PharmacoLearn

MPH201T Molecular Pharmaceutics (Nano Tech and Targeted DDS), M.Pharm Semester 2

Unit 4: Pulmonary and Intra Nasal Drug Delivery Systems

Free notes at pharmacolearn.fyi

4.1 Pulmonary delivery: rationale and deposition

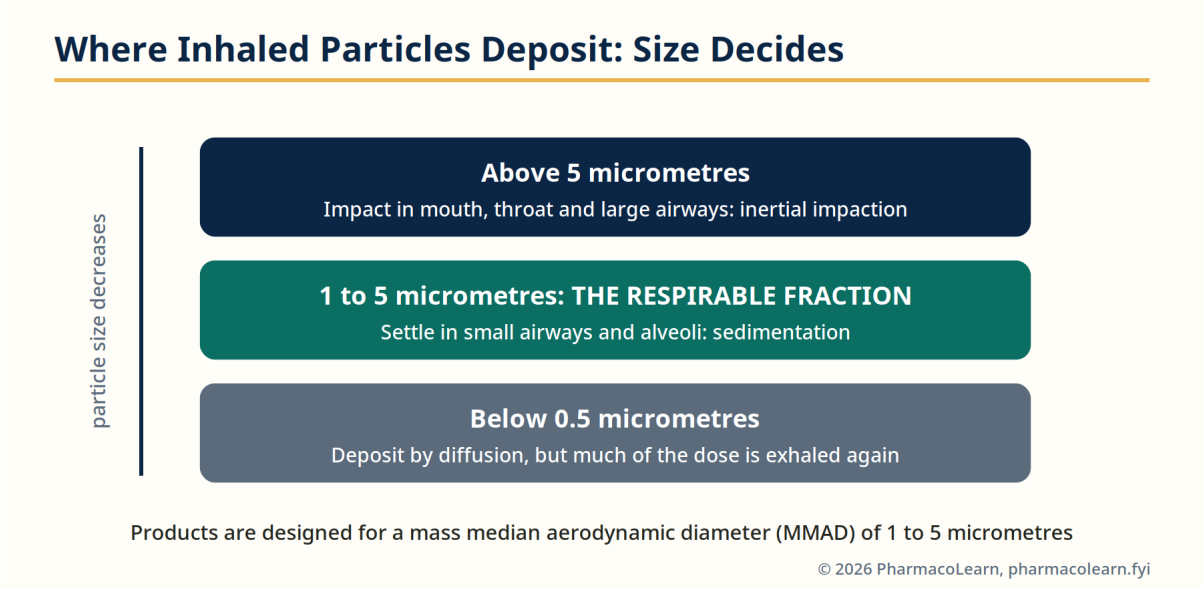

Figure: Aerodynamic particle size decides where an inhaled dose deposits; the 1 to 5 micrometre band is the respirable fraction products are designed for.

The lungs offer a very large absorptive surface (of the order of 100 square metres in an adult), a thin alveolar barrier (a fraction of a micrometre), rich blood supply and relatively low enzyme activity compared with the gut and liver. Pulmonary delivery is therefore used in two ways: for local treatment of airway disease (asthma, chronic obstructive pulmonary disease, infections, cystic fibrosis), where a small dose acts directly on the diseased tissue with little systemic exposure, and for systemic delivery of drugs that are poorly absorbed orally or destroyed in the gut, including peptides, although local therapy dominates in practice. The same routes and devices are studied in Unit 4 of MPH102T's companion teaching; here the emphasis is on the aerosol science and the evaluation of the systems.

Where an inhaled particle deposits is decided mainly by its aerodynamic diameter:

- **Inertial impaction:** particles larger than about 5 micrometres cannot follow the airstream around bends and impact in the mouth, throat and large airways; this dominates for large particles and fast inhalation.
- **Gravitational sedimentation:** particles of about 1 to 5 micrometres settle out by gravity in the smaller airways and alveoli, where the air moves slowly; a breath hold increases this deposition, which is why patients are told to hold the breath after inhaling.
- **Brownian diffusion:** particles smaller than about 0.5 micrometres deposit by diffusion, but a large fraction of very fine particles is simply exhaled again.

The practical result is that the respirable fraction, the mass fraction of the dose with an aerodynamic diameter of about 1 to 5 micrometres, is the part that reaches the lower airways; the mass median aerodynamic diameter (MMAD) and its spread (geometric standard deviation) are therefore core quality attributes of every inhalation product. Against delivery stand the lung's defences: the mucus layer and mucociliary escalator clear deposited material upwards, alveolar macrophages phagocytose particles, and

enzymes and the tight alveolar epithelium limit absorption of large molecules.

4.2 Pharmaceutical aerosols and propellants

A pharmaceutical aerosol is a pressurised dosage form in which the drug, in solution or suspension, is expelled from its container by the pressure of a compressed or liquefied gas propellant through a valve, as a fine spray or mist. A formulation contains the drug concentrate (with solvents such as ethanol and co-solvents and, for suspensions, surfactants such as oleic acid or sorbitan esters to keep particles dispersed and lubricate the valve), the propellant, and sometimes antioxidants and flavouring agents.

Propellants provide the pressure and also act as a solvent and the dispersing medium. The requirements are that they be non toxic, non flammable as far as possible, inert, compatible with the drug and container, and have suitable vapour pressure and density.

- **Chlorofluorocarbons (CFCs):** the original propellants (CFC 11, 12 and 114 blends) were withdrawn from inhalers because they destroy stratospheric ozone; their use was phased out under the Montreal Protocol.
- **Hydrofluoroalkanes (HFAs):** the current standard for metered dose inhalers, mainly HFA 134a (norflurane) and HFA 227 (apaflurane). They do not damage ozone, but they are different solvents from CFCs, so CFC formulations could not simply be refilled with HFA: surfactant solubility, valve elastomers and dose characteristics all changed and products had to be reformulated.
- **Hydrocarbons** (propane, butane, isobutane): used in topical and some oral aerosols; flammable, so limited in inhalation products.
- **Compressed gases** (nitrogen, carbon dioxide, nitrous oxide): used where a liquefied propellant is not wanted; pressure falls as the product is used, which limits their use in metered inhalers.

4.3 Containers and valves

The container must withstand the propellant pressure, protect the contents and not react with them. Materials are tinplate (tin coated steel, often with an additional lacquer coating), aluminium (light, seamless monobloc cans, often anodised or coated), stainless steel and glass (plastic coated glass for low pressure products). Coatings of epoxy or phenolic resins are applied where the formulation attacks the metal. The valve is the functional heart of the aerosol: it seals the container, and for a metered dose inhaler its metering chamber delivers a fixed volume (commonly 25 to 100 microlitres) at each actuation, so that the patient receives a reproducible dose. The actuator (the plastic mouthpiece) contains the orifice that shapes the spray, and its design affects droplet size and spray pattern. Gaskets and valve elastomers must be compatible with modern HFA propellants.

4.4 Types of pulmonary delivery systems and their preparation

- **Metered dose inhalers (MDI):** the pressurised aerosol described above. Preparation involves compounding the drug concentrate, filling it into cans, crimping the metering valve and pressure filling with propellant through the valve (or cold filling with chilled concentrate and propellant at low temperature for suitable products). The dose is reproducible, the device is small and portable, but it demands coordination between pressing and inhaling, and only a modest fraction of the dose reaches the lungs; spacers (holding chambers) are used to reduce throat deposition and coordination problems.
- **Dry powder inhalers (DPI):** breath actuated devices holding the drug as a micronised powder, alone or blended with a coarse lactose carrier or in engineered particles. Inspiration provides the energy to deaggregate the powder, so lung deposition depends on the patient's inspiratory effort. DPIs contain no propellant, are stable and simple, and include capsule based single dose devices and multi dose

reservoir and blister devices (for example Rotahaler, Diskus and Turbuhaler type designs). Preparation centres on producing respirable sized drug particles (micronisation, spray drying) and a blend or particle design that disperses well but flows and fills reproducibly.

- **Nebulisers:** devices that convert a drug solution or suspension into a continuous mist for tidal breathing over several minutes, used for patients who cannot use inhalers (children, the elderly, the very ill) and for large doses. Jet nebulisers use compressed gas through a venturi, ultrasonic nebulisers use a piezoelectric crystal, and vibrating mesh nebulisers push the liquid through a fine vibrating mesh to give a controlled mist with little residual volume.

Feature	MDI	DPI	Nebuliser
Driving energy	Propellant pressure	Patient's inhalation	External (gas, electricity)
Dose per use	Small, metered	Small, metered	Larger, continuous over minutes
Patient coordination	Needed (or use a spacer)	Not needed; needs adequate inspiratory flow	Not needed
Propellant	Yes (HFA)	No	No
Portability	High	High	Low (bench devices)

4.5 Evaluation of aerosol and inhalation products

- **Container and valve tests:** pressure testing and leak testing of cans, valve delivery (shot weight) and dose uniformity through the life of the can, including the number of actuations per container.
- **Spray characteristics:** spray pattern and plume geometry, and for topical products the rate of discharge.
- **Aerodynamic particle size distribution:** measured with cascade impactors (such as the Andersen cascade impactor) or liquid impingers, giving the MMAD, geometric standard deviation and the fine particle (respirable) fraction; this is the central performance test of an inhalation product.
- **Formulation tests:** moisture content (water promotes particle growth and valve problems), flammability of the spray, net contents, and microbial limits.
- **For DPIs:** delivered dose uniformity, fine particle dose at defined flow rates, and performance of the powder blend (flow, blend uniformity, moisture sensitivity).
- **For nebulisers:** output rate, total output, droplet size distribution and residual volume.

4.6 Intra nasal delivery: rationale and physiology

The nasal route is studied as a site specific system in its own right. The nasal cavity is lined by a highly vascular respiratory mucosa with a surface area of about 150 square centimetres, underlain by a rich blood supply that drains towards the systemic circulation. Drugs absorbed across it enter the blood quickly and avoid both gastrointestinal degradation and hepatic first pass metabolism, so the route suits potent drugs that are poorly absorbed orally, including many peptides at least in principle. Its limits are the small volume that can be given (a metered spray delivers about 50 to 140 microlitres per actuation, and volumes much above about 200 microlitres per nostril are swallowed or run out), the mucociliary clearance that sweeps the mucus blanket towards the throat with a transit time of roughly 15 to 20 minutes, nasal enzymes, and irritation with chronic use. Nasal absorption is mainly by passive diffusion across the respiratory epithelium for lipophilic small molecules, with carrier and paracellular pathways contributing for some compounds, and absorption enhancers and mucoadhesive polymers (chitosan, cellulose derivatives, carbomers) are used to prolong residence and open the pathway. Licensed nasal products include corticosteroid sprays for rhinitis,

calcitonin and desmopressin sprays, sumatriptan nasal spray for migraine and naloxone nasal spray for opioid overdose, which shows the range from local to rapid systemic action.

A second, specialised objective is nose to brain delivery: drug deposited on the olfactory region can reach the brain and cerebrospinal fluid along the olfactory and trigeminal nerve pathways, bypassing the blood brain barrier (Unit 1). This is an active research area, using solutions, gels and particulate carriers (mucoadhesive microspheres and nanoparticles) designed to deposit high in the cavity and resist clearance.

4.7 Types of intra nasal systems: preparation and evaluation

- **Nasal drops and simple solutions:** the simplest systems, instilled with a dropper; dose is imprecise and much of the dose is swallowed, but they are cheap and familiar.
- **Metered spray pumps:** the standard modern system. A mechanical pump delivers a fixed volume per actuation as a spray of controlled droplet size; the drug is formulated as a solution or suspension with preservative, viscosity modifier and tonicity agents, and filled into the pump bottle. Droplet size is kept coarse enough (mostly above 10 micrometres) to deposit in the nose rather than be inhaled into the lungs.
- **Nasal gels and mucoadhesive systems:** viscous or in situ gelling formulations (including thermosensitive poloxamer gels) that resist mucociliary clearance and prolong contact; prepared by dispersing the drug in the gel base under controlled conditions.
- **Nasal powders and particulate carriers:** dry powders, and microspheres or nanoparticles of mucoadhesive polymers such as chitosan and starch, prepared by the methods of Units 2 and 3 and administered by powder insufflators; particulates prolong residence and are the main platform studied for nose to brain delivery.
- **Pressurised nasal aerosols:** historically used, now largely replaced by pump sprays.

Evaluation covers: delivered dose and dose uniformity per actuation and through the container life, spray pattern and plume geometry, droplet or particle size distribution, pH, viscosity and tonicity of the formulation, mucoadhesion and residence time studies, in vitro permeation across excised nasal mucosa, ciliary toxicity screening (because preservatives and enhancers can damage the clearance mechanism the product depends on), and stability and microbial quality.

More free M.Pharm notes and unit wise PDFs at pharmacolearn.fyi
Free video lectures on the PharmacoLearn YouTube channel