Modified release

Chapter 21,32,33

Different principles for release?

- Immediate release
  - The active substance is released in the stomach: fast onset
- Extended release
  - The release is slower which will increase the duration
- Delayed release
  - The release is targeted to a specific part of the GI tract normally the small intestinal
Why use modified release formulations

- Improving the pharmacokinetic profile
  - Keeping the blood concentration within the therapeutic window
  - Avoiding high blood concentration peaks
  - Chronobiology
  - Reducing the total amount of drug administered
- Patient compliance
- Protecting active substance from the environment in the stomach
- Protecting the stomach from the active substance

Dosing over night and Chronobiologics.

- Short half-lives may give a risk for too low blood concentrations during night
- The body is in a different state during rest than when active and the hormone levels may differ naturally during the day.
  - Cortisone for rheumatism works better during the night
  - Heart attacks more common in the mornings
  - Child birth more common at nights and in the morning
  - The content of vasopressin is higher at night
Problems connected with modified release

- Dose dumping: the content of active substance in a controlled release formulation is higher than in an immediate-release formulation.
- Lack of precision in the controlled release mechanism leads to variation in dosage.
- Tablets may get lodged in the GI-tract which creates a risk for damages to the cell walls.
- Drugs with a short half-life (<1h) are difficult to formulate for controlled release because of high maintenance dose required.
- They are more time consuming to develop and more difficult to produce making them more expensive.

Different types of modified release

The Ideal situation: sustained release
Manipulates the duration of drug in the blood by ensuring a constant concentration of the drug at the site of adsorption.
- One portion of the drug provides a bolus dose
- Another portion of it provides a constant maintenance dose (zero order release)

Prolonged release: no bolus dose
Delayed release: release of the drug after a delay for example through the use of enteric coated tablets.
Other definitions of MR formulations

• Repeated action: Individual doses of the drug released at repeated intervals (pulsating release)
• Extended release (ER): slow release that provides therapeutic concentrations for 8-12 h at least two fold reduction of administration
• Controlled release (CR): a dosage form that release drug at a constant rate
• Modified release (MR): a dosage forms that gives drug release characteristic of time and/or location that are chosen to obtain therapeutic or convenience objective (USP definition)

Routes of delivery for MR formulations

• Injections and implants
  ➢ Can provide long periods of sustained release (years)
  ➢ Important for delivery of proteins
  ➢ Combined with device
  ➢ Used during surgical procedures (e.g. nerve blocking)
• Topical plasters
  ➢ Intermediate sustained release (weeks)
  ➢ Easy to remove
• Vaginal rings etc
  ➢ Sustained release for substantial periods
  ➢ Easy to remove
  ➢ Example
    • Oestrogen rings
• Oral formulations: the main route of delivery
Modified-release formulations for parenteral route

- Biodegradable formulations
  - Most common PLGA (poly lactic glyco acid) particles
  - New generations on the way, for example pure protein particles
- Implants
  - Not degraded in the body
  - Often composed of non degradable polymer such as polyethylene vinyl acetate
- Using oils for injections
- Injecting dispersions
- In-situ gelling polymers

Stents

- Operated into blood vessels after balloon surgery
- First generation: mechanical stabilisation
- Second generation includes drug for in-situ release of biodegradable polymers
Things to consider regarding parenteral formulations

- The material used must be biocompatible and not trigger immune or blood clotting responses.
  - Polyurethanes, titanium oxide, starch, PLGA, polyethylene vinyl acetate
- Dose dumping is of particular concern
- There is often a risk for burst effects.
- The active substance needs to be stable throughout the duration of the release.
- Accelerated dissolution methods for production control often need to be develop

Oral MR formulations

- MR-formulations are used to
  - Obtain extended or prolonged release
  - Avoid release in the stomach (enteric coating)
  - Target different parts of the GI tract (colon delivery)
  - Delay release from the stomach

Disadvantage
- Release and uptake of the drug can be affected by the passage through the gastrointestinal track
- Only limited periods of sustained release can be achieved this dependence on where in the GI tract uptake occurs
- True sustained release is often difficult to obtain
Basis for oral MR formulations

- Requirements placed on the active substance
  - Best for class I substances
  - Having a 2-6 hours biological half life
  - No active metabolites
  - Dos regime not exceeding 125-325 mg

- Drug-release mechanism
  - Hydration of the device
  - Diffusion of water into the device
  - Dissolution of the active substance
  - Diffusion of the active substance out of the device
  - Erosion of the formulation

- Triggers for delayed release
  - changes in pH
  - Enzymatic degradation
  - Timed erosion

Insoluble matrix systems

Principles
Diffusion of the substance out of the formulation controls release
The release rate is normally
\[ M = K t^{0.5} \]

Types
- Lipid matrixes: insoluble lipids (waxes) and soluble channelling agent
- Non-soluble polymers
  - Polyvinyl acetate, ethyl cellulose
  - Duretter (AstraZeneca)
Soluble matrix systems

Principle
Diffusion from or erosion of the tablet matrix controls release
Well-established technique - easy to produce

Steps
- Water penetrates the formulation
- The matrix may swell and the matrix material be dissolved
- The drug substance is exposed and is mixed with or dissolved into the gastrointestinal fluids

Composition
- Eroding waxes (erosion)
- Hydrophilic polymers - diffusion through the gel layer and erosion controls release
- Polymers: Carbopol, alginates, hydroxymethylpropyl cellulose

Membrane-controlled delivery

Principles
The diffusion of substance through the membrane controls release
Zero-order release as long as the solution inside the membrane is saturated

Formulation
- Film coating using a permeable membrane
- Film coating using a combination of a nonsoluble film and soluble pore formers (sugars, HPMC)
- A core of standard fillers but try to avoid substances that give osmotic effects

\[
M = CAK \frac{D}{t} \quad M = CAE \frac{D}{t}
\]

K is the partition coefficient between the solution and the membrane
E is porosity
Osmosis controlled release

Principle
- Osmotic transport of water into the release unit
- Dissolution of the drug
- Convective transport of a saturated solution by pumping the solution through one or several pores

Formulation
- Film coating that is permeable to water but not to the drug
- Holes produced by laser drilling
- The core has to contain a substance that produces the osmotic difference

Delivery to targeted parts of the GI tract

- Stomach: Trying to keep the formulation in the stomach as long as possible
  - Rafts
  - Floating formulations (floating gel Gaviscone)
  - Bioadhesive formulations
  - High-density particles
  - Retentive agents (food)

Colonic delivery
- Why
  - Local treatment
  - Enzymatically sensitive substances (proteins)
- How
  - GI-transit time
  - pH sensitive polymers (Eudragit)
  - Degradation by colonic bacteria (starch)
Multi-particle formulations versus non-disintegrating tablets

- Smaller size results in more uniform passage through the GI-tract
  - Pellets (< 2mm) leave quick
  - Single dose units (>7mm) can be retarded up to 10 h
- Less risk if the coating fails
- No risk of trapping of the whole tablet
- Often difficult to produce multi-particle tablets

Release mechanism

- Coating is the most common principle employed
- The overall release is the sum of the release from the individual particles
- Can be used to obtain pulsititative release
Coating of tablets and particles

Why
- To protect the ingredients
- To control release
- To improve appearance
- To mask taste
- To facilitate handling and improve mechanically stability of the tablets

How
- Sugar coating
  - Traditional, a thick coating, glossy
- Film-coating
  - Modern gives a thin film, used for modified release, and coating of particels
- Press coating
  - To avoid contact between incompatible materials

Formulation of film coatings

Film contains
- Polymer
- Plasticizer
  - Polyols PEG 400
  - Organic esters
  - Oils
  - Glycerides
- Colour
  - Iron oxide
  - Titan oxide
- Solution
  - Water (sometimes containing surfactants)
  - Organic solutions

Polymers
- Water-soluble films
  - Hydroxypropyl methylcellulose
  - Methacrylate amino ester above pH 4
- MR coatings
  - Ethyl cellulose
  - Ammonium methacrylate copolymers
- Enteric coating
  - Cellulose acetate phthalate
  - Polyvinyl acetate phthalate
  - Acrylic derivatives
Coating

• Equipment
  ➢ Accela Coata, Hi-coata, Driacoata
• A film solution is sprayed over the tablets in a tumbler and air-dried at the same time.
• Critical parameters
  ➢ Wetting of the tablets
  ➢ Mixing of the tablets
  ➢ Atomisation of the liquid
  ➢ Drying temperature

Terms to know from today's lecture

• Extended release; The release from a formulation is slower than for immediate release formulation
• Delayed release; the release is targeted to a specific part of the GI tract normally the small intestinal
• Enteric coating coating that hinders release in the stomach
• Extended release (ER): slow release that provides at least two fold reduction of administration
• Controlled release (CR): a dosage form that release drug at a constant rate
• Modified release (MR): a dosage forms that gives drug release characteristic of time and/or location that are chosen to obtain therapeutic or convenience objective