# Tablets and Capsules

**Aulton**

**16, 27-30**

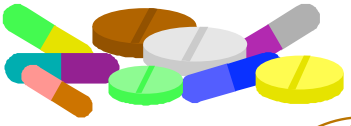
# Tablets

- Half of all pharmaceutical products are for oral use (tablets and capsules)
- Advantages: high patient compliance, relatively easy to produce, easy to market
- Disadvantages: the conditions in the GI tract that leads to degradation of some substance and that all substances are not absorbed through the epithelial cells of the GI-tract
- Can you think of other examples of advantages and disadvantages?

# Different types of tablets?

- Immediate release tablets
- Controlled release tablets
- Chewable tablets
- Effervescent tablets
- Lozenges
- Sublingual and buccal tablets
- Fast dissolving tablets (snow flakes)

- Other oral formulations
  - Capsules
  - Oral solutions
  - Oral Powders

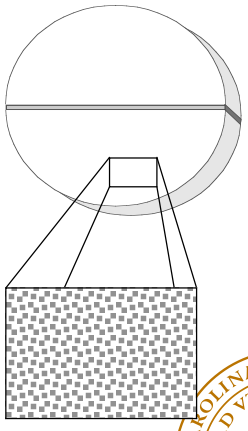


What reasons are there for choosing a particular type of formulations?

# What is a tablet

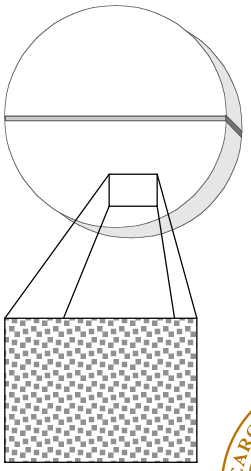
It is a compressed dispersion of particles in air.

This means that the same factors that are important for powders are also important for tablets



# What is a tablet composed of

- Active substances
- Filler
- Disintegrant
- Binder
- Gliadant
- Lubricant
- Antiadherent
- (Coating)
- (Colour, humectants, buffers)



# Filler - fyllmedel

- To give a reasonable size for the tablet ≥50 mg
- Properties
  - Chemically inert
  - Non-hygroscopic
  - Water soluble or hydrophilic
  - Good mechanical properties
  - Acceptable taste
  - Cheap

- Sugars
  - Lactose
  - Sucrose
  - Manitol
- Salts
  - Calcium phosphate
  - Calcium carbonate
- Polymers
  - Cellulose derivatives
- Fillers can be manufactured to be used for direct compression for example amorphous lactose

# Disintegrants -sprängmedel

- Ensure that the tablet breaks into small pieces when in contact with water
- Addition of disintegrants
  - Intragranular addition
  - Extragranular addition
  - Amount of disintegrant 1-10%

- Disintegration through wetting
  - Surfactants
- Disintegration through rupturing
  - Starch
  - Cellulose
  - Cross-linked polyvinyl porrolidone
  - Sodium starch glycolate
  - Sodium carboxymethyl cellulose


# Binder- bindemedel

- A binder is added to increase the cohesion between the particles in a granulate so as to ensure the mechanical stability of the granulate
- A binder can also improve tablet compression
- The normal concentration of the binder is 2-10%

- Dry powder that are mixed with the granulate and partly dissolved during granulation
- Wet binders that are dissolved in the granulation liquid
  - Gelatin and starch
  - Polividon and cellulose
- Dry binders that are used in dry granulation
  - Cross-linked PVP
  - Microcrystalline cellulose

# Lubricants and gliadants - Smörjmedel

- Gliadants are included to increase the flowability of the powder
- Excipients
  - Colloidal silica
  - Magnesium stearate
- Normally 1-2% but colloidal silica 0.2%

- Lubricants included to facilitate tabletting and ejection of tablets from tablet punches
- Excipients
  - Magnesium stearate (1-2%)
  - Polyethylene glycol
- Magnesium stearat should be mixed in late in production sequence
- It can affect release from the tablet and tablet strength
- One approach is to not include magnesium stearate in the formulation but to spray it on the punches during production.

# What influence the pharmacokinetics of tablets

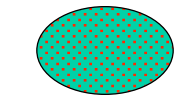
- Discus in groups of two for 5 minutes

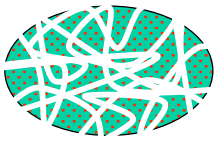
## How can the release rate and uptake from tablets be manipulated

- Increase the release rate
- Increase solubility of the active substance
- Delay the transport of the tablet in the GI tract
- Modified release
  - Time
  - Location
- Increase penetration over epithelial cells

## How can the release rate be increased

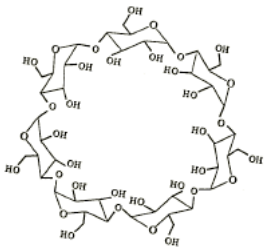
- Increasing the surface area (use of disintegrant)
  - Starch
  - Cellulose materials (Avicell)
- Including wetting agents
  - Surfactants
- Avoiding drug-excipient interactions
- Using solid dispersions or solid solutions

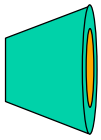




# Increase solubility of the active substance

- Change the salt form
- Use surfactants
- Complex formation
- “Nano” particles
- Cyclodextrins are crystalline , water soluble, cyclic, non-reducing oligosaccharides
  - Might also decrease irritation and give a better release profile
  - Example on cyclodextrine drugs
    - Brexidol
    - Rigidur



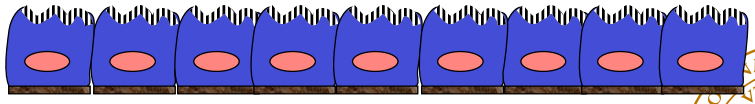


# Delay the transport of the tablet in the GI tract

- Floaters
  - Rafts
  - Floating particles
  - Floating foams or polymers
- Mucoadhesive systems
  - Bind to mucosa
  - Bind to the epithelial cells

# Increase penetration over epithelial cells

- Increase penetration over tight junctions
- Decrease efflux through P-glycoprotein
- Penetration enhancers

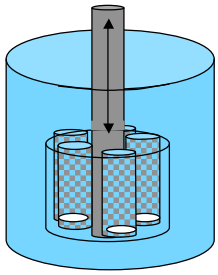


# Quality requirements on tablets

- Key quality requirement for all pharmaceutical products: Right dose at the right time
  - The right content of active substance often target content ± 5%
  - The right weight
  - The right dissolution profile
- Purity
  - Presence of impurity known and unknowns
- Other typical tablet properties
  - Hardness
  - Friability
  - Disintegration
- Factors that can be important
  - Moisture content
  - pH of a solution of dissolved tablets
  - Colour

# Disintegration

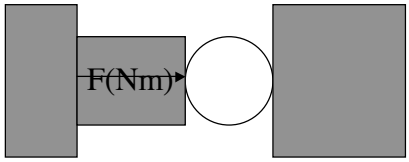
How the tablet disintegrates into its primary particle and not the release of active substance



# Mechanical properties

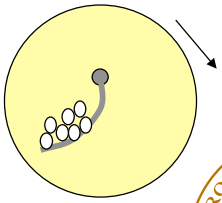
## Hardness

- Often measured as the force needed to crush the tablet often called the crushing strength although in reality it is linked to the failure force




## Friability

- Describes extent to which the powder tends to be removed from the surface of the tablet %: should normally be below 1%



# Factors affecting the solubility

**Solubility of solids in water**

- Hydrophobicity
- Type of salt
- Charged or uncharged form of active components
- Polymorphism, crystalinity, amorphous state
- Self-association
- pH: including buffers in the formulation

**Solubility of solids in solids**

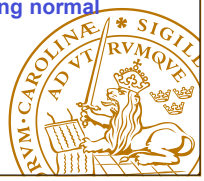
- The size of the solute is the same as that of the solvent (incorporation in crystal lattice)
- The solute is smaller in size than the solvent (solute molecules incorporated in the space of the lattice)
- Solid dispersions are more usual
- Eutectic mixtures can lower the melting point of some substances

# What affects the stability of a tablet?

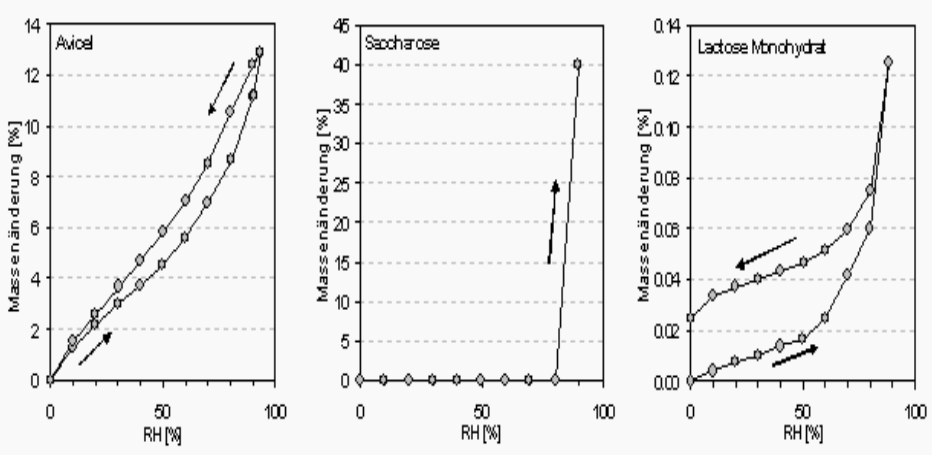
- **Water content**
  - Initial
  - Uptake during storage
- **Purity of the excipients**
  - Presence of metal ions
  - Oxygen and peroxides
- **Storage conditions**

# 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

# Capsules

- Advantages as compared with tablets
  - Better taste masking
  - Can be used for non solid systems: oils
  - Can handle poorly compressible drugs
  - Can easily be used for particular controlled release systems
- Types
  - Gelatin
    - Hard and soft
  - New capsule materials
    - Starch
  - Enterically coated

- Material filled into capsules
  - Powders
  - Granulates and pellets
  - Microtablets: keep incompatible material together in one formulation
  - Semisolids
  - Suspensions: protect active component, increase bioavailability or increase surface area
  - Solutions or oils

# Hard gelatin capsules

- Produced in two empty halves and filled separately
- Capsules of standardised sizes can be bought from capsule manufacturers
- Often coloured to help identify the drug
- Sensitive to water and other liquids that can penetrate into the capsule material (Capsule contains 13-16% water)
- Technologically simpler than soft capsules

**Content**

- Powder and granulates
  - Diluent, lubricant, gliadant, wetting agents and disintegrant
  - Wanted properties, good flow, no adhesion, Cohesion (plug-flow)
- Semi solids and non aqueus liquids
  - Pastes
  - Oils (capsules sealed with gelatin)
- Pellets and mintablets

# Soft gelatin capsules

- A soft gelatin shell surrounding a liquid film or a semisolid
- Production and filling occur simultaneously
- The gelatin capsule provides good protection against oxygen
- The low water content in the shell leads to protection against hydrolysis
- Faster release of active than for tablets

- Benefits of soft capsules
  - Increasing bioavailability (for example through the use of microemulsions)
  - Increased rate of adsorption (solutions)
  - High patient compliance easy to swallow good taste masking
  - Can be used for oils and for semisolid active substances
  - Dose uniformity for low dose drugs
  - Product stability
- Drawbacks
  - Not for high dosing of solids
  - Production of capsules are not as fast as for tablets

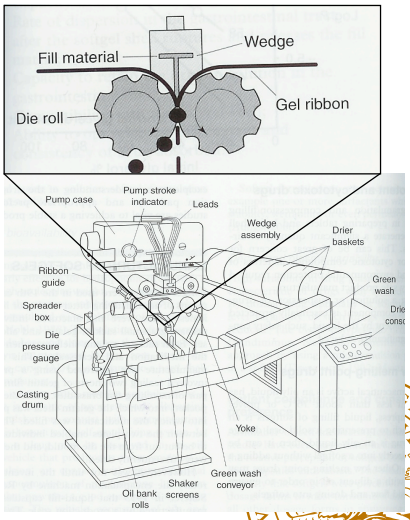
# Formulation of soft gelatin capsules

- Gelatin
  - Critical parameter: viscosity as measured by bloom strength
  - Low viscosity: thin weak films that take long time to dry
  - High viscosity: thick hard and often brittle films
- Plasticizers (glycerol/gelatin 0.35-0.76)
  - Glycerol
  - Sorbitol
  - Propylene glycol
- Water
  - 0.7-1.3 water /part gelatin
- Colours and opacifiers

- Contents
  - Liquids (oils and polar liquids such as PEG)
  - Water and ethanol max 10%
  - Self-emulsifying oils
  - Microemulsions
  - Suspensions

# Production of soft gelatin capsules

- Produced in an encapsulation machine employing a rotary die process
- A heated fluid of gelatin mixed with excipients is transported onto two flat ribbons on which the gel is formed.
- The ribbons are transported to the die where the liquid fill is injected.
- Injection of the liquid forces the gelatin to expand into the die forming the capsule
- The capsule is dried from 30% water in the formulation to less than 10% in finished product




# Quality of capsules

- **In-line controls**
  - The gel ribbon thickness
  - Soft gel seal thickness at the time of encapsulation
  - Fill matrix weight
  - Capsule shell weight
  - Soft gel shell moisture level
  - Soft gel hardness at the end of the drying stage
- **Excipient control**
  - Limit the presence of trace impurities such as aldehyde and peroxides which can cross-link the gelatin
  - Quality control of the gelatin
    - Viscosity of the melted gel
    - Bloom strength (hardness of the gel)

# Terms to know from today's lecture

- Disintegrating tablet: tablet that disintegrates in the stomach, normally used for fast uptake
- Immediate release: fast release of the active substance (all “normal” tablets)
- Filler: an excipient added to give a tablet the right weight and volume
- Disintegrant: an excipient added to disintegrate the tablet into its primary particles
- Binder: an excipient added to increase the cohesion of the granules and between particles in the tablet
- Gliadant: an excipient added to increase the flow of the powder
- Lubricant: an excipient added to lubricate the punches during tabletting
- Hardness and Friability measurement of the mechanical properties of tablets
- Disintegration: how fast the tablet disintegrates into its primary particles
- Dissolution: how fast the active substance is released from the formulation