Pulmonary Drug Delivery and Aerosols

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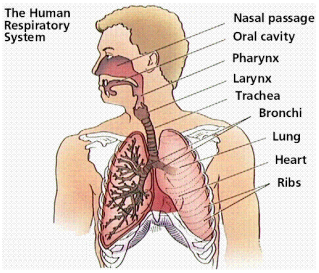
11/24/2015

Respiratory System



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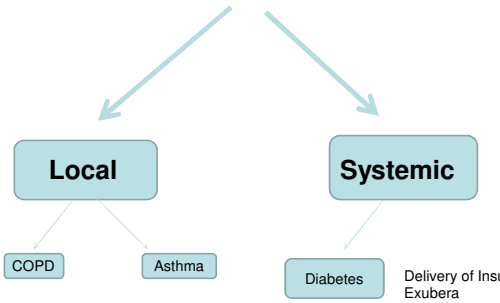
Pulmonary Drug Delivery



Delivery of Insulin. Exubera

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Aerosol Delivery of Insulin

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The Lung

1. Highly permeable membrane
2. Low in metabolic activity compared with the liver and intestine.
3. Large surface area 100 m^2 of absorptive area.
4. For the lungs (target organ) drug must be deposited past the oropharyngeal region.

To achieve therapeutic effectiveness

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Factors affecting drug absorption

1. Particle size influences the delivery of drug to the correct part of the Respiratory System.
   - Small particles penetrate more deeply and effectively dilate small airways in the lung.(figure14.11).
2. In solutions solubility of drug in HFA is a limiting factor.
   - How would you improve the solubility?
   - Suspension stability?

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***Some material in this handout was adopted from Dr. Atef's handouts

Pulmonary Drug Delivery

Treatment of local disease

1. Administered quickly → Rapid clinical response
2. Reduce systemic side-effects
3. Bypasses first-pass metabolism or avoid poor GI absorption.
4. Deliver high drug concentration to the diseased site.
5. Reduced dose in micrograms as opposed to mg

Treatment of systemic disease

1. Non-invasive delivery system.
2. Low enzymatic environment. Bypass first-pass metabolism.
3. Large surface area for absorption. Highly permeable membrane.
4. Aerosol particles <5 µm generally deposit within the lungs.
5. Prolonged residency in the lung due to slow mucociliary clearance.

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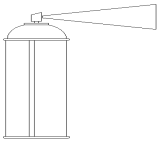
Aerosols



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Aerosols

- Pharmaceutical Aerosols are pressurized dosage forms containing one or more active ingredients which upon activation emit a fine dispersion of liquid and/or solid materials in a gaseous medium.
- They are dispersions.

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Aerosols

- Used to administer drug:

1. To the lung → Local or systemic.
2. Topical

- The aerosol has two principle ingredients:

1. The active.
2. The propellant.

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Aerosols

- Medication is in pressurized package.
- Pressure is achieved through one or more liquefied or gaseous propellants.
- Upon activation of the valve, pressure forces the content out.
- The physical form of aerosol depends on the formulation and the type of valve.

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Physical form of the product

- Fine mist, a coarse, wet, dry spray, steady stream, a stable or a fast-breaking foam.
- Fine mist can travel longer distance: e.g asthma (6µm bronchioles, 2 µm alveoli)
- Coarse(powder, wet spray, stream of liquid) → Dermatological
- Foams → Vaginal & Rectal

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Advantages of Aerosol

1. Easy to use, clean and convenient process.
2. The dose is withdrawn from the package without contaminating other doses.
3. Protect unstable drug from light, oxygen and moisture sensitive products.
4. Target sites need not to be touched e.g burns
5. Dose controlled sometimes through metered valve.

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Disadvantages

- Expensive
- Environmental hazards
- Dose measurement
- Dose may change with pressure change inside the aerosol.
- Performance can deteriorate during life of the product.
- Limited safety hazard
  - Flammable
  - Pressurized

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Aerosols

SAA enhances emulsification of concentrates & propellants and stabilizes the foam

1. Product concentrate: active ingredient combined with:
   - Antioxidants (ascorbic acid,..)
   - Dispersing agents, **SAA**
   - Solvent blends (water,ethanol, glycols..
2. Propellant: provides the driving force to expel product from container.

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Propellant

1. Compressed gases (N_2, CO_2)
2. Fluorinated hydrocarbons
   1. Chloroflurocarbons (CFC)
   2. Hydrofluoroalkanes(HFA)
3. Hydrocarbons

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Used when dose is not critical

Compressed Gas Propellants

- Advantage
- Low toxicity
- High stability
- High purity
- Inexpensive
- No environmental problems

- Disadvantage
- Produces coarse mist
- **Pressure falls during use**
- Require use of non-volatile solvents

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Fluorinated hydrocarbons Chlorofluorcarbons (CFCs)

- **Phased out**
- Nonflammable relative to the flammable hydrocarbons.
- They are gases at room temperature , liquefied by cooling
- Their use have been limited due to environmental issues .

- **Advantage**
- Low inhalation toxicity.
- High chemical stability.
- High purity.
- Good solvent.

- **Disadvantage**
- Destructive to ozone.
- High Cost.

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Propellant

3 conditions for Fluorinated hydrocarbon use

1. There is no alternative technique for chlorofluorocarbon (CFC).
2. The product provides substantial health benefit.
3. The use does not involve significant release of CFC.
   - Replacement of CFCs based MDIs with hydrofluoroalkanes (HFA) propellants.

Proventil ⟶ Proventil HFA

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Hydrofluoroalkanes(HFA)

- **Advantage**
- Low inhalation toxicity
- High chemical stability
- High purity
- Not ozone depleting

- **Disadvantage**
- Poor solvents
- High cost

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Hydrocarbons

•Most commonly used now
•n-butane, propane, iso-butane have largely replaced fluorocarbons for topical pharmaceutical aerosols.

- **Advantage**
- Inexpensive
- Minimal ozone depletion
- Minimal Global warming effect
- Excellent solvents

- **Disadvantage**
- Flammable
- Aftertaste
- Unknown toxicity following inhalation

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Why?

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Aerosol principle

- The gas propellant exerts pressure in all directions
- Upon actuation, the gas will push the liquid phase out.
- The propellant expands once it meets the air leaving the product concentrate in mist or dry powder.
- An equilibrium is established again in the aerosol if the propellant is a liquefied gas, the pressure inside remains constant. As long as part of the propellant is available as liquid

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Aerosol Phase Systems

1. *Two Phase System.*
2. *Three Phase System.*
3. *Compressed Gas System.*

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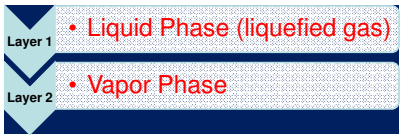
Two Phase Systems (Solution System)



- Product concentrate is dissolved in liquid phase= liquefied propellant . This solent creates a homogenous system.
- Simplest system.
- Co-solvents are added to enhance the solubility of the active ingredients.
- Produces a fine mist or wet spray for inhalation e.g nasal application.

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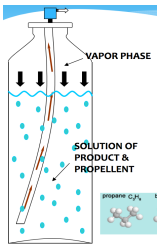
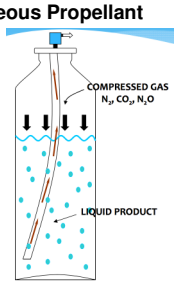
Two Phase Systems

Liquified propellant



Gaseous Propellant



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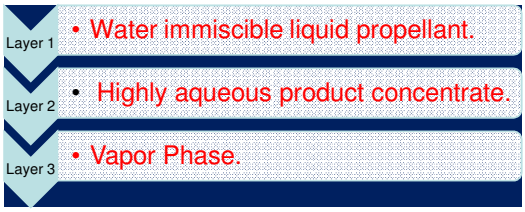
Three Phase System



1. Dispersion system (suspension)
2. Foam system (emulsion)
3. Water based system (solution)

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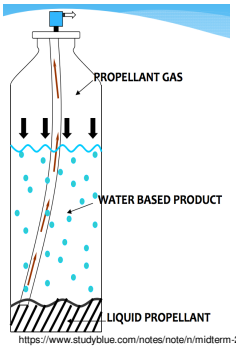
Three Phase System



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Compressed Gas System

- None liquefied gasses.
- Nitrogen gas is not soluble in the liquid concentrate
  - (inert and protect product from oxidation).
- CO_2 is slightly soluble, good if foamy consistency is required.
- The pressure diminishes as the product is used so higher gas pressure is required.

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Aerosol Container and Valve

- The effectiveness of the product is determined by the formulation, container and valve assembly.
- Formulation must not interact with the container.
- Container and valve must withstand pressure required by product.
- Container and valve must resist corrosion.
- Valve contributes to the form of the product emitted.

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Container

- **Glass:**
  - coated or uncoated (good compatibility)
- **Metal:**
  - Tin-plated steel
  - Stainless steel may be used when chemical resistance is required, very expensive
- **Plastic**
  - Permeability, interactions with drug are limitations

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Valve Assembly

- Actuator:
  - the button to open and close the valve,
  - contributes to the form of
  - discharged product and the particle size
- Stem: actuator supporter
- Gasket: to prevent leakage
- Spring: pushes the actuator back when closed
- Mounting cup
- Housing: determines the delivery rate and form
- Dip tube:
- Fig:14:13

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Types of Aerosols

1. Pressurized Metered dose inhalers (pMDI).
2. Dry powder inhalers (DPI).
3. Nebulizer.

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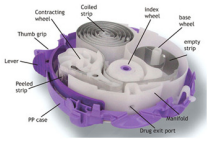

Google images

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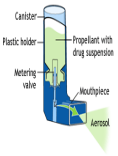
MDI



- Metering valves are used when formulation is potent.
- Translingual aerosol Nitroglycerin spray

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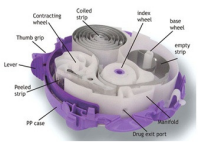
DPI

Dry powder devices are popular as they are
- Portable
- Require no Propellant.

- 1st generation: Rotahaler- single capsule.
- 2nd generation: Turbuhaler
- 3rd generation: Diskus



Aerosol Filling

A-Cold Filling: -34.5 to 40 ^{O}C

- Chilled product concentrate added.
- Cooling system may be a mixture of dry ice and acetone.
- Liquefied gas added.
- Valve is assembled.
- Is it suitable for aqueous system?

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Aerosol Filling

B- Pressure Filling

- The product concentrate is added to the can at room temperature.
- The valve is fitted.
- Propellant injected under pressure.
- Actuator is fitted and tested.

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Testing the container

- Leak testing
- Valve proper function
- The spray, amount, particle size
- Reproducibility of the dosage

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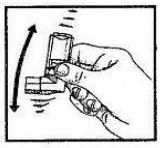
Patient Consultation



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Pharmaceutical Aerosols

Respiratory:
For bronchospasms Albuterol, anti-anginal
Topical aerosols

- Anti-infection : Povidone iodine
- Local anesthetics : Benzociane

Vaginal Aerosols

- Estrogenic and contraceptive (foam spray)

Rectal aerosols

- Hemorrhoidal treatment, pramoxine HCl (hydrocortisone)

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Questions

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