Aerosols

and Foams

OVERVIEW

1. Aerosol systems
2. Properties of aerosols
3. Aerosol Formulations
4. Sprays and foams
4. Propellant systems
5. Containers and valves

REFERENCES

- Florence and Attwood
  Physicochemical Principles of pharmacy
- Lieberman et al.
  Pharmaceutical Dosage Forms: Disperse Systems
- Lachman et al.
  Theory and Practice of Industrial Pharmacy
- Banker & Rhodes
  Modern Pharmaceutics

AEROSOLS

A large range of products -

- Inhalation via respiratory tract
- Nasal sprays
- Oral sprays
- Topical preparations
- Into body cavities

ADVANTAGES

1. Maintain sterility
2. Enhance stability of 0_2/H_20 sensitive compounds
3. Rapid action due to delivery of medication directly to the affected area
4. Unit dose concept (MDI = metered dose inhalers) delivers a constant dose
5. A reduction in systemic side effects
6. Avoidance of liver first pass effect
7. No gastrointestinal irritation
8. Can apply from a distance

DISADVANTAGES

1. Expensive - propellant and technology
2. Formulation and stability can be problematic
3. Limited applicability to certain drugs and conditions
4. Environmental concerns
5. Bulky size

Aerosol formulation considerations

- Require low dose
- Reasonably soluble
- Permeability
- Metabolism in respiratory tract and lungs
- Non-irritating to respiratory mucosa
- New toxicology profile required

AEROSOL SYSTEM

- A system that depends on the power of a compressed or liquefied gas to expel the contents from the container.

- Product concentrate
- Propellants
- Container
- Valve assembly

A colloidal dispersion system

Dispersed Phase	External Phase	Product
S	G	Solid Aerosol
L	G	Liquid Aerosol
G	L	Foam

The droplet size = 0.5 - 50 µm

The control over particle size is crucial depending on the desired therapeutic effect

CLASSIFICATION OF AEROSOL SYSTEMS

1. Homogeneous or Solution system
2. Heterogeneous or Suspension system
3. Emulsion system

The choice of system depends on
1. Physicochemical properties of the drug (e.g. solubility)
2. Therapeutic application

HOMOGENEOUS AEROSOLS

(Solution Systems)

Two phases

1. liquid phase - a solution of
   - active ingredients in
   - pure propellant or a mixture of propellant and co-solvent
2. vapour phase
   – propellant

Typical formulation for homogeneous aerosol system

- actives 0.1-5%
- co-solvent 0-20% q.s
- propellants to 100%

- Co-solvent in liquid phase of homogeneous aerosol formulation is used to:

1. dissolve active ingredients into the propellant solution
2. retard the rate of evaporation of the propellant to control the final particle size

Co-solvents in the solution aerosol retards the rate of evaporation of the propellant system

Co- solvents with higher boiling point evaporate more slowly ⇒ larger particle size

- No co-solvent in solution ⇒ propellant alone evaporates rapidly ⇒ a smaller aerosol particle size
- With co-solvent ⇒ retard the rate of evaporation of propellant ⇒ larger particle size

Control over particle size depends on –

- the type and concentration of propellant
- the choice of co-solvent
  e.g. ethanol is a good co-solvent
  – miscible with water and non-polar propellants
  – non-toxic
- the co-solvent/propellant ratio
- valve design

Upon depression of the valve -

- active/co-solvent/propellant is emitted
- as the propellant vaporizes, it breaks up the size of the expelled liquid droplets
- produces the final particle size range 5-100 um
- MDI systems typically deliver particle size < 8 μm

HETEROGENEOUS AEROSOLS (Suspension Systems)

- For actives that are insoluble in the propellant mixture
- When co-solvent is not desirable
- Active ingredients are dispersed in the propellant system
- When the aerosol suspension is emitted, propellant vaporizes leaving behind the finely divided solid drug

Typical formulation for heterogeneous aerosol system:

- actives 0.1-5%
- dispersing agent 0 -10%
- propellant to100%

Suspension Aerosol Formulation considerations

- particle size of solid
  - uniform dispersion of drug particles in the propellant
  - therapeutic application
- solubility of active ingredients
  - "All in" or "All out" approach
- % H_20
  - Stability
- Use of dispersing agents
  - sorbitan oleate, lecithin, oleic acid for inhalation
  - isopropylmyristate for topical application

Heterogenous formulation can be problematic due to:

- caking
- agglomeration
- particle size growth
- clogging of valve with solid drug
- powder adhere on container $\Rightarrow$ uneven "unit dose"

"All in" or "All out" approach

- common formulation principle for suspension aerosols and oral suspensions
- As solid drug is present, tend not to use co-solvent in these systems as best to have drug "all in" or "all out"
- otherwise $\rightarrow$ crystal growth through Ostwald ripening

OSTWALD RIPENING

- Smaller particles tend to redissolve and then precipitate out on larger particles
- The smaller particles tend to have a higher solubility and dissolve while the larger particles will grow (or) "ripen"
- Particle growth
  - Physical instability
  - Therapeutic failure
  - Adverse effects

Solution *vs* Suspension systems

- Solution based aerosols are "easier" to formulate
- Suspension systems are often preferred as –
  - closer control over the final particle size
  - the stability is often better than solution systems

EMULSION AEROSOL SYSTEMS

- Many drugs are water soluble and water is the common formulation vehicle
- But water and liquid propellants are not miscible
- Emulsion aerosol formulations using surfactants

Emulsion aerosol

1. active ingredients
2. vehicle (aqueous or non-aqueous)
3. surfactant
4. propellant system
   - three phases
   1. vapour phase (force to expel contents from the can)
   2. liquid phase
   3. emulsified phase

- depending on the formulation, emulsion aerosol can produce either foam or a spray

Spray

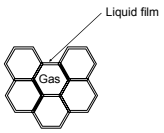
- The propellant is the external phase
- Water is in the internal phase
- w/o emulsion
- When the formulation is dispensed, the propellant vaporises directly into the atmosphere leaving a fine wet spray

FOAM

- The propellant is the internal phase
- Water is in the external phase
- o/w emulsion
- When dispensed, propellant vaporised forming gas in liquid –
- i.e. foam

FOAMS

- Topical preparations
  - Vaginal products
  - Rectal products
  - Spermicidal
  - Thermal (exothermic)
- A foam is a gas in liquid dispersion where gas is surrounded by an intact liquid film



- It is the composition of the liquid film that will enable a foam to form
  - e.g. foam will not form in pure H_20

Time	Solute components
0	pure solvent
sec	inorganic salts
minutes	low MW alcohols/acids
days, months	SAA

- require film stabilizers $\Rightarrow$ surfactant based systems
- The charged SAA generally produce more stable foam than the non-ionic SAA

1.Dilute foam
- nearly spherical bubbles separated by rather thick films of a viscous liquid

2.Concentrated foam
- mostly gas phase separated by a thin liquid film

Foam stability issues

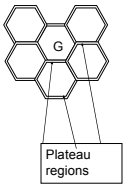
Highly unstable due to -
- large surface area
- high free energy

- The major destabilizing factors are:

1. tendency of film to drain and become thinner
2. tendency to rupture as a result of random disturbances
3. evaporation & gas diffusion through film

Foam drainage

- upon formation, the film is quite thick
- thinner under the influence of gravity
- tend to flow to plateau regions



Factors affecting film thinning

- VDW attractive forces → thinning
- EDL → opposes thinning
- Viscosity → opposes thinning

SELF HEALING FOAM

- local stretching of film ⇒ film thinning
- ↑ surface area ⇒ relative ↓ in concentration of SAA in the deformed region⇒ ↑ in the surface tension ⇒
- diffusion of extra SAA to region of ↓ [SAA] to restore concentration ⇒
- SAA bring water of hydration with it
- thickening of the film ⇒ film recovery

- Surface elasticity is the property that is responsible for the durability of the foam

Anti-Foaming agents can break foams by:

- reduce or eliminate surface elasticity
- ↑ speed of drainage
- make foam less viscous
- ↓ EDL repulsion

Foam and aerosol sprays

- Need to form the emulsion within the can by shaking ⇒ SHAKE THE CAN
- The nozzle/orifice design is also important in determining the "particle size".

PROPELLANT SYSTEMS

- provide the force to expel contents
- Influence the characteristics of the expelled material e.g. foam or spray

2 major propellant systems

1. liquefied gas propellant
2. compressed gas propellant

LIQUEFIED GAS PROPELLANTS

- low boiling point, low or no odour, non-toxic, non-irritating
- vapour pressure of the propellant controls the pressure within the container
- as long as liquid propellant present, the vapour pressure will be constant
- generally use a mixture of propellants to obtain required pressure, particle size and spray characteristic
- May be subjected to hydrolysis

- e.g. liquefied propellants: CFCs
  - Global concerns over effects on ozone depletion (1981-1987)
- CFCs are replaced with non-ozone-depleting chemicals called hydrofluroalkanes (HFA).
- HFA does not alter the active ingredients delivered to the lungs.
- A different taste and warmer sensation with HFA.
- HFA delivers constant amount of medication even at very low temp e.g. -10 C.

Liquefied hydrocarbons

- Propane, butane, iso-butane
- 1/10 cost of CFC's
- similar performance to CFC's
- FLAMMABILITY
- not suitable for personal products

COMPRESSED GAS PROPELLANTS

- N_2, 0_2, CO_2, N_20 (laughing gas)
- used a lot in food products
- best use is when large amounts of water present
- these systems will produce a wet spray

N_2 is generally favoured as non-toxic, colourless and tasteless for solution systems

CO_2 and N_20 generally used with foam systems

Compressed gas propellants

- no dispersing power compared with liquefied gases
- do not vaporize ⇒ valve design to produce different sprays
- as the can is used, there will be ↓ in pressure ⇒ start off with higher pressure

AEROSOL FORMULATION AND STABILITY ASPECTS

- 2 major components of the aerosol formulation
  - product concentrate
  - the propellant system
- Product concentrate may contain:
  - Active ingredients
  - solvent
  - anti-oxidant
  - surfactant
  - dispersing agent

Formulation considerations continued –

- aim for the drug to be either "all in" or "all out" of solution
- Re-dispersability of the suspension
- small amount of H_20
- aim for ideal vapour pressure
- foams
- temperature testing of the container

"Manual" Sprays

- These systems do not rely upon a propellant system to expel contents
- Various manual spray systems are designed to deliver finely divided particle or droplets to the nasopharyngeal region and the upper respiratory tract.

- Insufflator
  - Inhaled air draws powder to the required region
  - The particle size is governed by the original formulation
    - e.g. Intal spin haler (Sodium Cromoglycate)
- Nebulizer
  - operated through face mask and a pump with a curved chamber that controls the final particle size
    - E.g. Ventolin nebuliser
- Atomisers
  - Designed to discharges liquid in fine spray
  - Vacuum type atomiser
  - Pressure type atomiser

CONTAINERS AND VALVES

- Safety concerns → rigorous standards for containers
- Different valves are designed to produce different spray formation and patterns

Containers
- Metal
- Glass
- Plastic

Metal containers

Tin
- most common
- thickness → pressure rating
- potential for corrosion

Aluminium
- more expensive
- lighter in weight
- bursting strength is higher
- corrosion resistant
- a "one-piece" container
- good permeation barrier

Glass containers

- potential for breakage
- resists corrosion
- good permeation barrier
- compatibility with formulation components
- generally use plastic coated glass to avoid potential safety concerns
- aluminium systems have replaced a lot of glass based containers.

Plastic containers

- strong and resistant
- easy to mould
- plasticizer migration problems
- permeability concerns
- some odour problems

Valves

•a large variety of designs

•valve designs for "unit dose" systems

•choice depends upon the product, and required particle size