants are the source of propulsive energy, providing the pressure necessary to expel the contents in the desired particle size. They may also act as solvents or carriers for the active drug.

Propellant Class	Examples	Boiling Point (°C)	Application
Chlorofluorocarbons (CFCs) – Banned	CFC-11, CFC-12, CFC-114	–30 to +24	Historic MDIs (phased out – Montreal Protocol)
Hydrofluorocarbons (HFCs)	HFA 134a (CH_2FCF_3), HFA 227ea	–26 to –16.5	Modern MDIs; zero ozone depletion
Hydrocarbons	Propane, n-Butane, Isobutane	–42 to –1	Topical & non-inhalation aerosols
Compressed Gases	N_2, CO_2, N_2O	N/A (gas at RT)	Solution aerosols; foam systems (N_2O)
Dimethyl ether (DME)	CH_3-O-CH_3	–24.9	Topical foams; solvent–propellant

Desirable Properties of Propellants

- Adequate vapour pressure (15–90 psi) at room temperature
- Non-toxic, non-flammable (preferred for inhalation)
- Chemically stable and inert toward container, valve, and drug
- Odourless, tasteless (critical for oral/nasal aerosols)
- Reasonable cost; availability

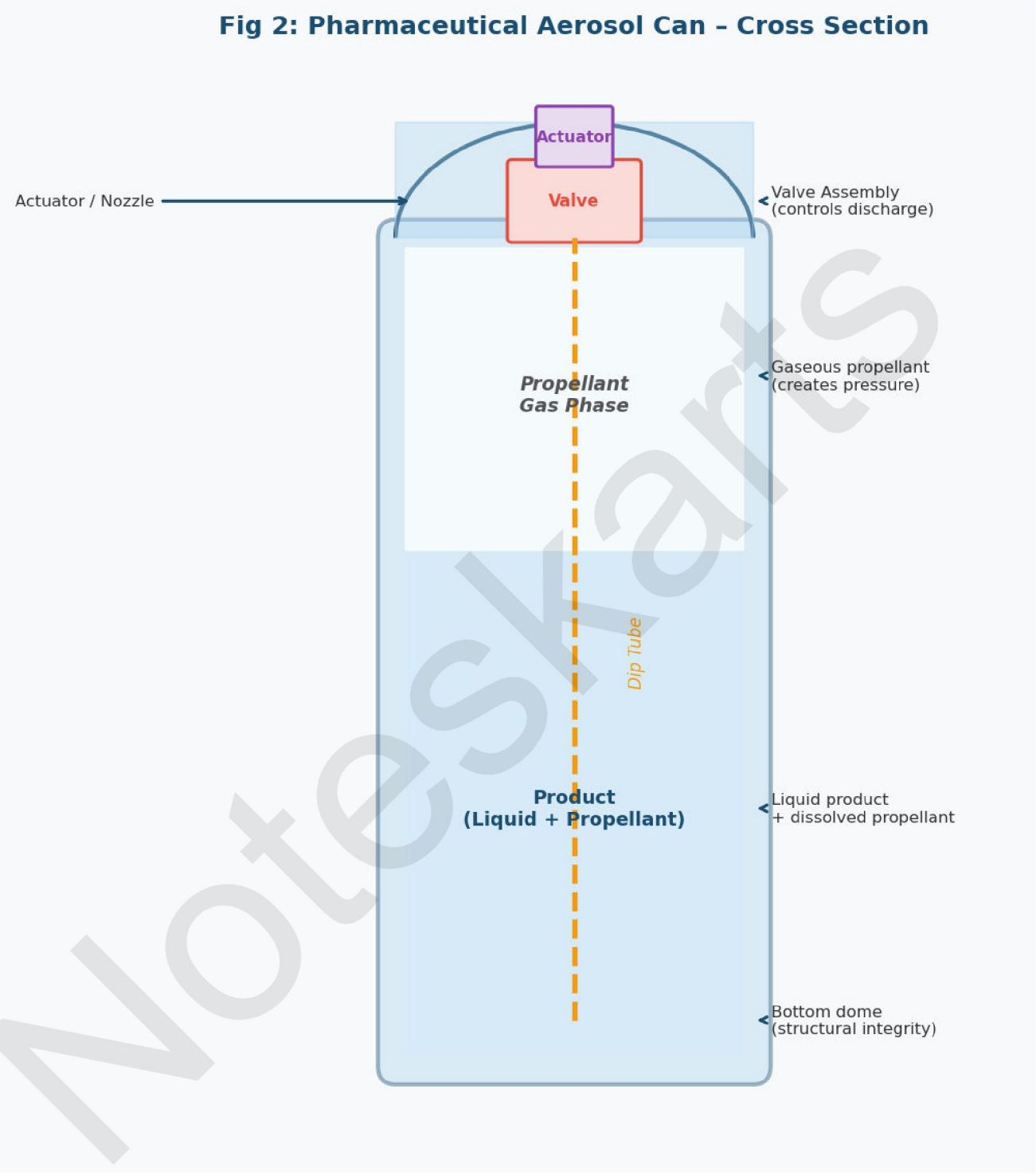

Fig 2: Pharmaceutical Aerosol Can — Internal Cross Section

Container Type	Material	Pressure Rating	Advantages	Disadvantages
Tinplate	Steel + tin coating	Up to 180 psi	Cheap, versatile, printable	Corrosion risk with aqueous products
Aluminium	Aluminium alloy	Up to 150 psi	Lightweight, corrosion-resistant, seamless	More expensive than steel
Stainless Steel	304/316 SS	Very high	Maximum chemical resistance	Expensive; heavy
Glass (coated)	Borosilicate glass + PVC sleeve	Up to 60 psi	No metal–drug interaction; clarity	Fragile; limited pressure
Plastic (HDPE/PP)	High-density polyethylene	Low (<25 psi)	Lightweight; flexible shapes	Limited to low-pressure systems

Valves

The valve is the most critical engineering component of an aerosol. It controls the rate, pattern, and dose of product delivery. Types include:

Valve Type	Description	Application
Continuous-spray valve	Delivers product as long as actuator is depressed	Topical sprays, insecticides
Metered-dose valve (MDV)	Delivers a precise, reproducible dose per actuation (25–100 µL)	MDIs for asthma, COPD
Foam valve	Incorporates a foam actuator; releases product as foam	Shaving cream, wound foam
Powder valve	Large orifice; avoids clogging with micronised powders	Topical powder aerosols, DPIs

Valve Components

- Mounting Cup / Ferrule: Crimped to can; holds valve in place
- Valve Body / Housing: Chamber that holds metered dose volume
- Stem: Central rod with orifice; depressed by actuator to open valve
- Spring: Returns stem to closed position after actuation
- Gaskets (Inner & Outer): Provide pressure seal; critical for leakage prevention
- Dip Tube: Extends to bottom of can; allows liquid uptake

Types of Aerosol Systems

System Type	Propellant Role	Product Form	Examples
Solution System	Solvent + propellant; drug dissolved	Fine liquid mist	Salbutamol MDI (HFA 134a)
Suspension System	Propellant; micronised solid suspended	Mist of fine particles	Beclometasone MDI
Emulsion / Foam System	Dispersed in water-based product	Foam or lotion	Topical steroid foam
Powder System (DPI)	None or compressed gas only	Dry powder cloud	Turbuhaler, Accuhaler
Two-phase System	Liquefied propellant + product	Spray/mist	Topical antiseptics
Three-phase System	Propellant + aqueous + concentrate	Foam or spray	Hair mousse, shaving gel

Formulation of Pharmaceutical Aerosols

Key Formulation Considerations

- Particle Size: For pulmonary deposition — MMAD 1–5 µm; nasal — 5–10 µm
- Propellant Selection: HFA 134a / HFA 227ea for inhalation; LPG for topical
- Co-solvents: Ethanol (up to 15%) to increase drug solubility in propellant
- Surfactants / Lubricants: Oleic acid, lecithin — prevent valve clogging, stabilise suspension
- pH / Tonicity: Important for nasal aerosols; 6.0–7.4 for nasal solutions
- Preservatives: Benzalkonium chloride (nasal), benzyl alcohol (topical)

Manufacture of Aerosols

Cold Filling Process

1. Cool propellant (and concentrate if applicable) to −30°C to −40°C.
2. Fill pre-chilled concentrate into can at low temperature.
3. Add liquefied propellant quickly (< 30 seconds) to minimise vaporisation.
4. Crimp valve immediately while product is still below boiling point.

Used for: systems where product cannot withstand pressure; simple solution aerosols.

Pressure Filling Process

1. Place concentrate in container; crimp valve onto can.
2. Connect filling head to valve stem.
3. Inject propellant under pressure through the valve into the sealed container.
4. Check for leaks; verify net fill weight.

Used for: most pharmaceutical aerosols; preferred for good GMP control.

Under-Cap Filling (Gassing Method)

1. Fill concentrate into open container.
2. Place valve loosely over opening.
3. Inject propellant under cap before crimping under high-speed machines.

Evaluation of Aerosols

Test	Method / Equipment	Acceptance Criteria
Spray Rate / Output	Weigh before and after 5-second actuation; calculate g/s	Within ±10% of label claim
Net Fill Weight / Content	Gravimetric; tare can then weigh	Within ±5% label claim
Delivered Dose Uniformity	Dose Uniformity Sampling Apparatus (DUSA); n=10	RSD ≤ 15%; all doses 75–125% label
Particle Size (MMAD)	Cascade impactor (NGI / ACI); laser diffraction	MMAD 1–5 µm for inhaled
Fine Particle Fraction (FPF)	NGI — mass fraction < 5 µm	FPF ≥ 20–40% (product dependent)
Pressure Test	Pressure gauge at 20°C and 55°C	Pressure within label specification
Leakage Test	Weigh at t=0 and t=3 days; calculate loss	Loss ≤ 3.5% per year (BP)
Valve Delivery / Shot Weight	Actuate; collect and weigh	CV ≤ 5% between actuations
Number of Deliveries	Count actuations until no spray	≥ Stated number on label
Identification & Assay	HPLC / UV spectroscopy	Drug content 90–110% label
Moisture Content	Karl Fischer titration	Specified limit (critical for CFC-free)

Quality Control and Stability Studies

Quality Control Tests

- Sterility Test: Aseptic technique / membrane filtration (for sterile aerosols)
- Particulate Matter: Light obscuration or membrane filtration
- Label Claim (Assay): Drug content per actuation by HPLC
- Microbial Limit Test: Non-sterile aerosols must comply with BP/USP limits
- Container Inspection: Seam integrity, dent-free, no corrosion

Stability Studies — ICH Q1A Guidelines

Storage Condition	Temperature / RH	Duration	Parameters Monitored
Long-term (Zone I/II)	25°C / 60% RH	12–24 months	Assay, DDU, MMAD, leakage, valve function
Accelerated	40°C / 75% RH	6 months	All above; accelerated degradation
Intermediate	30°C / 65% RH	6 months	If significant change at 40°C
Photostability	ICH Q1B conditions	Per protocol	Appearance, assay, propellant stability
Inverted / Horizontal	25°C	3 months	Valve clogging, leakage, foam collapse

Stability Failure Indicators

- Loss of propellant pressure — valve/crimp failure
- Decrease in delivered dose — valve corrosion or drug degradation
- Increase in MMAD — aggregation/growth of suspension particles
- Drug precipitation in solution aerosols
- Corrosion of metal container by aqueous formulations

Packaging Materials Science

Introduction

- Pharmaceutical packaging is an integral part of a drug product.
- It protects the drug from physical, chemical, and microbiological deterioration, ensures safety and integrity during distribution, and provides information to the user.
- The packaging system includes the primary, secondary, and tertiary containers.

Packaging Level	Definition	Examples
Primary Container	In direct contact with the drug product	Ampoule, blister, bottle, vial
Secondary Container	Encloses primary container; not in direct contact	Carton, sleeve, tray
Tertiary/Transport	Bulk grouping for distribution and transport	Corrugated box, shipper, pallet

Materials Used for Packaging

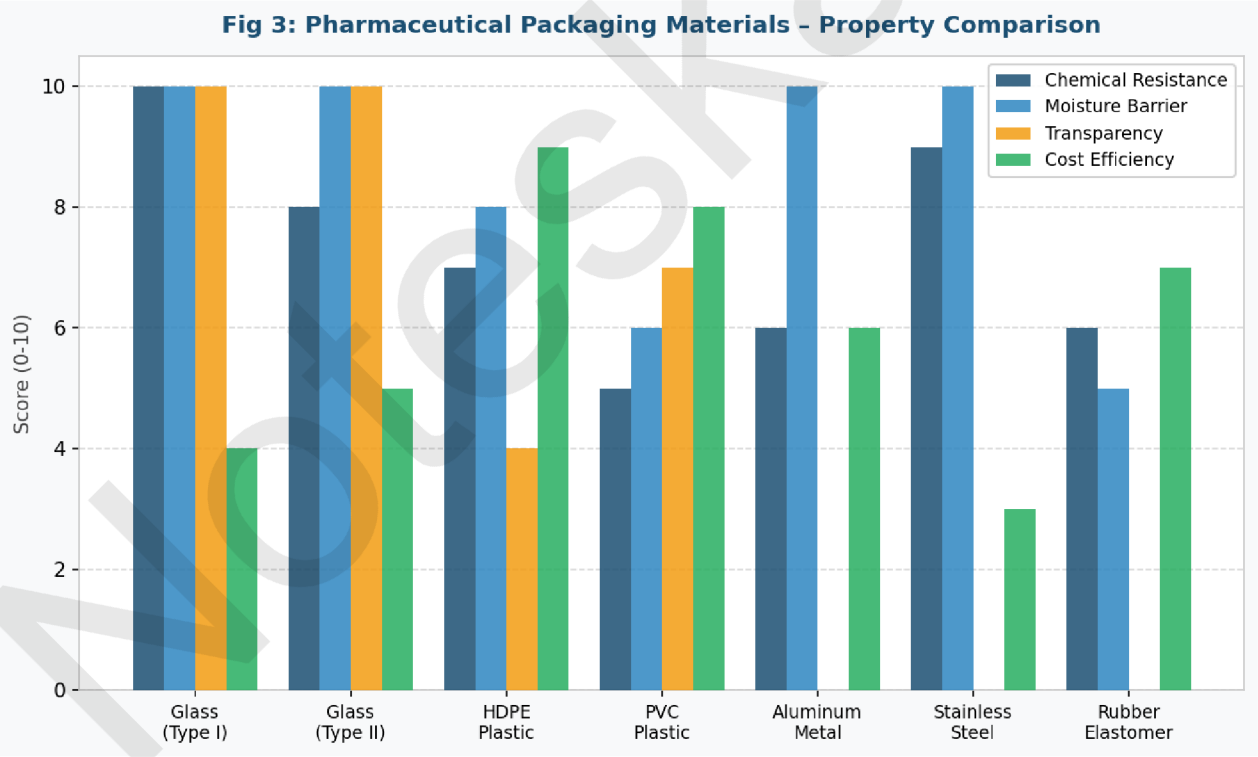

Fig 3: Pharmaceutical Packaging Materials — Property Comparison

A. Glass

Glass is the most widely used pharmaceutical packaging material owing to its chemical inertness, impermeability, and transparency.

Glass Type	Description	Hydrolytic Resistance	Typical Use
Type I (Borosilicate)	High boron content; very low thermal expansion	Highest (USP Class I)	Injections, biological products, SVP/LVP
Type II (Treated Soda-lime)	Soda-lime + sulphur/ammonium treatment	High (USP Class II)	Aqueous injections (neutral/acidic pH)
Type III (Soda-lime)	Regular soda-lime glass; higher leachables	Moderate (USP Class III)	Oral/topical liquids, parenteral powders
Type NP (General Purpose)	Non-parenteral soda-lime	Lowest	Oral liquids, tablets, capsules

B. Plastic Polymers

Polymer	Key Properties	Pharmaceutical Use
HDPE (High-Density PE)	Chemically resistant, rigid, moisture barrier	Tablet/capsule bottles, LDPE dropper bottles
PET (Polyethylene Terephthalate)	Clarity, strong gas barrier, lightweight	Oral liquid bottles, medical devices
PVC (Polyvinyl Chloride)	Flexible, formable, good clarity	Blister packs, IV bags, tubings
Polypropylene (PP)	Autoclavable (121°C), rigid, heat-stable	Syringes, closures, infusion bags
PVDC (Polyvinylidene Chloride)	Excellent moisture and gas barrier	Blister foil laminate (aluminium-PVDC)
COP/COC (Cyclic Olefin)	Ultra-low extractables, clarity, low protein binding	Pre-filled syringes, vials for biologics

C. Metals

- Aluminium: Excellent barrier properties; used for blister foil (cold-form or push-through), aerosol cans, tubes, collapsible tubes. Anodised or lacquered to prevent drug–metal interaction.
- Stainless Steel: Used in manufacturing equipment and high-pressure containers.
- Tin-plated Steel: Aerosol cans, ointment tins.

D. Rubber and Elastomers

- Used as closures (stoppers, plungers, tip caps) for vials, syringes, and cartridges.
- Natural Rubber (latex): Good elasticity; allergy risk — being replaced.
- Butyl Rubber (IIR): Low gas permeability; excellent for multi-dose vials (withstands repeated needle puncture).
- Bromobutyl / Chlorobutyl: Better chemical resistance; widely used for parenteral products.
- Silicone Elastomers: Very inert; used as lubricant coating on plungers, or in combination prefillable syringes.

E. Paper, Board, and Laminates

- Paper/Cardboard: Secondary packaging; printed inserts, cartons.
- Aluminium-Polymer Laminates: Strip packs, sachets for sachets and pouches.
- Foil-Paper-Foil Laminates: Ultra-high moisture protection for effervescent tablets, freeze-dried products.

Factors Influencing Choice of Containers

Factor	Consideration
Nature of drug product	Solid, liquid, sterile, biological — dictates material compatibility and barrier requirements
Chemical compatibility	No interaction between drug and container (leaching, adsorption, sorption)
Physical properties	Transparency needed (injectables inspection), rigidity, flexibility
Barrier requirements	Moisture (water vapour transmission rate), oxygen, light, CO2
Intended route of administration	Parenteral requires Type I glass or COC; oral can use HDPE
Sterilisation method	Autoclaving → glass/PP; radiation → HDPE/PET; chemical gas → compatible polymers
Patient compliance	Child-resistant closures, easy-open for elderly, unit-dose convenience
Environmental conditions	Stability zone (I–IV) determines barrier specification
Cost and availability	Commercial viability, supply chain reliability
Regulatory requirements	Compendial standards (USP/BP/IP), local pharmacy laws

Legal and Official Requirements for Containers

Pharmacopoeial Standards

- United States Pharmacopoeia (USP): <660> Containers — Glass; <661> Plastic; <381> Elastomeric Closures; <671> Containers — Permeation.
- British Pharmacopoeia (BP): Monographs specify type of container; Appendix XIX defines types.
- Indian Pharmacopoeia (IP): Similar provisions; Schedule L & L1 detail container standards.
- European Pharmacopoeia (Ph.Eur): 3.2.1 Glass containers; 3.2.2 Plastic containers; 3.2.9 Rubber closures.

Regulatory Requirements

Requirement	Regulatory Basis	Key Points
Container specification	ICH Q6A/Q6B; CTD Module 3.2.P.7	Full characterisation, extractables/leachables study

Child-resistant packaging	Poison Prevention Packaging Act (US); UK SI 1998/2078	Required for OTC drugs (aspirin, iron, etc.)
Tamper-evident closures	US FDA 21 CFR 211.132; EU GMP Annex 1	Evidence of tampering before first opening
Light-resistant containers	USP <661>; must protect from 290–450 nm	Amber glass; opaque outer carton
GMP requirements	ICH Q7; EU GMP Part I; 21 CFR 211	Material qualification, vendor audits, CoA review
Extractables & Leachables	ICH Q3E (draft); BPSA; PQRI guidance	Threshold of Toxicological Concern (TTC)
Labelling	21 CFR 201; EU Dir 2001/83/EC; IP Schedule D	Name, strength, storage, batch, expiry, Rx symbol

Stability Aspects of Packaging Materials

Drug–Container Interactions

Interaction Type	Definition	Example
Leaching	Migration of packaging component INTO the drug product	Plasticiser (DEHP) from PVC IV bags into infusion; antioxidant from rubber stopper into vial
Sorption (Adsorption + Absorption)	Drug molecules bind to or absorb INTO container surface	Insulin adsorption to glass vials; nitroglycerin absorption into PVC tubing
Permeation / Transmission	Gas/moisture moving through container wall	O2 permeation through HDPE bottle causing oxidation; moisture ingress into strip pack
Chemical Reaction	Drug reacts with container or leachate	Acid drug reacting with alkaline leachates from glass; zinc oxide from rubber staining

Factors Affecting Packaging Stability

- Temperature: Elevated temperature accelerates leaching from plastics and degradation of closures; rubber stiffening at low temperature.
- Light: UV/visible light causes photodegradation of both drugs and polymers (PP, HDPE yellowing); amber glass or foil over-wrap used.
- Humidity: High RH increases moisture permeation; affects tablet hardness, capsule brittleness, and lyophilised product reconstitution.
- Oxygen: Oxidation of drug; antioxidants (BHA, BHT) in packaging plastic or inert gas flush (N2, Ar) in headspace.
- Mechanical Stress: Vibration during transport may cause container abrasion, glass delamination, or breakage.

Glass Delamination

Delamination is the flaking of thin glass layers (lamellae/flakes) from the interior surface of glass vials or ampoules into the drug product. It is a critical quality concern, especially for injectable biologics. Causes include high pH formulations, Type II/III glass, and aggressive processing (lyophilisation cycles, steam sterilisation). Detected by visual inspection, particle counting, and SEM-EDS analysis of flakes.

Quality Control Tests for Packaging Materials

A. Glass Container Tests

Test	Method	Acceptance Criterion
Hydrolytic Resistance (Powdered Glass)	USP <660>: autoclave glass powder in water; titrate HCl consumed	≤ 0.10 mL for Type I
Hydrolytic Resistance (Water Attack)	USP <660>: whole container; water, autoclave, titrate	Varies by type and volume
Arsenic Release	Atomic absorption spectroscopy	≤ 0.1 µg/100 mL
Thermal Shock Resistance	Rapid temperature change (60°C → ice water)	No cracking
Light Transmission	Spectrophotometer; measure %T at 290–450 nm	≤ 10% T for amber glass
Dimensional Check	Calliper / gauge; height, diameter, wall thickness	Within ± tolerance

B. Plastic Container Tests

- Light Transmission: UV/Vis spectrophotometry; amber/opaque containers ≤ 10% T.
- Water Vapour Transmission Rate (WVTR): Gravimetric test per USP <671>; mg/day/container.
- Extractables Test: Immerse in specified solvents; GC-MS, ICP-MS for extractable organics and metals.
- Leachables Study: Accelerated/real-time contact studies with the actual drug product; HPLC, GC-MS.
- Biological Reactivity (USP <88>): In-vitro cytotoxicity; in-vivo implantation test.
- Physicochemical Tests (USP <661>): Buffering capacity, non-volatile residue, heavy metals, residue on ignition.

C. Rubber Closure Tests (USP <381>)

- Penetrability: Ease of needle insertion; force required.
- Self-sealing: Liquid/microbial leakage after multiple punctures.
- Fragmentation: Number of rubber particles shed during puncture.
- Extractables: UV absorbance, non-volatile residue, heavy metals, reducing substances, pH change.
- Biological Tests: Systemic injection test (mouse), intracutaneous test (rabbit).

D. General Container Tests

Test	Purpose	Applicable To
Container Closure Integrity (CCI)	Detect microbial / physical leaks using helium leak, dye ingress, or vacuum decay	All sterile products
Drop Test	Simulate handling/transport; no breakage or leakage	Glass ampoules, bottles
Stacking / Compression Test	Resistance to vertical loads during storage	Plastic bottles, cartons
Torque Test	Child-resistant closure open/close torque specification	Screw-cap bottles
Seal Integrity (Blister)	Dye immersion or vacuum method	Blister and strip packs
Sterility / Pyrogen Test	USP <71> / LAL test	Sterile containers & closures