### Lecture 3

**Inhaled Drugs Reaching Site of Action**

**Spherical and distribution:** quantifies particle size & distribution; takes into account that particles are NOT spherical and are heterogeneous in size

- $D_{aero} =$ diameter of perfect spherical object, with density of 1 g/cm$^3$ & has the same falling velocity as the drug particle
  - Higher the falling velocity, the larger the diameter of the 1 g/cm$^3$ sphere
  - If a drug particle has a density of 4 g/cm$^3$, its aerodynamic equivalent (with a density of 1 g/cm$^3$) would have a larger diameter (would appear larger) than the actual drug particle
- For any given particle, $D_{aero}$ can be calculated from its falling velocity
  - Falling velocity = constant speed a particle will assume when falling, after the initial acceleration phase, due to the forces of buoyancy and drag counteracting that of gravity
  - Falling velocity is affected by the particle’s density, volume & drag coefficient

**Aerodynamic Diameter**

- Determined by $D_{aero}$ of particle

**Corticosteroids:** target intracellular steroid receptors & reduce transcription of pro-inflammatory mediators within the airway wall

- Generations 1-22
- Airway epithelium, submucosal gland cells, inflammatory cells (reduces recruitment & activation)

**Target for Asthma Drugs**

**$\beta_2$-agonists:** target $\beta_2$ adrenergic receptors located on autonomic nerve terminals in the smooth muscle of large & small airways

- Generations 1-22
- Autonomic nerve terminals not located in alveoli because there’s no smooth muscle

**ADVANTAGES OF INTRAPULMONARY DRUG DELIVERY:**

1. Preferable pharmacokinetics $\rightarrow$ enhanced therapeutic efficacy
   - Faster onset of action; full therapeutic concentration of drug attained at site of action quickly
   - Reduced time to peak therapeutic effect
   - Slower clearance of drug deposited in the airways compared to systemic drug clearance
2. Minimization of adverse effects & toxicity
   - Because drug is delivered to the site of action, a lesser dose is required to attain the therapeutic effect
   - Also means less systemic exposure to the drug

**Mechanisms of Intrapulmonary Particle Deposition**

**Inertial Impaction:** $\geq$ 8-10 µm

- High momentum upon inspiration
- Unable to change direction with airflow at branch points in airways $=$ impacts itself at back of mouth, trachea, branch points, etc
- Largely deposited in URT

**Sedimentation:** 0.5 – 5 µm = Ideal Particle Size

- Momentum allows for change of direction with airflow = reaches lower airways
- Mass sufficient such that gravitational force allows for particle sedimentation in mucous layer of airway wall (mostly alveoli)

**Diffusion:** $\leq$ 0.5 µm

- Low momentum, readily changes direction with airflow & Brownian motion occurs
- Deep penetration into airways & alveoli, but poor impaction
- Low mass, so gravity cannot readily facilitate sedimentation into mucous layer of airway wall
- Much is exhaled upon expiration

**Drug Clearance From Lung**

- Exhalation
- Systemic circulation
- Lymphatic uptake
- Enzymatic degradation (in cells, interstitial fluid, mucus linings) – ex/CYP450, peptidases, esterases
- mucociliary escalator clearance: particles are expectorated or swallowed
  - Cells lining upper airways covered with cilia that beat at 1000 beats/min in an upward motion toward throat
  - Particles impacted in upper airways is trapped in mucus & moved by ciliary transport, aided by coughing & sneezing
AEROSOL: a suspension of fine solid particles or liquid droplets, or solid particles dispersed within liquid droplets, within a gas phase
> Ex / fog, perfume spray, haze (pollution), clouds, sunscreen spray
> Aerosols don’t necessarily originate from pressurized system

pMDI aerosol: a pressurized delivery system that, upon actuation, emits a fine dispersion of liquid droplets and/or solid particles containing one or more active ingredient in a gaseous medium

METERED DOSE INHALERS

OVERVIEW
- Multidose, versatile devices
- Drug is expelled in a metered volume of “Liquefied Gas Propellant” (LGP) from a pressurized container
  - Other excipients may be used
- Formulated as solutions or suspensions
- Particle size = critical issue (target = 0.5 to 5 \( \mu m \))

pMDI aerosol formation: actuation opens valve, allowing LGP + drug to exit nozzle
> Upon evaporation of propellant from aerosol, solid particles form and agglomerate = residual particles – have the correct MMAD, allowing delivery to desired regions of respiratory tract with inhalation = residual particles

Propellant physiochemical properties & requirements:
- Boiling point must be well below ambient temperatures
- Within a closed, pressurized container, forms a two-phase system comprised of saturated vapor + liquid, in dynamic equilibrium
- Gives constant vapor pressure with varying volumes of liquid within the closed container system (i.e. must be highly volatile)
- Non-flammable, non-toxic
- Compatible with drug

Dose metering in pMDIs:
1. Canister not depressed: metering of a single dose (liquid enters chamber)
2. Canister partially depressed: disconnects metering chamber
3. Canister fully depressed: discharge of dose from metering chamber

Factors affecting residual particle size (MMAD):
- Chemical nature of propellant, including co-solvents, and its rate of evaporation
- Orifice diameter of actuator nozzle
- Solutions tend to generate finer residual particles than suspensions
  - In susp: size of suspended particles affects residual particle MMAD

HFA-134A: major propellant used
- Boiling point: -26.3°C (at 1 atm); vapor pressure: 5.6 atm (at 20'); somewhat non-polar (LogP = 1.1)
- Formulation with HFA challenging due to solubility issues
  - No clear correlation b/w drug LogP & solubility in HFA
  - Approved surfactants to aid with drug wetting/solubility are insoluble in HFA

HFA Solutions: despite poor solubility, solutions are made possible via use of co-solvents (almost all ethanol \( \pm \) water)
> Ethanol can aid with dissolution of hydrophilic drugs via H-bonds, and via van der waals for hydrophobic drugs
> Water can aid with drug dissolution via H-bond formation
  - Not completely evaporated prior to inhalation, therefore can maintain particle MMAD above a minimum threshold
- Co-solvents also lower vapor pressure inside the canister, and generally increases the MMAD of residual particles
- Ethanol can affect the structural morphology and aerodynamic diameter of the aerosolized drug particles generated (above 10% w/w, MMAD > 5\( \mu m \))
- Single use of a marketed HFA-ethanol pMDI was found to have a BAC of 0.015 mg/100mL

HFA Suspensions: crystalline drug must be processed to yield particles having a suitable size & size distribution (milling, spray drying, supercritical fluid methods) prior to susp. In HFA
> Size of suspended particles to yield residual particles with the correct MMAD & size distribution must be determined experimentally

MDIs in asthma: for \( \beta_2 \) agonists, pMDI are not better than other DDS, but are cost-effective = GOLD STANDARD
SPACER DEVICES
- Increases distance between orifice and oropharynx
- Decreases velocity of spray entering the oropharynx, facilitating less impaction of drug particles in the back of mouth (due to less momentum) = increased proportion of residual particles that can be delivered to targets = IMPROVED LUNG DEPOSITION AND INCREASED EFFICACY
- Allows more time for LGP vaporization/evaporation, so droplet size is smaller (which can enhance lung deposition
- Actuation/inhalation synchronization is less or not important
- Reduced oropharyngeal side effects for steroids (throat irritation, dysphoria, thrush)

DRY POWDER INHALERS (DPI)

**Overview:** designed to eliminate coordination problems associated with MDIs, and to eliminate CFC-containing MDIs
- No propellants = PURE DRUG or DRUG-CARRIER MIXTURE delivered from device as dry powder
- Devices are BREATH ACTUATED = powder inhaled only when patient inhales
- Drug particles have been processed for size reduction into critical particle MMAD size

**Drug carriers:** carriers prevent drug particle aggregation (strong tendency with fine particles/powder due to increased surface free energy) → ensures that DPI system can deliver de-aggregated drug particles which have the correct MMAD
  > Lactose powder (particle size 30-100 µm) commonly used as a carrier

**Factors influencing lung deposition**
1. **Particle de-aggregation:** poor lung deposition associated with inefficient drug particle deaggregation
   > To ensure particle de-aggregation:
     a. Use lactose as a carrier
     b. Generate turbulent airflow within the DPI device (no carrier or other excipient needed EXCEPT in Oxeze)
2. **Inspiratory flow rate:** poor lung deposition is associated with a poor inspiratory flow rate (IFR)
   > DPIS are passive systems, so pt must provide energy to disperse powder from device
   > Higher shear forces lead to greater proportion of de-aggregated drug particles, which depends on pts ability to pull a certain airflow through the device
   > Pts with compromised respiratory fxn may not be able to generate sufficient IFR
3. **Ambient temperature and humidity:** exposure of powder to moisture and changes in temp. could compromise efficacy of device
   > Moisture/temperature fluctuations could cause drug dissolution, recrystallization and particle aggregation

**Stripping of drug from lactose carrier particles:**
1. Dry powder formulation is a drug-carrier mixture (static powder bed)
2. Drug/carrier mixture dilates and forms an aerosol
3. With continuous airflow, drug aerosol is stripped from lactose carrier
4. Lactose particles impact, while drug particles go to target site

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**Diskus:** unit-doses of drug-carrier mixture are contained in foil blister packs within the device
  > Index wheel guides the blister pack strip to the mouthpiece (via a “ratchet mechanism”) and peels off the foil lid
  > On inhalation, the powder moves into the airstream

**Turbuhaler:** inhaled airstream picks up powder loaded in dosing unit, passes through inhalation channels and through mouthpiece
  > The spiral inhalation channel facilitates TURBULENT AIRFLOW sufficient to cause de-aggregation of drug powder (or drug-carrier mixture for Oxeze)

**Spiriva HandiHaler:** blister-packed capsules containing TIOTROPIUM BROMIDE, blended with lactose carrier
  > Capsules that are exposed to air and not used immediately should be discarded (humidity)
  1. Capsules placed into centre chamber of HandiHaler device & is pierced by pressing & releasing button on side
  2. Drug-carrier mixture is dispersed into the airstream when pt inhales through mouthpiece, and drug is stripped from carrier with airflow for deposition to the target regions of the lung

**Nebulizers:** liquid in separate unit-dose nebul (diluted wi/ water or saline) → placed in a reservoir/nebulizer unit → compressed air continuously fed into unit & creates aerosol → aerosol droplets inhaled (mouthpiece, face mask
  > Lung deposition is variable, depending on nebulizer device & operating condition – most air or O₂ is lost