Tablets and Capsules

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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
- Glidant
- 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
  - Mannitol

- 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 porrorolidone
  - 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 stearate 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, glidant, wetting agents and disintegrant
  ➢ Wanted properties, good flow, no adhesion, Cohesion (plug-flow)
• Semi solids and non aqueous 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