Unit-3

Novel Drug Delivery Systems

B.Pharma 7 Sem Notes

Unit: 3

Transdermal Drug Delivery Systems:

Introduction, Permeation through skin, factors affecting permeation, permeation enhancers, basic components of TDDS, formulation approaches

Gastroretentive drug delivery systems:

Introduction, advantages, disadvantages, approaches for GRDDS – Floating, high density systems, inflatable and gastroadhesive systems and their applications

Nasopulmonary drug delivery system:

Introduction to Nasal and Pulmonary routes of drug delivery, Formulation of Inhalers (dry powder and metered dose), nasal sprays, nebulizers

TRANSDERMAL DRUG DELIVERY SYSTEMS (TDDS)

Introduction to Transdermal Drug Delivery Systems

Transdermal Drug Delivery Systems (TDDS) are dosage forms designed to deliver drugs through the intact skin into the systemic circulation. The drug is applied to the skin surface, permeates through skin layers, reaches the dermis, is absorbed into blood capillaries, and enters the systemic circulation — bypassing the gastrointestinal tract and hepatic first-pass metabolism.

📌 **Key Point:** TDDS = Drug delivery via skin → systemic circulation. Avoids oral route, GI degradation, and hepatic first-pass effect. Ideal for drugs with short t½, poor oral bioavailability, or GI side effects.

Historical Development

- 1979: First TDDS product — Transderm-Scop (scopolamine patch) for motion sickness — approved by FDA.
- 1981: Nitrodisc (nitroglycerin) patch for angina pectoris.
- 1990: Nicotine patches (NicoDerm, Habitrol) for smoking cessation.
- 1995: Fentanyl patch (Duragesic) for chronic cancer pain.
- 2000s: Testosterone, Estradiol, Rivastigmine, Rotigotine, Clonidine patches developed.
- Present: Microneedle patches, iontophoresis, and smart TDDS under development.

Ideal Candidate Drugs for TDDS

Property	Ideal Value / Criteria
Molecular weight	< 500 Da (small molecules permeate better through skin)
Log P (lipophilicity)	1–3 (lipophilic enough for SC penetration but not too lipophilic)
Melting point	< 200°C (lower MP = better skin partitioning)
Therapeutic dose	Low (< 10 mg/day — high dose not feasible through small patch)
Biological half-life	Short to moderate (justifies continuous skin delivery)

Oral bioavailability	Low due to first-pass metabolism — TDDS bypasses this
Skin irritation	Non-irritating; not a sensitizer
Protein binding	Moderate — not excessively protein bound
Aqueous solubility	Reasonable — must dissolve in sweat/sebum to permeate
Drug stability	Stable in solid/semisolid form at skin temperature (~32°C)

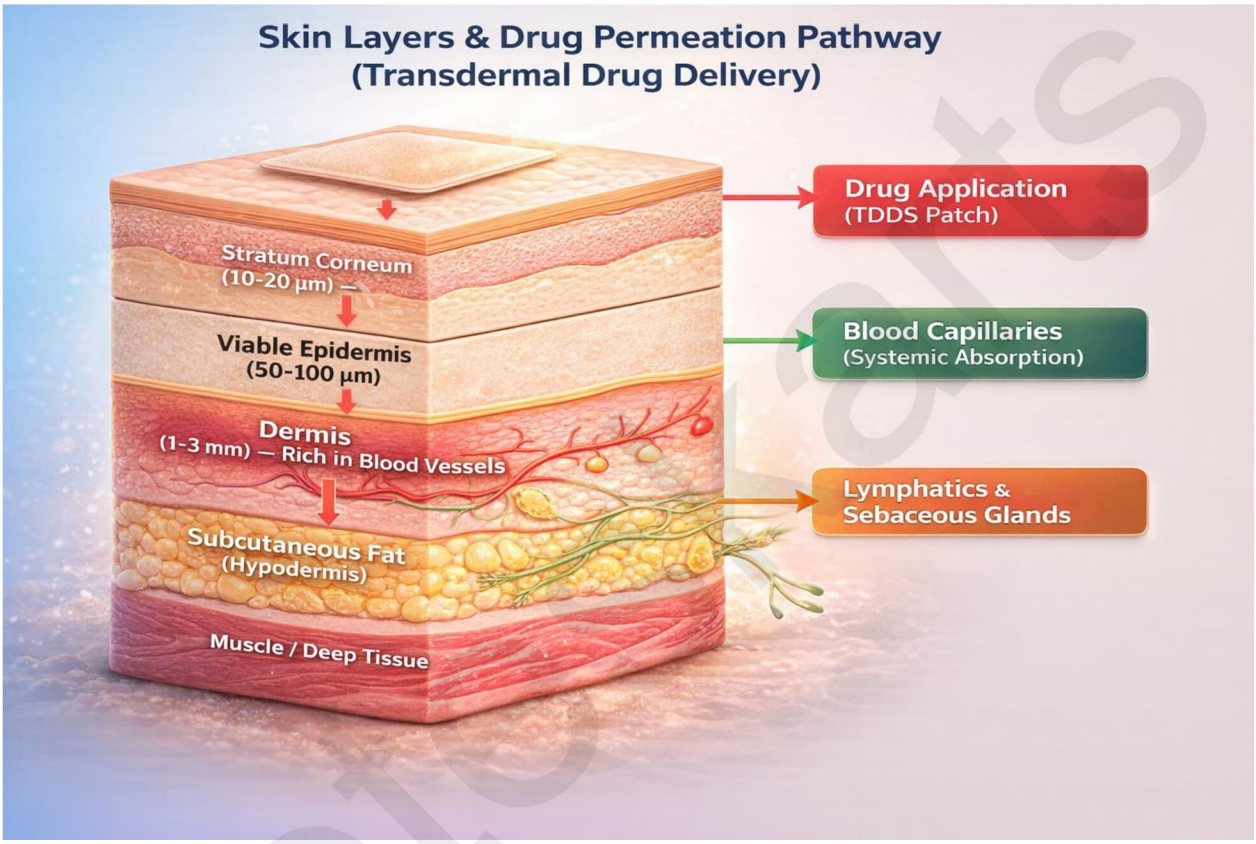

Figure 1: Skin Layers and Drug Permeation Pathway in TDDS

Permeation Through Skin

The skin is a complex multi-layer barrier. Understanding drug permeation through skin layers is fundamental to TDDS formulation. The stratum corneum is the primary rate-limiting barrier to drug absorption.

Skin Structure Relevant to Drug Permeation

Skin Layer	Thickness	Composition	Role in Drug Permeation
Stratum Corneum (SC)	10–20 µm	Dead corneocytes embedded in lipid bilayers	PRIMARY BARRIER — rate-limiting step for most drugs

		(ceramides, cholesterol, fatty acids)	
Viable Epidermis	50–100 µm	Living keratinocytes (no blood vessels)	Enzymatic barrier; drug diffuses through aqueous medium
Dermis	1–3 mm	Collagen, blood vessels, lymphatics, nerve endings	Rich vascular plexus — drug absorbed into blood here
Hypodermis	Variable	Fat cells, connective tissue	Fat depot for lipophilic drugs; acts as reservoir

Routes of Drug Permeation Through Skin

Transepidermal Route (Main Route)

- **Transcellular (through cells):** Drug passes directly through corneocytes and lipid bilayers. Path is tortuous; suitable for small, amphiphilic molecules.
- **Intercellular (between cells):** Drug passes through continuous lipid matrix between corneocytes. DOMINANT PATHWAY for most TDDS drugs. Lipid bilayers = ceramide, cholesterol, fatty acids.

Transappendageal Route (Shunt Route)

- Drug permeates through hair follicles, sweat glands, and sebaceous glands.
- Bypasses stratum corneum — provides faster onset.
- Covers only 0.1% of total skin surface — minor contribution for steady-state delivery.
- Important for: Ionic drugs, large molecules, nanoparticles (follicular targeting).

Mathematical Models of Skin Permeation

Permeation through skin follows Fick's laws of diffusion:

$$\textbf{Flux (J)} = \textbf{Km} \times \textbf{D} \times \Delta\textbf{C} / \textbf{h} = \textbf{Pm} \times \Delta\textbf{C}$$

Where: Km = partition coefficient (SC/vehicle), D = diffusion coefficient in SC, ΔC = concentration gradient, h = SC thickness, Pm = permeability coefficient

- Flux is maximized by: High Km (drug partitions well into SC), High D (fast diffusion), Thin SC, High concentration gradient.
- Lag time (tlag): Time before steady-state flux is achieved. $t_{lag} = h^2 / 6D$

- Permeability coefficient (Pm): Pm = D × Km / h. Ranges from 10^{-6} to 10^{-2} cm/hour for different drugs.

Factors Affecting Transdermal Permeation

Drug-Related Factors

Factor	Effect on Permeation
Molecular weight (MW)	Inversely related to permeation. MW < 500 Da: good permeation; MW > 800 Da: very poor
Lipophilicity (Log P)	Optimal Log P = 1–3. Too hydrophilic: cannot partition into SC. Too lipophilic: cannot partition into dermis.
Ionization	Unionized form permeates better. pKa of drug and skin pH (4.5–5.5) determine fraction unionized.
Melting point	Lower melting point = higher thermodynamic activity = better permeation.
Aqueous solubility	Drug must dissolve in skin surface moisture before permeating.
Drug concentration	Higher concentration gradient = higher flux (Fick's law).
Particle size	Smaller particles permeate more easily through appendageal route.

Formulation-Related Factors

- **Vehicle/base:** Determines drug release rate and concentration gradient at skin surface. Hydrophilic bases (gels, lotions) promote release; lipophilic bases retain drug.
- **pH of formulation:** Affects drug ionization. Optimal pH maintains unionized drug for permeation.
- **Drug concentration in vehicle:** Higher concentration → higher flux according to Fick's law.
- **Penetration enhancers:** Chemicals that reversibly reduce skin barrier — improve permeability.
- **Surfactants:** Disrupt lipid bilayer organization in SC — increase permeability.
- **Occlusion:** Occlusive patch traps moisture → hydrates SC → increases permeability 5–10 fold.

Biological/Skin-Related Factors

- **Skin hydration:** Hydrated SC has 3–5× higher permeability. Water plasticizes keratin; expands intercellular spaces.

- **Skin temperature:** Higher temperature → increased diffusion coefficient and vasodilation → more absorption.
- **Skin thickness:** Sole/palm (thick) < 2 mm: poor absorption. Postauricular, inner forearm: thin skin = better absorption.
- **Skin age:** Aged skin: thinner, less hydrated, reduced lipid content → altered permeability.
- **Disease state:** Eczema, psoriasis, burns → damaged SC → greatly increased permeation.
- **Skin surface pH:** Normal skin pH = 4.5–5.5 (acid mantle). Affects drug ionization.
- **Blood flow:** Increased dermal blood flow → reduced drug accumulation in dermis → better absorption.
- **Site of application:** Permeability order: Scrotum > Postauricular > Scalp > Chest > Abdomen > Forearm > Sole.

Site	Relative Permeability (compared to forearm)
Scrotum	42× more permeable than forearm
Postauricular (behind ear)	6× more permeable — preferred site for patches
Scalp	3.5× more permeable
Forehead	6× more permeable
Abdomen	2× more permeable
Forearm	Baseline reference (1×)
Sole of foot	0.14× (very thick SC — poorest absorption)

Permeation Enhancers

Permeation enhancers (also called penetration enhancers, absorption promoters, or accelerants) are substances that temporarily and reversibly reduce the barrier resistance of the stratum corneum, thereby increasing drug flux through the skin without causing permanent damage or irritation.

✓ **Ideal Criteria:** Ideal permeation enhancer: Pharmacologically inert, non-toxic, non-irritating, non-sensitizing, cosmetically acceptable, reversible action, odorless, inexpensive, and compatible with all drug/excipients.

Mechanisms of Permeation Enhancement

Mechanism	Explanation
Lipid fluidization	Enhancers (fatty acids, terpenes) disorder lipid bilayers in SC → increase drug diffusivity
Protein modification	Enhancers (surfactants, fatty acids) interact with keratin → alter protein structure → widen intercellular spaces
Solvent drag	Vehicles (DMSO, ethanol) partition into SC → carry drug molecules into skin
Hydration of SC	Occlusion or humectants → water absorption → SC swells → opens aqueous pores
Increase drug thermodynamic activity	Co-solvents or supersaturation increase activity → higher driving force across SC

Classification of Chemical Permeation Enhancers

Category	Examples	Mechanism / Notes
Solvents	DMSO, DMF, ethanol, propylene glycol (PG), NMP	Partition into SC lipids; carry drug; increase drug solubility in SC
Surfactants	SLS, Brij 35, Tween 80, Span 20	Disrupt lipid bilayer; increase permeability. Ionic surfactants more effective but more irritating.
Fatty acids	Oleic acid (C18:1), Lauric acid (C12:0), Linolenic acid	Insert into lipid bilayers → create 'kink' → increase drug diffusion. Oleic acid = most studied.
Fatty alcohols	Oleyl alcohol, Lauryl alcohol	Similar to fatty acids; less irritating.
Terpenes	Menthol, Limonene, Carvacrol, 1,8-cineole	Extract from natural sources; disrupt SC lipids; generally well-tolerated.
Azone (Laurocapram)	1-dodecylazacycloheptan-2-one	Highly effective; partitions into lipid bilayers; creates disordering effect. Used at low concentrations (1–5%).
Binary systems	Ethanol + oleic acid, PG + fatty acid, DMSO + laurocapram	Synergistic enhancement — combination more effective than individual components.
Cyclodextrins	HP-β-CD, DM-β-CD	Improve drug solubility and membrane partitioning; complexation increases driving force.
Amino acids / peptides	L-arginine, penetratin	Open tight junctions; carrier-mediated paracellular transport.

Bile salts	Sodium deoxycholate, sodium taurocholate	Open tight junctions; disrupt lipid organization.

Physical Permeation Enhancement Methods

Method	Principle	Application
Iontophoresis	Low electric current drives charged drug molecules through skin	Ionized drugs, peptides, proteins (Lidocaine iontophoresis, insulin delivery)
Electroporation	Brief high-voltage pulses create transient aqueous pores in SC	Protein/DNA delivery; vaccine antigens
Sonophoresis (Ultrasound)	Low-frequency ultrasound (20 kHz) disrupts SC lipids (cavitation)	Proteins (insulin, erythropoietin) through skin
Microneedles	Micrometer-length needles create microchannels in SC without pain	Vaccine delivery, insulin, glucose monitoring
Laser ablation	Laser pulses ablate SC creating microchannels	High MW drugs; precise, controlled depth
Jet injection	High-pressure liquid jet creates transient pores	Needle-free injection of vaccines, insulin
Radio-frequency (RF)	RF energy creates aqueous channels in SC	Macromolecule delivery; cosmetic applications
Thermophoresis	Heat gradient across skin drives drug permeation	Heat-triggered drug release from patches

Basic Components of TDDS

Figure 2: Layered Structure of a Transdermal Drug Delivery Patch

Component	Function	Materials Used
Backing membrane	Impermeable outer layer; protects drug from environment; gives structural support	Polyester, polyurethane, polyethylene, metallized foils, Scotchpak
Drug reservoir / Matrix	Contains the drug (in solution or suspension in polymer)	EVA, PVP, HPMC, polyisobutylene, polyacrylate
Rate-controlling membrane	Controls rate of drug release from reservoir to skin	Microporous polypropylene, EVA (2–9% VA content), cellulose acetate
Pressure-sensitive adhesive (PSA)	Adheres patch to skin; should be hypoallergenic; must not impede drug release	Polyisobutylene (PIB), polyacrylate, silicone-based adhesives
Permeation enhancer	Incorporated to improve drug flux through skin	Oleic acid, propylene glycol, ethanol, menthol

Release liner	Removable protective layer over adhesive; removed before application	Siliconized polyester, fluoropolymer-coated paper
Drug	Active pharmaceutical ingredient — must meet TDDS criteria	Nitroglycerin, fentanyl, scopolamine, nicotine, estradiol

Formulation Approaches for TDDS

Reservoir-Type System (Membrane-Controlled)

- Drug is present as a separate reservoir (liquid, gel, or suspension) surrounded by rate-controlling membrane.
- Rate of delivery = constant (zero-order) as long as saturated drug concentration maintained in reservoir.
- Rate controlled by: Membrane permeability, thickness, drug concentration in reservoir.
- Advantages: Zero-order release; rate controlled independent of skin variation.
- Disadvantages: Risk of dose dumping if membrane ruptures; complex manufacturing.
- Examples: Transderm-Scop (scopolamine), Catapres-TTS (clonidine), Estraderm (estradiol).

Matrix-Type System (Drug-in-Adhesive)

- Drug uniformly dispersed in polymer matrix; no separate reservoir.
- Drug diffuses through matrix to skin surface.
- Release follows Higuchi kinetics ($\sqrt{t}$ relationship).
- Advantages: Simpler manufacturing; no risk of dose dumping; thin and flexible.
- Disadvantages: First-order release (decreasing rate over time); drug exhausted from surface first.
- Examples: Nitrodur, NicoDerm CQ (nicotine), Duragesic (fentanyl), Climara (estradiol).

Microreservoir System

- Combines reservoir and matrix principles.
- Drug dispersed as microscopic reservoirs (drug-in-water suspension) uniformly distributed in silicone polymer matrix.
- Each micro-reservoir surrounded by silicone matrix acting as rate-controlling barrier.

- Example: Nitrodisc (nitroglycerin) — microsealed drug delivery system.

Comparison of TDDS Formulation Approaches

Feature	Reservoir System	Matrix System	Microreservoir
Drug form	Liquid/gel in reservoir	Dissolved/dispersed in polymer	Micro-droplets in matrix
Release kinetics	Zero-order	Higuchi (√t)	Zero-order
Dose dumping risk	Yes (membrane rupture)	No	Very low
Manufacturing	Complex	Simple	Moderate
Thickness	Thicker	Thinner	Moderate
Examples	Transderm-Scop, Estraderm	NicoDerm, Duragesic	Nitrodisc

Marketed TDDS Products

Brand Name	Drug	Indication	Patch Type / Duration
Transderm-Scop	Scopolamine 1.5 mg	Motion sickness	Reservoir; 72 hours
Catapres-TTS	Clonidine 0.1/0.2/0.3 mg/day	Hypertension	Reservoir; 7 days
Duragesic	Fentanyl 25–100 µg/hr	Chronic cancer pain	Matrix; 72 hours
NicoDerm CQ	Nicotine 7/14/21 mg/day	Smoking cessation	Matrix; 24 hours
Estraderm / Climara	Estradiol 25–100 µg/day	Menopausal symptoms, HRT	Reservoir/Matrix; 3–7 days
Vivelle-Dot	Estradiol 0.025–0.1 mg/day	HRT	Matrix; 3–4 days
Androderm	Testosterone 2.5/5 mg	Testosterone deficiency	Reservoir; daily
Exelon Patch	Rivastigmine 4.6/9.5 mg/day	Alzheimer's disease	Matrix; 24 hours
Neupro	Rotigotine 2–8 mg/day	Parkinson's disease	Silicone matrix; 24 hours
Lidoderm	Lidocaine 700 mg patch	Post-herpetic neuralgia	Matrix (local); 12 hours on

GASTRORETENTIVE DRUG DELIVERY SYSTEMS (GRDDS)

Introduction to Gastroretentive Drug Delivery Systems

Gastroretentive Drug Delivery Systems (GRDDS) are specialized oral drug delivery systems designed to be retained in the stomach for an extended period (4–12 hours or more), allowing prolonged and controlled drug release in the gastric environment.

Normal gastric emptying time for non-digestible solids in the fasted state is 1–2 hours (migrating motor complex, MMC cycles). GRDDS aims to extend this residence time to achieve sustained drug delivery in the stomach or upper small intestine.

📌 **Key Point:** GRDDS is indicated for: (1) Drugs absorbed in upper GI tract (window absorption), (2) Drugs unstable in intestinal pH, (3) Drugs for local gastric therapy, (4) Drugs with narrow absorption window (NAW), (5) Drugs to treat H. pylori infection.

Rationale for GRDDS

Rationale	Explanation
Drugs with narrow absorption window (NAW)	Some drugs absorbed ONLY in stomach or upper duodenum (e.g., Riboflavin, Metformin, Levodopa, Ciprofloxacin). GRDDS keeps drug at absorption site.
Drugs degraded in intestinal pH	Drugs stable only in gastric pH (pH 1–3) benefit from prolonged gastric retention.
Local drug action in stomach	H. pylori eradication (amoxicillin), peptic ulcer treatment — drug delivered directly to gastric mucosa.
Drugs requiring GI preparation	Sustained presence in stomach allows gradual drug release for rest of GI tract.
Improved bioavailability	Prolonged residence → more complete absorption → better bioavailability for absorption-limited drugs.
Avoidance of colonic degradation	Drug absorbed from stomach avoids bacterial metabolism in colon.

Advantages of GRDDS

Advantage	Explanation
Enhanced bioavailability	Prolonged gastric residence increases absorption for drugs with NAW.
Reduced dose frequency	Extended release from gastric system allows once-daily dosing.
Sustained drug levels	Constant drug release from stomach maintains therapeutic plasma levels.
Local gastric therapy	Direct delivery to gastric mucosa for peptic ulcer, gastritis, H. pylori.
Reduced GI side effects	Lower drug concentrations in intestine — reduced intestinal irritation.
Better patient compliance	Fewer doses per day.
Overcome colonic drug degradation	Avoids enzymatic and microbial degradation in colon.

Disadvantages of GRDDS

Disadvantage	Explanation
Not suitable for all drugs	Drugs with uniform GI absorption do not benefit; drugs degraded by gastric acid/enzymes unsuitable.
Food effect	Gastric emptying highly variable with food — floating may be disrupted in fed/fasted states.
Gastric pH variability	Gastric pH varies (pH 1–7) especially in achlorhydric patients — affects drug release.
Supine position limitation	Floating systems may not work effectively in lying-down patients.
Drug irritation risk	Prolonged gastric contact of irritating drugs may cause mucosal damage.
High density not always achievable	Density > 3 g/mL difficult to achieve with pharmaceutical excipients.
Complex manufacturing	Effervescent systems, inflatable systems are difficult to manufacture and scale up.

Figure 3: Classification of Approaches for Gastroretentive Drug Delivery Systems

Approaches for Gastroretentive Drug Delivery Systems

Floating Drug Delivery Systems

Floating systems have bulk density less than the density of gastric fluid (< 1.004 g/mL). They float on gastric contents, remaining in the stomach for extended periods while releasing drug continuously.

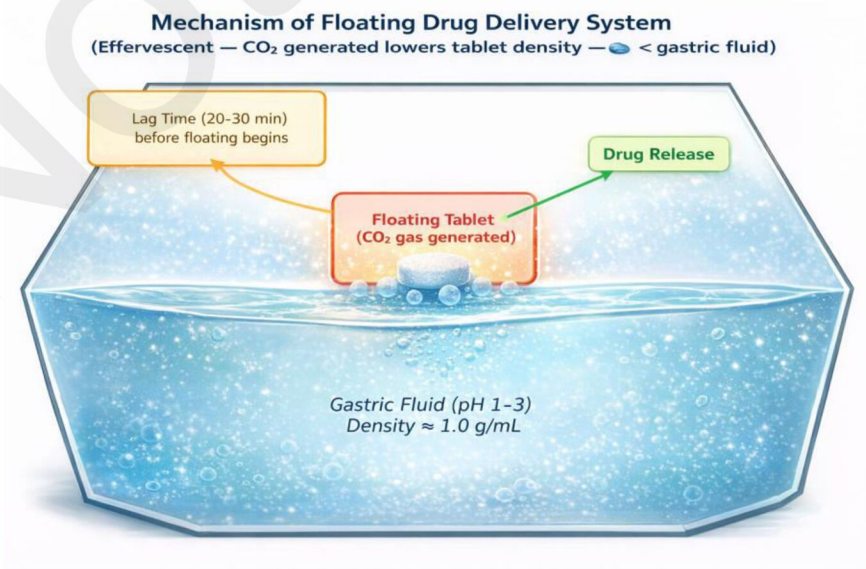

Figure 4: Mechanism of Effervescent Floating Drug Delivery System in the Stomach

Effervescent Floating Systems

- Mechanism: CO_2 gas generated in situ by reaction between effervescent couple (citric acid + sodium bicarbonate) and gastric acid.
- CO_2 generated is trapped in swelling polymer matrix → bulk density decreases below 1 g/mL → formulation floats.
- Steps: Tablet contacts gastric fluid → CO_2 generated → tablet floats (after ~20–30 min lag time) → drug released slowly.
- **Key polymers:** HPMC K4M, K15M, K100M (gel-forming matrix); Carbopol 934 (gel strength); PVP (disintegrant); MC, HPC.
- **Effervescent agents:** Citric acid + Sodium bicarbonate (most common); Tartaric acid + $NaHCO_3$.
- Lag time: Time before floating begins = 20–30 minutes. Reduced by increasing effervescent agent concentration.
- **Examples:** Ciprofloxacin floating tablets, Metformin floating tablets, Ranitidine floating capsules.

Non-Effervescent Floating Systems

- Density < 1 g/mL achieved by incorporating low-density materials or trapping air within the formulation.
- Types:
  - Hydrodynamically Balanced Systems (HBS): Drug + hydrophilic gels (HPMC) → swells on contact with gastric fluid → gel density < 1 g/mL → floats.
  - Microporous compartment systems: Drug enclosed in microporous chambers with low-density chambers.
  - Hollow microspheres (Microballoons): Hollow microspheres with drug in wall and air in core → floats.
  - Lipid floating systems: Drug in fatty matrix (oils, waxes) with density < 1 g/mL.
- **Example:** Propranolol HBS capsules, Verapamil floating tablets (Isoptin SR).

Feature	Effervescent	Non-Effervescent
Mechanism	CO_2 generation lowers density	Low-density materials or gel swelling
Lag time	20–30 min before floating	Very short or immediate
Floating duration	4–12 hours	4–12 hours

Stability	CO_2 agents moisture-sensitive	More stable on storage
Manufacturing	More complex (CO_2 agents)	Simpler
Examples	Ciprofloxacin, Metformin FT	Propranolol HBS, microballoons

High Density (Sinking) Systems

High density systems have density greater than gastric fluid (> 3.0 g/mL). They sink to the bottom of the stomach (pyloric antrum), avoiding gastric emptying with the liquid phase.

- Density achieved by incorporating heavy inert materials: Barium sulfate ($BaSO_4$), iron powder, bismuth subnitrate, zinc oxide.
- Particles sink to the lower part of the antrum — retained during peristaltic contractions.
- Drug released as pellets erode in gastric environment.
- Advantages: No dependence on posture or fed/fasted state (unlike floating). Suitable for liquids and granules.
- Disadvantages: Heavy materials may feel unpleasant; limited drug loading due to high excipient mass.
- **Density requirement:** > 3.0 g/mL for reliable sinking (water density = 1 g/mL; gastric contents ≈ 1.004 g/mL).
- **Examples:** Compressed pellets with $BaSO_4$, high-density Metronidazole pellets, Barium sulfate tablets (also used as radiological contrast).

Inflatable and Expandable Systems

Inflatable systems are initially small enough to be swallowed, but expand in the stomach to a size too large to pass through the pylorus (> 12.8 mm). This mechanical retention prevents gastric emptying.

Inflatable Balloon Systems

- Compressed drug formulation + CO_2-generating agents enclosed in an inflatable balloon.
- On contact with gastric fluid, CO_2 inflates the balloon to large size (> 15 mm).
- Balloon retained in stomach; drug released from pores in the balloon membrane.
- After drug release is complete, balloon deflates and is expelled.

- **Example:** Scott's inflatable drug delivery system — reported in early GRDDS research.

Accordion Pill / Geometric Constraint

- Tightly folded polymer film containing drug — fit into a gelatin capsule.
- Capsule dissolves → film unfolds to a large geometric structure (star, disc, or accordion shape).
- Retained by geometric constraint (too large to exit pylorus).
- Drug slowly releases from the film over 12–24 hours.
- **Example:** Accordion Pill (Intec Pharma) — ciprofloxacin, carbidopa/levodopa.

Swellable/Expandable Matrix Systems

- Tablet or capsule expands significantly on contact with gastric fluid.
- Superporous hydrogels: Swell rapidly (30 seconds to 1 minute) to size > 12 mm.
- Superporous hydrogel composites: HEMA, acrylamide-based hydrogels with open pores allow rapid water absorption.
- **Example:** Pulsincap, Egalet, superporous polyacrylamide hydrogel tablets.

Gastroadhesive (Mucoadhesive) Systems

Gastroadhesive systems adhere to the gastric mucosa using mucoadhesive polymers. The polymer chains interact with mucin glycoproteins in the gastric mucous layer, prolonging residence time in the stomach.

- Mechanism: Mucoadhesive polymer hydrates → chains interpenetrate with mucin → non-covalent bonds (H-bonding, van der Waals, electrostatic) → adhesion.
- Polymers used:
  - Carbopol (PAA): Strongest gastric mucoadhesion; forms ionic bonds with mucin.
  - HPMC: Moderate mucoadhesion; gel-forming.
  - Chitosan: Cationic; electrostatic interaction with anionic mucin — excellent adhesion.
  - Na-CMC: Ionic interaction; film-forming.
  - Polycarbophil: Similar to Carbopol; strongly mucoadhesive.
- Limitations: Rapid mucus turnover in stomach (4–6 hours); continuous mucus secretion dilutes adhesion over time.
- New approach — Thiolated polymers (Thiomers): Form covalent disulfide bonds with cysteine-rich mucin → superior and prolonged adhesion.

- **Examples:** Carbopol-containing Metronidazole bioadhesive tablets for H. pylori, Mucoadhesive Amoxicillin tablets.

Other Approaches to GRDDS

Approach	Mechanism	Example
Magnetic systems	Ferrite particles incorporated; external magnet positioned over stomach retains device	Ferrite-loaded tablet retained by external magnet (research stage)
Ion exchange resins	Drug-resin complex retained in stomach; drug released by ionic exchange	Cholestyramine-drug complexes
Controlled swelling	Tablet swells to size > 13 mm (pyloric diameter) — mechanically retained	Superporous hydrogels, expandable tablets
Osmotic systems	OROS with delayed delivery — absorbed first in stomach	OROS-CT, L-OROS systems (some gastric applications)

Applications of GRDDS

Drug	Indication	Rationale for GRDDS
Furosemide	Heart failure, edema	Absorbed in upper GI; bioavailability improved by GRDDS
Metformin	Type 2 diabetes	Absorption window in upper GI; GRDDS improves bioavailability
Ciprofloxacin	H. pylori, GI infections	Local action in stomach; NAW in upper GI
Amoxicillin	H. pylori eradication	Local gastric mucosal delivery; acid-stable
Riboflavin (Vit. B_2)	Nutritional supplement	Absorbed ONLY in upper GI (active transport); floating improves absorption
Levodopa	Parkinson's disease	Absorbed in upper GI; first-pass avoided by prolonged gastric delivery
Captopril	Hypertension	Short t½ (2 hrs); GRDDS allows once-daily use
Ranitidine	GERD, peptic ulcer	Local gastric action; floating SR formulation reduces dose frequency
Verapamil	Hypertension, angina	Absorption in upper GI; Isoptin SR as floating tablet
Misoprostol	Peptic ulcer	Local gastric protective action

NASOPULMONARY DRUG DELIVERY SYSTEMS

Introduction to Nasal and Pulmonary Routes

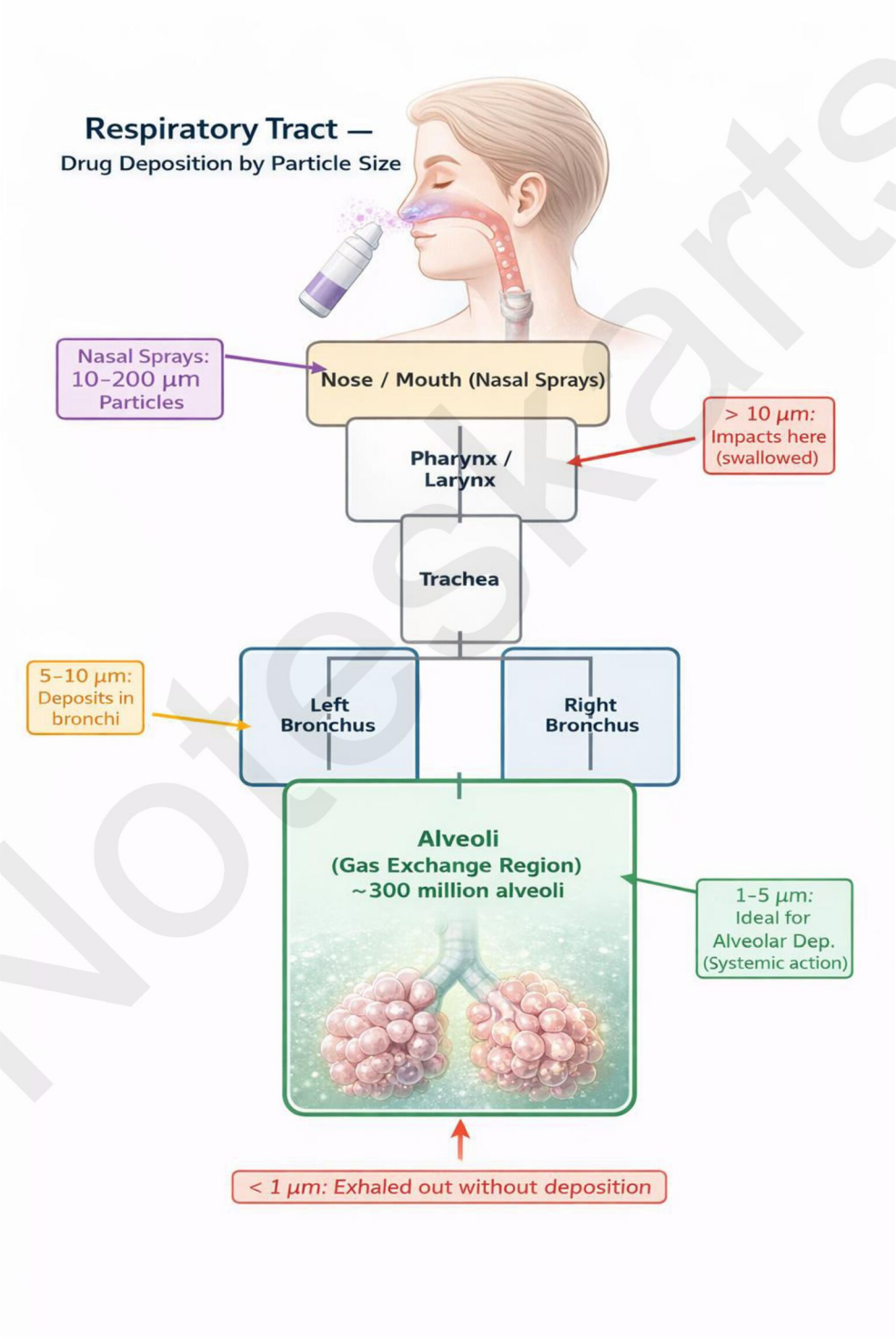

Figure 5: Respiratory Tract — Drug Deposition Map Based on Particle Size

Nasal Route of Drug Delivery

The nasal route delivers drugs to the nasal cavity via the nasal mucosa for either local (nasal decongestants, antihistamines) or systemic (hormones, vaccines, analgesics) effects.

Feature	Value / Description
Nasal mucosal area	~150 cm² (total); ~100 cm² absorptive area
Epithelium	Pseudostratified columnar epithelium with cilia
Blood supply	Rich vascular supply — rapid systemic absorption
pH of nasal secretions	5.5–6.5 (adult); 5.0–7.0 (child)
Mucociliary clearance	~6 mm/min — clears deposited particles toward nasopharynx in 20–30 min
Molecular weight limit	< 1000 Da for efficient passive absorption (MW < 300 Da ideal)
Avoids first-pass	YES — nasal venous drainage bypasses liver via superior vena cava
Nasal enzymes	Aminopeptidases, proteases limit peptide absorption

📌 **Key Point:** Nasal route advantage: Direct nose-to-brain (N2B) pathway — drug can reach CNS via olfactory nerves without crossing BBB. Used for CNS-targeted peptide delivery.

Pulmonary Route of Drug Delivery

The pulmonary (inhalation) route delivers drugs directly to the lungs via the airways. It is used for both local pulmonary therapy (asthma, COPD) and systemic drug delivery (proteins, peptides).

Feature	Value / Description
Total lung surface area	~70–140 m² (alveolar surface)
Alveolar epithelium	Type I (90% surface) and Type II pneumocytes; very thin (0.1–0.2 µm)
Alveolar blood flow	~5 liters/min — entire cardiac output passes through
Mucociliary clearance	Tracheobronchial region only — alveoli have macrophages
Particle size for alveolar dep.	1–5 µm (MMAD — Mass Median Aerodynamic Diameter)

pH of lung fluid	6.9–7.2
Drug metabolizing enzymes	CYP1B1, CYP2B6, proteases — less than liver
Advantages over IV	Local high concentration; rapid onset; avoids hepatic metabolism

Particle Size and Deposition in Lung

Particle Size (MMAD)	Deposition Site	Action
> 10 µm	Oropharynx — impacted, swallowed	No pulmonary effect; GI absorption
5–10 µm	Trachea and large bronchi	Local bronchial effect; mucociliary clearance removes quickly
1–5 µm	Bronchioles and alveoli	OPTIMAL — deep lung deposition; local and systemic action
0.5–1 µm	Alveoli (deposited by sedimentation)	Good alveolar deposition; systemic absorption
< 0.5 µm	Exhaled out without deposition	No therapeutic benefit

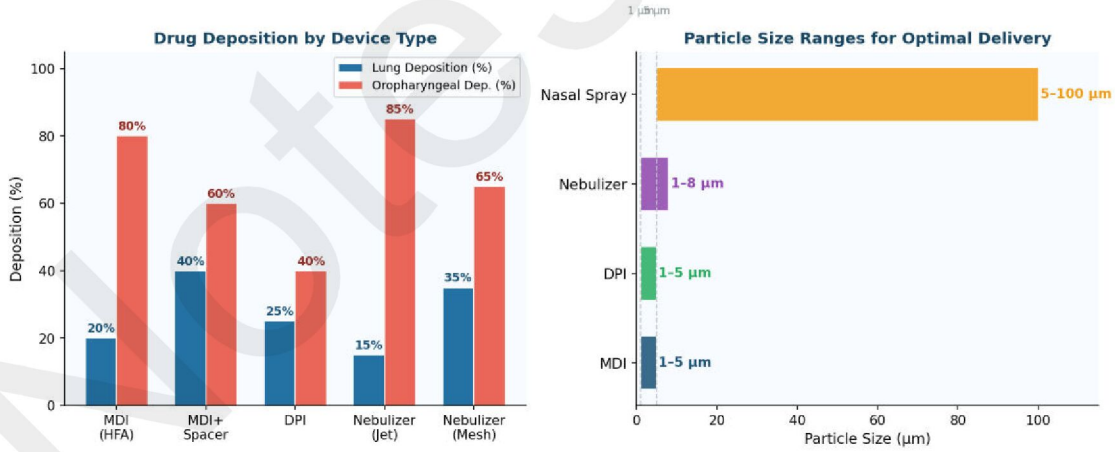

Figure 6: Drug Deposition by Device Type and Optimal Particle Size Ranges

Formulation of Metered Dose Inhalers (MDI)

A Metered Dose Inhaler (MDI) is a pressurized inhaler device that delivers a precise, pre-measured dose of drug in aerosol form using a liquefied propellant gas. It is the most widely used inhaler device globally.

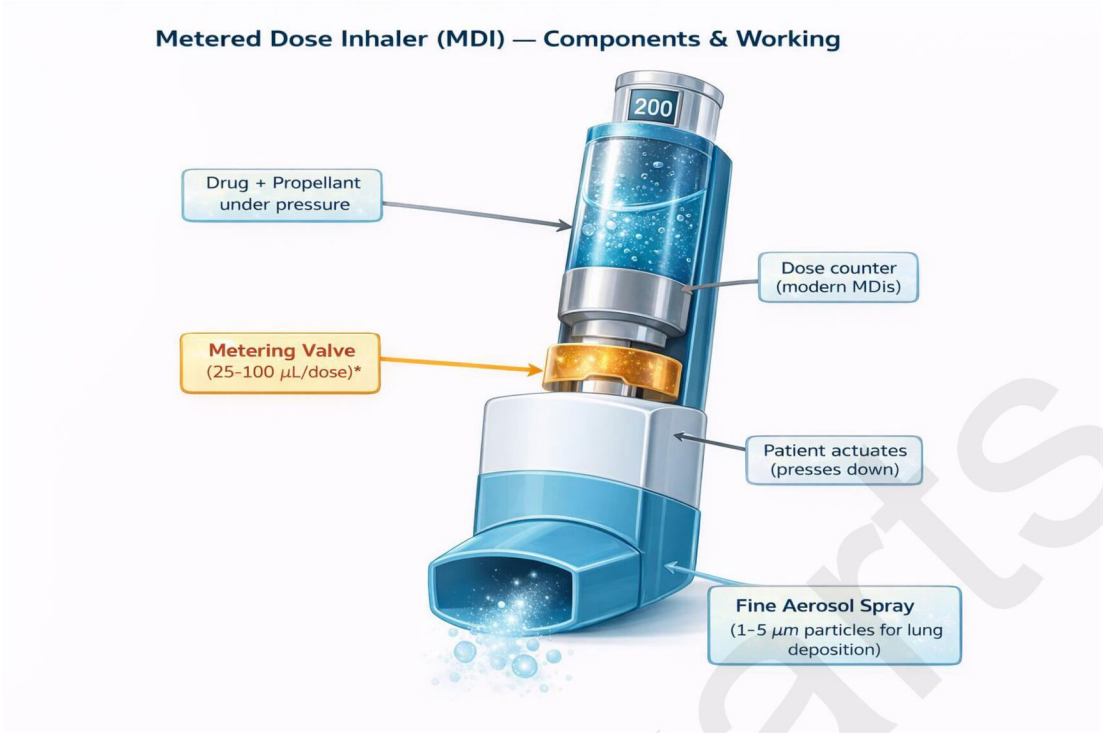

Figure 7: Metered Dose Inhaler (MDI) — Components and Working Mechanism

Components of MDI

Component	Description / Function	Material
Pressurized canister	Metal can holding drug suspension/solution + propellant under pressure	Aluminum (coated)
Metering valve	Precisely measures 25–100 µL per actuation; opens when canister pressed	Stainless steel, polymers (Delrin, nylon)
Actuator (mouthpiece body)	Plastic housing; converts valve opening to aerosol spray via nozzle	Polypropylene, polyethylene
Propellant	Liquefied gas providing pressure; carries drug; evaporates after spray	HFA 134a, HFA 227ea (replaced CFC after Montreal Protocol)
Drug formulation	Drug dissolved or suspended in propellant; surfactant prevents aggregation	Micronized drug + HFA + surfactant (oleic acid, lecithin, ethanol)
Dose counter	Tracks remaining doses in modern MDIs	Mechanical/electronic counter
Spacer (optional)	Attaches to mouthpiece; reduces oropharyngeal deposition; allows slower inhalation	PVC, polycarbonate chamber; valves

Propellants Used in MDI

Propellant	Type	Properties	Status
CFC-11, CFC-12	Chlorofluorocarbons	Low toxicity; good spray properties; ozone-depleting	BANNED — phased out under Montreal Protocol 1987
HFA 134a (Norflurane)	Hydrofluoroalkane	Non-ozone-depleting; higher vapor pressure; different spray pattern	Currently approved — standard MDI propellant
HFA 227ea (Heptafluoropropane)	Hydrofluoroalkane	Similar to 134a; slightly different pressure	Currently approved — used in some products
CO_2, N_2O (low pressure)	Gas propellants	Used in some nasal sprays; insufficient for MDI	Limited use

MDI Formulation — Solution vs. Suspension

Feature	Solution MDI	Suspension MDI
Drug state	Drug dissolved in propellant (+ co-solvent)	Drug micronized particles suspended in propellant
Drug requirements	Must be soluble in HFA propellant	Must be insoluble in propellant; particle size critical
Particle size control	Determined by nozzle/valve design	Micronization required (1–5 µm MMAD)
Stability	Chemical stability concern	Physical stability (aggregation, settling) concern
Surfactant	Less critical	Required (lecithin, oleic acid) to prevent aggregation
Examples	Proventil HFA (albuterol solution)	Flovent HFA (fluticasone suspension)

Working of MDI

- Patient removes cap, shakes canister (if suspension), exhales completely.
- Patient places mouthpiece in mouth, begins slow steady inhalation.
- Patient presses canister top — actuates metering valve.
- Liquefied propellant + drug released → rapid evaporation of propellant → fine aerosol produced.
- Aerosol enters airways — particles 1–5 µm deposit in bronchioles/alveoli.
- Larger particles (> 10 µm) impact oropharynx — swallowed.

- Bronchodilator onset: 2–5 minutes; peak effect: 15–30 minutes.

Problems with MDI and Solutions

Problem	Cause	Solution
Poor coordination	Patient cannot synchronize actuation and inhalation	Use breath-actuated MDI (BA-MDI) or add spacer
High oropharyngeal deposition	Aerosol impacts at back of throat	Add spacer device; improves lung deposition from 20% to 40%
Dose variation	Shaking, orientation, temperature affect spray	Standardize technique; store at room temp; shake before use
Drug formulation change	CFC to HFA changed spray characteristics	Reformulation required; patients needed re-education
Remaining dose unknown	Cannot see remaining drug in opaque canister	Dose counter (mandated by FDA since 2004 for new MDIs)
Freeze effect	Cold propellant on throat causes cold sensation	Use spacer; allow MDI to warm to room temperature

Formulation of Dry Powder Inhalers (DPI)

Dry Powder Inhalers (DPIs) deliver drug in dry powder form. The powder is deaggregated by the patient's inspiratory airflow and delivered to the lungs. Unlike MDIs, DPIs are breath-actuated and do not require propellants.

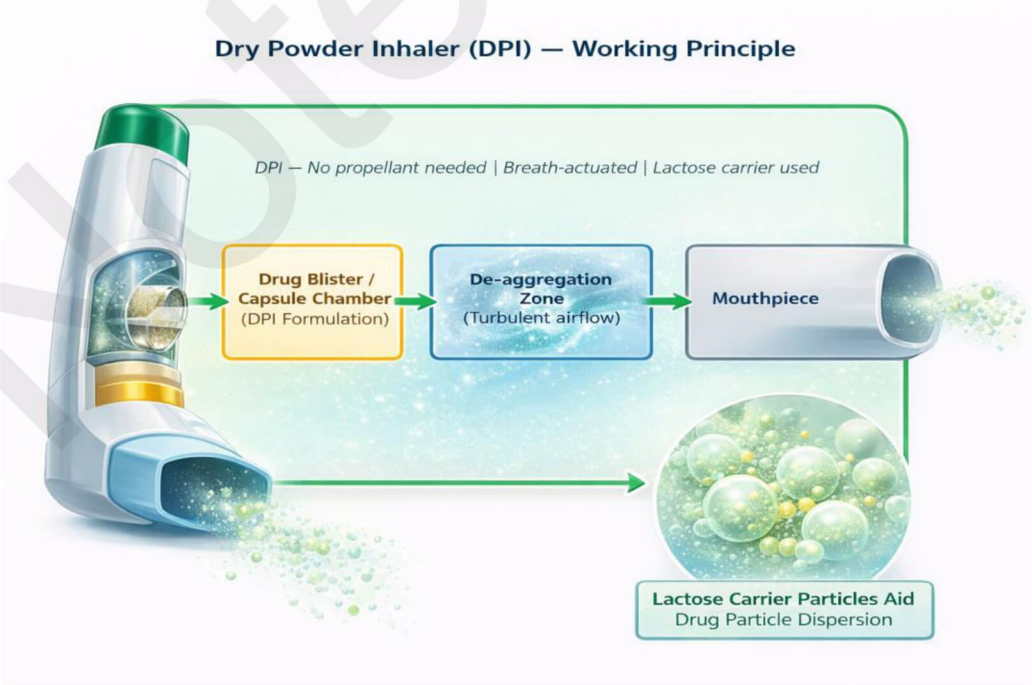

Figure 8: Dry Powder Inhaler (DPI) — Working Principle and Components

Types of DPI Devices

Type	Description	Examples
Single-dose (capsule-based)	Drug in hard gelatin capsule; capsule pierced; powder inhaled in single breath	Spiriva (tiotropium) HandiHaler; Foradil Aerolizer
Multi-dose (blister)	Drug in individual blisters on disc or strip; blister peeled, drug inhaled	Advair Diskus (fluticasone + salmeterol); Seretide
Multi-dose reservoir	Drug powder in reservoir; dose metered by device mechanism	Turbuhaler (budesonide); Easyhaler; Clickhaler
Passive (breath-actuated)	Patient's inhalation force deaggregates powder — most common	Turbuhaler, Diskus, HandiHaler
Active (motor-driven)	External energy (compressed gas, vibration) deaggregates powder	Exubera (insulin — discontinued); NEXT DPI

DPI Formulation Components

Component	Role	Details
Drug (micronized)	Active ingredient	Must be micronized to 1–5 µm MMAD for lung deposition
Carrier particles	Lactose monohydrate (most common); mannitol, glucose	Coarse particles (50–150 µm) carry drug to device; separate in turbulent airflow; deposited in oropharynx (not lung)
Fine particle fraction (FPF)	Fraction of drug with size < 5 µm	Determines lung deposition; FPF > 30% desirable for good efficacy
Anti-adherents / Force control agents	Magnesium stearate, leucine, lipids	Reduce cohesion/adhesion of drug particles → improve dispersion
Moisture barrier packaging	Blister strips, desiccant, foil packaging	DPI powder highly moisture-sensitive; humidity increases aggregation and reduces FPF

Advantages and Disadvantages of DPI vs MDI

Feature	DPI	MDI
Propellant	Not needed — environment-friendly	HFA propellant required

Coordination	Breath-actuated — no coordination needed	Requires actuation-inhalation coordination
Dose accuracy	Good (multi-dose devices)	Good with metering valve
Moisture sensitivity	HIGH — powder degrades in humidity	Lower (sealed canister)
Inspiratory flow needed	HIGH (>30 L/min) — limits use in severe bronchoconstriction	Low flow needed
Patient age	Adults and older children (need flow)	Any age with spacer
Environmental impact	Low (no propellant)	Higher (HFA has GWP)
Cost	Usually higher	Moderate
Examples	Turbuhaler, Diskus, HandiHaler	Ventolin HFA, Flovent HFA, Advair HFA

DPI Products

Brand	Drug	Device Type	Indication
Ventolin Rotahaler	Salbutamol	Capsule-based DPI	Asthma, COPD
Turbuhaler (Pulmicort)	Budesonide	Reservoir DPI	Asthma
Seretide Accuhaler/Diskus	Fluticasone + Salmeterol	Blister disc DPI	Asthma, COPD
HandiHaler (Spiriva)	Tiotropium bromide	Capsule-based DPI	COPD
Relenza Diskhaler	Zanamivir	Blister disc DPI	Influenza treatment
Foradil Aerolizer	Formoterol fumarate	Capsule-based DPI	Asthma, COPD
Incruse Ellipta	Umeclidinium	Blister strip DPI	COPD
Bevespi Aerosphere	Formoterol + Glycopyrrolate	Suspension MDI	COPD

Nebulizers

A nebulizer is a device that converts a liquid drug formulation into a fine mist (aerosol) for inhalation. Unlike MDI and DPI, nebulizers do not require active patient participation in inhaler technique — making them suitable for infants, elderly, and critically ill patients.

Types of Nebulizers

Jet Nebulizer (Pneumatic Nebulizer)

- Working: Compressed air/oxygen passes through a narrow jet → creates Venturi effect → liquid drug drawn up → atomized into aerosol droplets.
- Baffles within device remove large droplets (> 5 µm) — only fine mist exits.
- Particle size: 2–5 µm MMAD.
- Flow rate: 6–8 L/min compressed air needed.
- Treatment time: 10–20 minutes per nebulization session.
- Drug waste: 30–50% drug remains in nebulizer cup (residual volume) — not delivered.
- Advantages: Inexpensive, simple, works with any drug solution, no patient coordination needed.
- Disadvantages: Bulky, requires power source, long treatment time, significant drug waste, loud.
- **Examples:** PARI LC Plus, DeVilbiss PulmoAide, Philips Respironics SideStream.

Ultrasonic Nebulizer

- Working: Piezoelectric crystal vibrates at ultrasonic frequency (1–2 MHz) → vibrations transmitted to liquid drug → surface waves → aerosol droplets formed at peaks of waves.
- No compressed air needed — operates on electricity.
- Particle size: 1–5 µm MMAD.
- Output rate: Higher than jet nebulizers — faster treatment.
- Disadvantages: Heat generated during ultrasonic vibration may degrade thermolabile drugs (proteins, peptides, budesonide). Cannot nebulize suspensions effectively.
- Not suitable for: Protein drugs, suspensions (separation issues).
- **Examples:** DeVilbiss Ultraneb, Omron MicroAir (compact ultrasonic).

Vibrating Mesh Nebulizer (VMN)

- Working: Drug solution passes through a mesh membrane with thousands of microscopic holes (2–5 µm). Mesh vibrates at low frequency (100–200 kHz) → liquid forced through mesh → fine aerosol produced.
- Particle size: 1–4 µm MMAD — finest and most consistent.
- Drug efficiency: > 70% drug delivered (very low residual volume vs. 30–50% waste in jet nebulizer).

- Silent operation; portable; battery-operated.
- Suitable for: Solutions and suspensions; protein drugs (no heat generated).
- Disadvantages: Expensive; mesh can block with viscous or crystalline drugs.
- **Examples:** PARI eFlow, Philips InnoSpire Go, Aerogen Solo (ICU), AERx Essence.

Feature	Jet Nebulizer	Ultrasonic Nebulizer	Vibrating Mesh Nebulizer
Mechanism	Compressed air (Venturi)	Ultrasonic piezoelectric	Vibrating mesh membrane
Particle size	2–5 µm	1–5 µm	1–4 µm (finest)
Suitable for	Solutions	Solutions only (not suspensions)	Solutions AND suspensions
Drug efficiency	Low (50–70% lost)	Moderate (60–70%)	High (> 70%)
Protein drug compatible	Yes	No (heat degrades)	Yes
Portability	Bulky	Moderate	Compact; portable
Treatment time	10–20 min	5–10 min	5–10 min
Noise	Loud	Quiet	Very quiet / silent
Cost	Low (Rs. 500–2000)	Moderate	High (Rs. 5000–20000)
Examples	PARI LC Plus	DeVilbiss Ultraneb	PARI eFlow, Aerogen Solo

Nasal Sprays

Nasal sprays deliver drugs as fine droplets directly into the nasal cavity. They are used for: local nasal therapy (congestion, allergic rhinitis, nasal polyps) and systemic delivery (hormones, antiemetics, analgesics).

Types of Nasal Spray Devices

Type	Description	Example
Pump spray (unit-dose pump)	Metered dose pump; delivers 25–200 µL per actuation	Nasonex (mometasone), Avamys (fluticasone furoate)
Pressurized metered-dose nasal spray	Propellant-driven; canister with valve for nasal delivery	Beconase AQ (beclomethasone)

Squeeze bottle	Simple squeeze delivers liquid; unmetered — variable dose	OTC nasal saline rinses
Nasal gel	Bioadhesive gel applied to nasal mucosa; prolonged contact	Nitrostat nasal gel, Desmopressin nasal gel
Nasal powder insufflator	Dry powder delivered into nasal cavity; breath actuated	Onzetra Xsail (sumatriptan) — nasal powder

Formulation of Nasal Sprays

Drug

- Must be stable in aqueous solution; water-soluble preferred for nasal spray.
- Molecular weight: Ideally < 1000 Da for good nasal absorption.
- Log P: Moderate (allows membrane permeation after dissolution in nasal secretions).

Formulation Excipients

Excipient	Examples	Function
Preservatives	Benzalkonium chloride (BZK), phenylethyl alcohol, thimerosal	Prevent microbial contamination in multi-dose sprays
Buffers	Phosphate buffer, citrate buffer (pH 5.5–6.5)	Maintain pH compatible with nasal mucosa
Tonicity adjusting agents	NaCl, dextrose (isotonic = 270–330 mOsm/L)	Match osmolality with nasal secretions
Viscosity modifiers	HPMC, MC, HPC, microcrystalline cellulose	Improve droplet retention; reduce drip down throat
Mucoadhesive polymers	Chitosan, Carbopol, HPC	Prolong nasal residence time; improve absorption
Permeation enhancers	Cyclodextrins, chitosan, surfactants	Improve nasal mucosal permeability for poorly absorbed drugs
Antioxidants	Sodium metabisulfite, BHA, ascorbic acid	Protect oxidation-sensitive drugs

Marketed Nasal Drug Products

Drug	Brand Name	Indication	Route / Type
Mometasone furoate	Nasonex	Allergic rhinitis	Nasal aqueous spray

Fluticasone propionate	Flonase	Allergic rhinitis, nasal polyps	Nasal aqueous spray
Desmopressin (DDAVP)	Stimate, DDAVP	Diabetes insipidus, nocturnal enuresis	Nasal spray (systemic)
Calcitonin	Miacalcin	Osteoporosis	Nasal spray (systemic)
Sumatriptan	Imitrex Nasal	Migraine	Nasal spray (rapid onset)
Zolmitriptan	Zomig ZMT	Migraine	Nasal spray
Influenza vaccine	FluMist	Influenza prevention	Intranasal live attenuated vaccine
Naloxone	Narcan	Opioid overdose reversal	Nasal spray (emergency)
Ketorolac	Sprix	Moderate to severe pain	Nasal spray (systemic)
Budesonide	Rhinocort	Allergic rhinitis	Nasal aqueous suspension spray

Comparison: MDI vs DPI vs Nebulizer vs Nasal Spray

Feature	MDI	DPI	Nebulizer	Nasal Spray
Drug form	Suspension/solution in propellant	Dry powder with carrier	Liquid solution/suspension	Aqueous solution/suspension
Propellant	Yes (HFA)	No	No	No (pump-driven)
Coordination required	Yes (critical)	Less (breath-actuated)	None (tidal breathing)	Minimal
Particle size	1–5 µm	1–5 µm	2–5 µm	5–100 µm (nasal cavity)
Drug deposition	Lung (~20%)	Lung (~25%)	Lung (~15%)	Nasal mucosa (~90%)
Suitable patients	Cooperative adults	Cooperative adults	All (infants to ICU)	All ages
Portability	Highly portable	Highly portable	Bulky (jet)	Portable
Dosing frequency	Multiple times/day	Multiple times/day	Sessions 2–4×/day	1–2×/day (steroids)
Example products	Ventolin, Seretide HFA	Turbuhaler, Diskus	PARI LC Plus, eFlow	Nasonex, Flonase, Narcan

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