Powder

Aulton
Chapter 8-10,14,24

Powders

Powders are important in the development of pharmaceutical products since many formulations either is powders or contain powders
Pharmaceutical powders

- Different types of powders
  - Oral powders
  - Topical powders, dusting powders
  - Powders for inhalation
  - Insufflations

- Powders as a starting material
  - Capsules
  - Tablets
  - Dispersions
  - Injections
    - Suspensions
    - Reconstituted

Oral powders

- Types of powders
  - Bulk powders > 5 ml
  - Divided powders
  - Granulates or free powders
  - Oral antibiotics

- When are drug formulated as oral powders
  - When the substance is sensitive to water
  - When large dosing volumes make tablets unsuitable
  - When the powder cannot be compressed
  - When rapid onset of the therapeutic effect is desired
Pharmacokinetics of powders

- Depends on the route of delivery
- The solubility of the formulation
- The size of the particles

Pharmacokinetics the oral route

- Depends on
  - Conditions in the GI-tract
  - Transport in the GI-tract
  - Release from formulation
  - Transport over epithelial cells
- Rate of uptake
  - solution > dispersion > powder > tablets
The GI-track

- A “hostile” environment for many drugs due to
  - pH
  - Enzymatic degradation
- The environment changes drastically during transport
- The gastric emptying differs for large and small objects.
  - Non-disintegrating tablets 0.5-4.5 H
  - Small particles gradually over around 1.5 hours
- Gastric emptying is influenced by:
  - Food
  - Body position
  - Drugs (for example morphine)

Physiological conditions in the gut

<table>
<thead>
<tr>
<th></th>
<th>pH</th>
<th>Membrane</th>
<th>Adsorption</th>
<th>Surface Area</th>
<th>Transit Time</th>
<th>Bypass liver</th>
</tr>
</thead>
<tbody>
<tr>
<td>BUCCAL</td>
<td>approx 7</td>
<td>thin</td>
<td>good, fast absorption with low dose</td>
<td>small</td>
<td>short unless controlled</td>
<td>yes</td>
</tr>
<tr>
<td>ESOPHAGUS</td>
<td>5 - 6</td>
<td>very thick, no absorption</td>
<td>-</td>
<td>-</td>
<td>short</td>
<td>-</td>
</tr>
<tr>
<td>STOMACH</td>
<td>1 - 3</td>
<td>normal</td>
<td>good</td>
<td>small</td>
<td>30 – 60 minutes</td>
<td>no</td>
</tr>
<tr>
<td>DUODENUM</td>
<td>6 - 6.5 bile duct</td>
<td>normal</td>
<td>good</td>
<td>large</td>
<td>very short, window effect</td>
<td>no</td>
</tr>
<tr>
<td>SMALL INTESTINE</td>
<td>7 - 8</td>
<td>normal</td>
<td>good</td>
<td>very large</td>
<td>about 3 hours</td>
<td>no</td>
</tr>
<tr>
<td>LARGE INTESTINE</td>
<td>5.5 - 7</td>
<td>-</td>
<td>good</td>
<td>not very large</td>
<td>long, up to 24 hr</td>
<td>No rectum yes</td>
</tr>
</tbody>
</table>
Loss of substance in the GI-tract

- pH-induced degradation (Losec)
  - Enteric-coated tablets
  - Pro-drugs
- Enzymatic degradation
  - Stomach: Pepsin
  - Pancreatic enzymes
    - Trypsin & Chymotrypsine
    - Carboxypeptidase
    - Lipases
    - Amylase
    - Deoxyriboonuclease
- Complex formed between the drug and normal components in GI tract
- Mucine and Streptomycin
- Interaction with food
  - Milk Ca²⁺ and Tetracyclines
- P-glycoproteins
  - Transport certain active compound such as verapamil out of the cell
  - Are a reason for failure of cancer therapy

What decides the Quality of Powders

- What influences the release of a powder?
- What influences the dosing of a powder?
- What influences the chemical (and microbiological) stability of a powder?
- What influences patient compliance of a powder?

Discuss in groups
Important properties of powders

- Particle size
- Flowability
- Particle morphology
- Physical properties of the solid
  - Hardness and brittleness
  - Surface energy
- Water content and uptake

For oral powders
- Taste
- Texture and mouth feel
- Homogeneity

Particle size

- Effects
  - Dissolution
  - Bioavailability
  - Transport and filling
  - Content
  - Mixing and demixing
  - Volume

- Important characteristics of particle size
  - Average particle size
  - Particle size distribution
  - Skewness of particle size distribution
  - The results from particle size measurements will be affected on shape of the particles
**Measurement of particle size**

- **Projected circles**
  - Projected perimeter
  - Projected area
- **Ferret diameters**
  - Mean = the mean over several orientations
  - Y = largest
  - X = smallest
  - Elongation = Y/X
- **Equal spheres**
- **Aerodynamic diameter**
  - The diameter of a sphere with similar density that settles with the same speed

**Particle size distribution**

- **Mean diameter**
  - Standard mean
  - Geometric mean = median
  \[ D_g = \sqrt[n]{\prod D_i} \]
- **Standard deviation**
  - Geometric
- **Skewness**
  \[ IQCS = \frac{(D_{75%} - D_g) - (D_g - D_{25%})}{(D_{75%} - D_g) + (D_g - D_{25%})} \]
Methods to measure particle size

• Sieving
  ➢ Measures: projected perimeter, square or circle
  ➢ Size range: 5-125 000 µm
  ➢ Principle of operation
    • The weight of particles collected on individual sieves in a stack of sieves.
    • The sieves may be mechanical vibration for preset time and speed
    • Air-jet sieving: use of individual sieves at a reduced pressure and with a stream of air that blows away oversize particles that block the sieve

• Microscopy
  ➢ Measures: two dimensional projection of the particle
    • Ferret diameters
    • Equal circles
  ➢ Size range: 0.001-1000 µm
  ➢ Principles of operation
    • Light or electron microscopy
    • Projection screen or circles
    • Image analysing programs

Powder grades according to BP

<table>
<thead>
<tr>
<th>Description</th>
<th>Sieve diameter µm</th>
<th>A sieve that does not allow more than 40% to pass µm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coarse</td>
<td>1700</td>
<td>355</td>
</tr>
<tr>
<td>Moderate coarse</td>
<td>710</td>
<td>250</td>
</tr>
<tr>
<td>Moderate fine</td>
<td>355</td>
<td>180</td>
</tr>
<tr>
<td>Fine</td>
<td>180</td>
<td></td>
</tr>
<tr>
<td>Very fine</td>
<td>125</td>
<td></td>
</tr>
</tbody>
</table>
Other methods of size determinations

<table>
<thead>
<tr>
<th>Light scattering area diameter, or volume diameter</th>
<th>Size range</th>
<th>Principe of operation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.0001-1000 µm</td>
<td>Measuring the the scattering of light Fraunhofer diffraction, in the forward mode, measurement of diffraction patterns Small particles: side scattering of different wavelengths and different polarity</td>
</tr>
<tr>
<td>Sedimentation Frictional drag diameter, or stoke diameter</td>
<td>0.3-200 µm</td>
<td>Sedimentation in the gravitational field Sedimentation due to centrifugal forces</td>
</tr>
<tr>
<td>Coulter counter Volume diameter</td>
<td>0.1-1000 µm</td>
<td>Measuring changes in resistance when a particle passes through a small hole in a sapphire crystal</td>
</tr>
<tr>
<td>Cascade impactors Measure: aerodynamic volume, and drug content</td>
<td></td>
<td>Imitating the turouity of the respiratory tract. Catching the particles on plates and using analytical methods or measurement of mass to determinate the amount on each plate</td>
</tr>
</tbody>
</table>

Flow properties

- **Affect**
  - The uniformity of feed from bulk storage, and from hoppers during tabletting
  - The reproducibility of the filling of tablet dies and capsules
  - Transport
  - Homogeneity during storage
  - Mixing

- **Are affected by**
  - Particle size
    - Fine particles are more cohesive than larger ones
  - Particle geometry and surface roughness
    - Spherical particles have the best flow properties
  - Particle density
    - Dense particle usually show the largest flow
Flow properties and powder density

- Angle of repose
- Bulk density
  - Tapping density
  - Carrs index
    \[ \text{Carrs index} = \frac{\text{tapped} - \text{poured density}}{\text{tapped density}} \]
  - Hausner ration
    \[ \text{Hausner ratio} = \frac{\text{tapped density}}{\text{poured density}} \]

<table>
<thead>
<tr>
<th>Flow character</th>
<th>Angle</th>
<th>Carrs index</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very good</td>
<td>&lt;20</td>
<td>5-15</td>
</tr>
<tr>
<td>Good</td>
<td>20-30</td>
<td>12-16</td>
</tr>
<tr>
<td>Ok</td>
<td>18-21</td>
<td></td>
</tr>
<tr>
<td>Poor</td>
<td>30-34</td>
<td>25-35</td>
</tr>
<tr>
<td>Very poor</td>
<td>33-38</td>
<td></td>
</tr>
<tr>
<td>Extremly poor</td>
<td>&gt;40</td>
<td>&gt;40</td>
</tr>
</tbody>
</table>

Surface properties and morphology of particles

- Properties
  - Roughness of the surface
  - Morphology of the particles
  - Surface energy
  - Composition
- Influences
  - Stability
  - Total area
  - Particle size reduction
  - Adsorption of other substances to the surface
  - Aggregation
  - Release of adsorbed material
  - Flow
To evaluating surface energy - contact angles

- Provides information on how easily a liquid wets a surface.
- The surface energy can be determined by measuring the contact angle of several liquids of known surface tension.
- A small contact angle with water for hydrophilic surfaces.
- Contact angle hysteresis indicates:
  - A chemically heterogeneous surface.
  - Surface roughness.
  - That the surface changes when wetted.

Homogeneity of the powder

- Powders normally neutral mixtures
- Homogeneity obtained by mixing
- Problems
  - Obtain homogeneity
  - Contain homogeneity
- Tricks
  - Same size particles
  - Same density
  - Ordered mixtures
Physical state of the solid material

• Melting temperature
• Amorphous or crystalline
• Polymorphism- Different crystalline structures - with different stability
• Hydrates- often several different types of hydrates
• Crystal habit- External shape of crystal for example needles, spheres cubes

• Effects
  ➢ Solubility
  ➢ Dissolution
  ➢ Chemical stability
  ➢ Physical stability
  ➢ Water adsorption
  ➢ Bioavailability
  ➢ Acceptable process conditions

Water content

• Effects
  ➢ Chemical, physical and microbiological stability
  ➢ Hardness of tablets
  ➢ Adhesion of the powder
• Analytical methods
  ➢ Drying: weighing
  ➢ DSC
  ➢ Adsorption of water at controlled Rh% and then weighing

• Bound water
  ➢ Difficult to remove by drying
  ➢ Not available for chemical reactions
  ➢ Does not freeze
  ➢ The first layer of water molecules around a particle
  ➢ Crystal water
• Free water
  ➢ Capillary water (Still difficult to remove by drying)
  ➢ Other water trapped in the structure but having normal vapour pressure
Water adsorptions isotherm

Water content in of various powders at different levels of relative humidity

Terms to know from today's lecture

- Insufflation: medical powders that are blown into a region of the body, such as the ears, nose or throat
- Skewness: the presence of non uniform particle-size distribution
- Angle of repose
- Tapping and poured density: the density of a powder after and before it has been compacted
- Bound water: water that has different properties than bulk water as it is bound to other molecules or structures in the formulation