Polymers, suppositories and primary packing material

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Consider when polymers are used

• What polymers have you encountered in your drug products,
• What were there function
• How do they obtain this function
• 5 minutes discussion
Typical uses of polymers in pharmaceutics

Semi soluble polymers

• Surface activity
  ➢ Stabilisation of foams, dispersions and emulsions
  ➢ Adsorb to biological tissue
  ➢ Binders and flocculates
  ➢ Solubilizers

• Rheological properties
  ➢ Thickener in oral solutions, creams etc
  ➢ Stabilisation of foams, dispersions and emulsions

• Interaction with water
  ➢ Humectants
  ➢ Dissintegrant

• Film coatings

Cross-linked polymers

➢ Gels
➢ Particles

Plastics

• Packing materials
  ➢ Bottles- PE, PVC, PET
  ➢ Blister packs

• Implants
  ➢ Contraceptives often polyurethanes

Some key polymers in pharmaceutics

• Cellulose based
  ➢ Cellulose Acetate Phthalate (CAP)
  ➢ Hydroxypropylmethyl cellulose (HPMC)
  ➢ Hydroxypropylcellulose (HPC)
  ➢ Ethylcellulose
  ➢ Methylcellulose
  ➢ Sodium carboxy methyl cellulose

• Other carbohydrates
  ➢ Xanthan gum
  ➢ Carrageenan
  ➢ Starch

• Polyvidon or Polyvinylpolypyrrolidone (PVP)
• Polyvinyl Acetate Phthalate (PVAP)
• Carbopol
• Gelatine
• Hyaluronic acid
How do polymers differ from monomers?

The pKa of a polymer might differ from that of a monomer. There might be a range of pKa values.

The polymer might not be mixable with other polymers and thus form aqueous two phase systems - Effect of excluded volume.

Typical properties of water soluble polymer:

- They are more or less polydisperse
- Their properties are strongly dependent on their interaction with the solvent
- They often have a strong tendency to adsorb to surfaces
- They often increase viscosity and might form gels
Novel use of polymers

- Thermoreversible gels or pH reversible
  - In-situ gel formation to obtain controlled release or slower clearance
  - Thermoreversible
    - poly(ethylene glycol) (PEG)-block-poly(propylene glycol)
    - block-type amphiphilic poly(vinyl ether)
    - Polyaminoacids
  - pH reversible
    - Chitosan
    - Carbopol

- Nanoparticles
  - particles between 10 nanometres (nm) and 1000 nm
  - Inhalation, injectabilia and oral
  - to increase uptake and for targeting
  - Produced for example by self-assembling polymers

Suppositories

- Where
  - Rectal
  - Vaginal
  - Nasal buggies
- Why
  - Local treatment
  - Patients that has trouble swallowing
  - Sensitive or irritating drugs
- Why not
  - Cultural problems
  - Slow and incomplete adsorption

- Typical products
  - Painkiller and products against rheumatoid diseases
    - Alvedon
    - Panodil
  - Local inflammation
    - Asacol
    - Mesasal
  - Against nausea
    - Torecan
  - Laxatives
Suppositories - Pharmacokinetic

- Factors that are special for the rectal route
  - Low amount of available water
  - pH 7.5
  - Can partially avoid first pass effects
- Factors important for the drug formulation
  - Induce spreading
  - Not induce too much uptake of water - painful for patients

Suppositories - Formulations

Lipid based suppositories
- Excipients
  - Synthetic vehicle
  - Triglycerides C12-C18
  - Saturated lipids
- Requirements on the vehicle
  - Melt at body temperature
  - Small melting range to make production possible
  - Rapid solidification
  - Rheological properties
  - Not form emulsion in situ

Water soluble suppositories
- Excipients
  - Glycerol-gelatine (laxatives)
  - Soaps-fatty acids (laxatives)
  - Macrogol - mixture of polyethylene glycols
- Requirements on the vehicle
  - Not too large effects of hygroscopicity
    - Add 20% water to the system
Suppositories - production

- Produced both in laboratory scale 10-20 and in production scale.
- Production includes:
  - Melting of suppository base
  - Mixing with active substance
  - Dispensing into a mould
  - Solidification
  - Packing
- Things to consider:
  - Content of uniformity
    - Sedimentation of particular drug substance
  - Removal from mould form
  - Control parameters:
    - Appearance
    - Weight
    - Disintegration
    - Melting
    - Mechanical strength
    - Release

Function of packages

- Protect a product from:
  - Mechanical damage
  - Microbiological contamination
  - Evaporation of volatile components
  - Uptake of water
  - Air
  - Light
  - Tampering
- Make dispensing of a dose simple
- Sell the product
- Identify the product
Choosing a packaging

- What form of packaging would you prefer for the following products. Discuss this in groups. Describe in as much detail as possible. Be inventive but motivate. Consider what things may be important for your choice
  - Contraceptive pills
  - Insulin
  - A pain killer for rheumatoid arthritis patients
  - Effervescent tablets for headaches
  - A cough medicine

Things to consider when choosing packaging material

- What does my product need protection from
  - Light
  - Humidity
  - Microorganisms
- What kind of risk do I have that the packaging material may interact with or contaminate my product?
  - Adsorption of drugs and excipients to the packaging material
  - Leakage of substance from the packaging material
- What requirements may a specific country have
  - Tamper evidence
  - Child security
- What type of consumer does the product aim at
  - Health care professionals
  - Patients who have difficulties to open a container
  - Children
- What kind of reinvestment in production capacity would be needed
FDA:s concerns regarding packages for common drug products

<table>
<thead>
<tr>
<th>Degree of concern associated with delivery route</th>
<th>Likelihood of packing component-dosage form interaction</th>
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</thead>
<tbody>
<tr>
<td>High</td>
<td>High, Medium, Low</td>
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<tr>
<td>High</td>
<td>Inhalation aerosols and solutions</td>
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<tr>
<td>High</td>
<td>Sterile powders</td>
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<tr>
<td>High</td>
<td>Inhalation powders</td>
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<tr>
<td>Medium</td>
<td>Solutions and suspensions for injection</td>
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<td>Medium</td>
<td>Inhation powders</td>
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<tr>
<td>Medium</td>
<td>Ophthalmic solution</td>
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<tr>
<td>Medium</td>
<td>Transdermal ointments and patches</td>
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<tr>
<td>Low</td>
<td>Nasal sprays</td>
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<tr>
<td>Low</td>
<td>Topical solutions and aerosols</td>
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<tr>
<td>Low</td>
<td>Oral solutions and suspensions</td>
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<tr>
<td>Low</td>
<td>Topical powders</td>
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<tr>
<td>Low</td>
<td>Oral powders</td>
</tr>
<tr>
<td>Low</td>
<td>Oral tablets and capsules</td>
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</tbody>
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Type of packaging material for tablets and capsules

- Bottles or tubes
  - Normally of plastic material such as PVC or PE of injection moulded or blow back type. In special cases metal containers may be used.
  - Often contains a desiccant.
  - If they are of good quality they provide a reasonable good protection against humidity.
  - Considerable possibility for variation in design.
  - Easy for health-care personal to repack.

- Blisters
  - Easier for the patient to keep track of whether the pill has been taken or not.
  - Usually higher water penetration for "normal" blisters than for bottles.
  - Special blisters like Alu-Alu blisters provides complete protection from water vapour.
Things to consider regarding plastic materials

- They can contain monomers and plasticizer that can leak out
- The tools used in manufacturing of the containers may age which lead to changes in container properties
- The plastic material may fail:
  - Stress cracking: Occur for polyethylene in combination with surfactants
  - Poor impact resistance: Occur for polystyrene and PVC
  - Panelling and cavitation due to the adsorption of gas during autoclaving
- Plastic materials differ in their permeability to gases such as CO₂
- Plastic allows for some penetration of light if it is not coloured black

packaging materials -solutions

- Ideal packaging for parenterals
  - Does not affect the content
  - Is not affected by sterilisation procedures
  - Keeps the product sterile
  - Is cheap enough for disposal
  - Is transparent enough to permit detection of particles

- Types of packaging material
  - Ampoules of glass
  - Vials of glass and rubber
  - Pre-filled syringes of glass or plastic
  - Plastic bottles and bags
Packing material and device

- Use compliance
  - Prefilled syringes
  - Multi- or single-dose containers
  - Pumps
  - Needle free delivery
  - Laws in some states in the US that benefits needle-free or safe needle delivery

- Safety
  - Integrity of the packing material
  - Avoiding contamination of the product from packing material
  - Stopping the sharing of needles

Requirements placed on parenteral packaging material

Low amounts of contamination the product by extractable compounds from the packaging material to
- Glass: alkali
- Plastic: monomers, plasticizers
- Rubbers: additives to the rubber

Low losses of the active substance and of excipients (bactericides) due to chemical reactions, adsorption or absorption
- Adsorption: all types of material
- Absorption: rubber and plastic

Ensuring microbiological integrity
- All ampoules should be tested for cracks and small holes: Pinhole testing
- Vials - validating the capping procedure to ensure that there are no leakage through the stopper

Withstand sterilisation procedures
- Important for plastic and rubber materials
  - Increased stickiness
  - Becoming more brittle
Glass containers

- Three types of standard glass
- Type I: neutral containing boric oxide to eliminate alkali. 2-3 time as expensive as normal glass but should be used for pH sensitive products
- Type II: the surface treated with sulphur dioxide or ammonium sulphate to reduce amount of alkali. Needs to be washed prior to use
- Type III: soda or alkali glass

Extraction and interaction

- Extraction studies: testing that specifically involves exposing a sample of the component to an appropriate solvent system at extreme conditions in order to maximise the amount of extractables from the packaging in the solvent.
- Interaction studies: studies to detect any effects between plastic packaging component an product leading to unacceptable changes in the quality of the product or the packaging under normal storage/use conditions.
- Migration: release of substances (leachables) from the plastic component into the content of the container under conditions which reproduce those of the intended use.
Water penetration over package

- Testing to what extent water is removed from the package
  - Oral solutions
  - Nasal sprays
- Testing to what extent water is taken up by the package
  - Tablets
  - Powders

USP method for water uptake

- Fill 10 containers to 1/3 with anhydrous calcium chloride, and use 2 containers filled with glass beads as control
- Close with a pre-decided torque and store at 23°C, 75% rH
- Record the difference in weight after 336±1 hour and calculate the water permeability per day.
- Tight container not more than 1 container takes up more than 100 mg water per litre and day

Child resistance and tamper evidence

Child resistance
- Tested on three-year old children
- Testing their ability to open a package without instructions
- Testing their ability to open a package after seeing someone else open it

Tamper evidence
- Ring or some other marker that shows if the package has been opened
packaging

- Important matters to consider
- Environment
  - Temperature
  - Humidity
- Line clearance
- Control of if the package contains the correct amount of product
- Speed and performance of equipment employed

Quality control

- Controls of the package prior to production
  - Identity of the material
  - Dimensions of the package
  - Extractable
  - (Water penetration)
  - Strength
- In-process controls
  - Fill volume
  - Seal torque
  - Seal integrity

- Controls of the packaged product
  - Seal integrity
  - Visual control to detect cracks, contamination, etc.
  - Injectabilia require control of every single unit
Terms to know from today’s lecture

- Excluded volume, the volume a polymer takes up in a solution
- Suppository; formulation for rectal or vaginal delivery
- Tamper evidence: Mechanical proof that the seal of a package has not been broken or tampered with
- Blister-pack: packaging in which a product is sealed in plastic, often with a cardboard backing.
- Ampoules: heat-sealed glass containers
- Vials: glass containers normally sealed with a rubber stopper
- Extraction studies: ensuring that chemicals are not leaking out of packaging material
- Interaction studies: ensuring that the active substance does not interact unfavourably with the packaging material