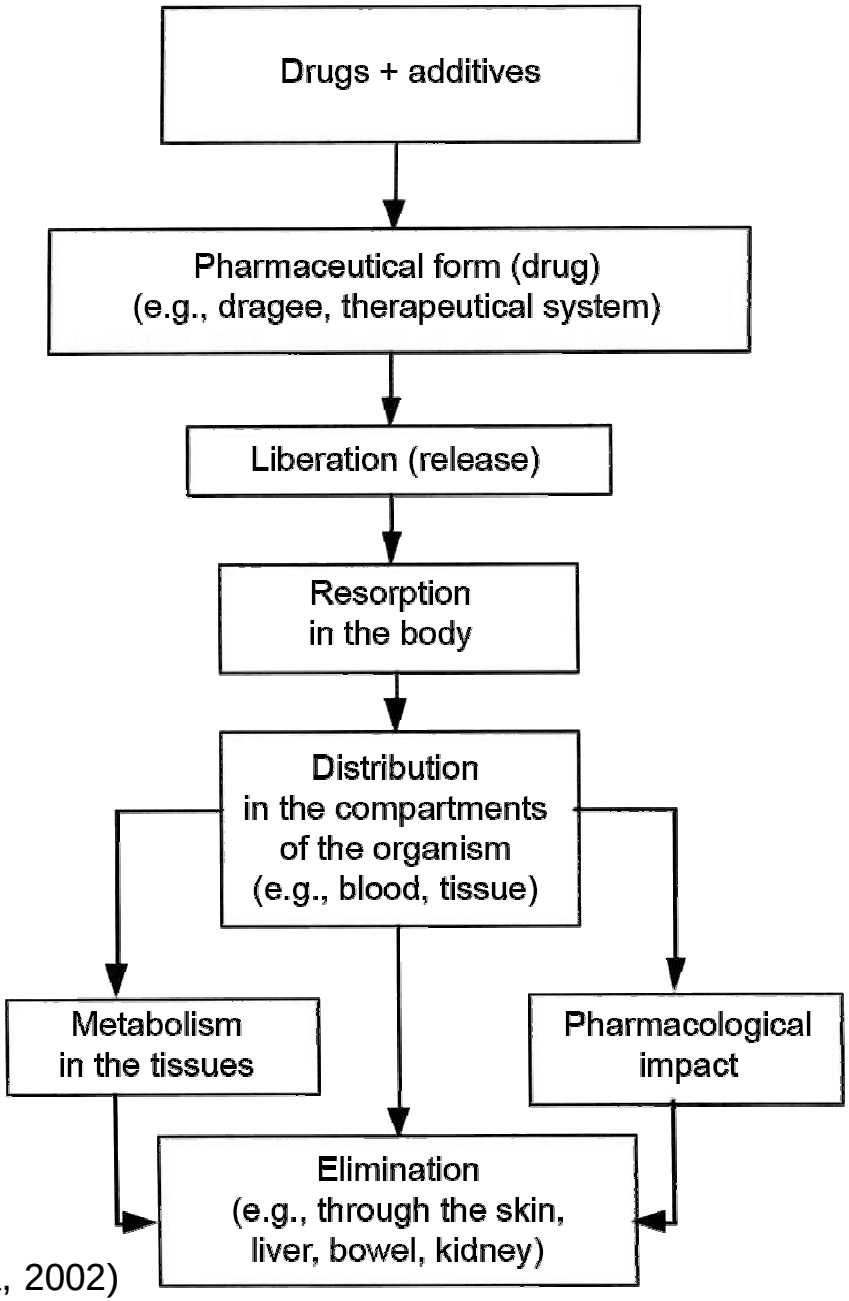
Controlled Drug Delivery Systems



(E. Wintermantel / S.-W. Ha, 2002)

Concept

- Aim: Controlled release of the drug with a constant rate, i.e. equilibrium between supply and elimination
- Result: An equal drug level in plasma and tissue over a defined period -> Significant reduction in the amount of drug needed in comparison with conventional pharmaceutical forms (consequence for the patient: reduction of adverse reaction and increased safety of the medicamentous therapy)
- Components:
  - Drug
  - Carrier
  - Control unit
  - Energy source
  - Therapeutic program

Therapeutic System

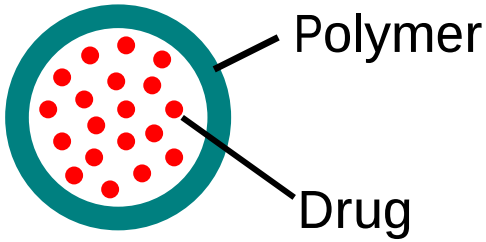
- Definition: Dosage form, liberating continuously one or more drugs at predetermined rate over a fixed period to a defined site of application
- Examples:
  - Glaucoma treatment: release rate 20 µg/h
  - Artificial tears: release rate 40 µg/h

Requirements

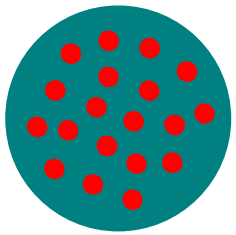
- Biocompatibility
- Reproducible and constant release rate
- Easy application
- Safeness against overdose
- Little secondary effects due to smaller dosage
- Lower application rate in comparison to other systems
- Low price and easy processing

Controlled Therapeutic Systems

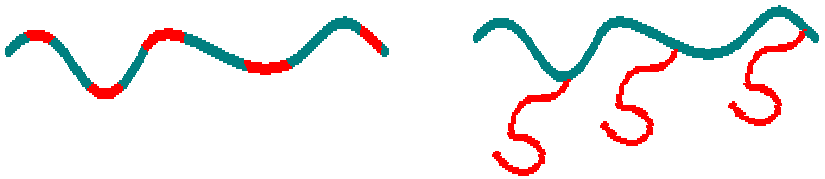
- Membrane systems



- Matrix systems



- Carrier systems



main-chain bound active agents side-chain bound

Requirements on Polymers as Carrier Materials

- Biocompatibility
- Stability during sterilisation if needed
- (Bio)degradable/Bioerodible
- Solubility and easy processing
- Coupling of drugs
- Cell specific reaction

Polymers in Controlled Therapeutical Systems

Pharmaceutical Form	**Polymers**
Matrix systems	PE, PEO, PP, PVA, PUR, polysiloxane, hydrogels
Membrane systems	PEO, PVA, PVAC, PUR, polysiloxanes, cellulose, hydrogels
Biodegradable systems	PGA, PLA, PLA-co-PGA, polyorthoester

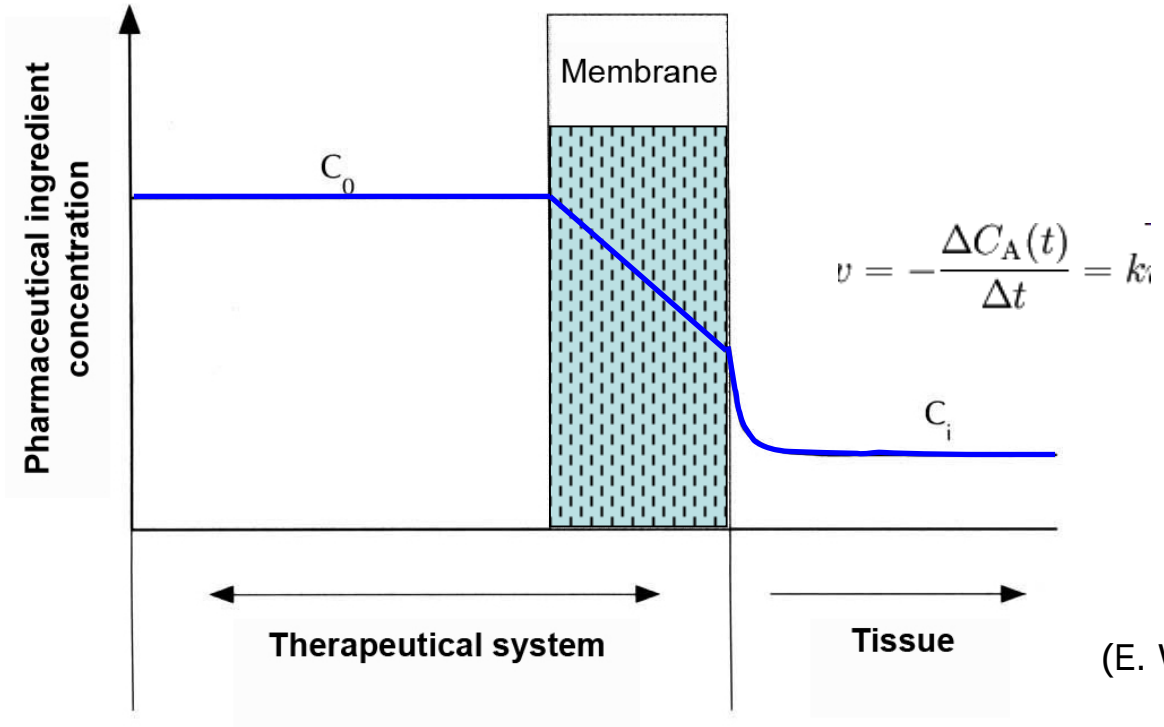
(E. Wintermantel / S.-W. Ha, 2002)

Influences on the diffusion of the polymer

Influence		Influence on diffusion coefficient
Molar mass	↑	↓
Crosslink density	↑	↓
Stiffness of the main chain	↑	↓
Molecule interactions	↑	↓
Crystallinity	↑	↓
Plasticizer content	↑	↑
Filler content	↑	↑

(E. Wintermantel / S.-W. Ha, 2002)

Membrane Systems



$$v = -\frac{\Delta C_A(t)}{\Delta t} = k$$

v ... reaction rate
$C_A(t)$ ... concentration of the drug at time t
t ... time
k ... rate coefficient (constant)

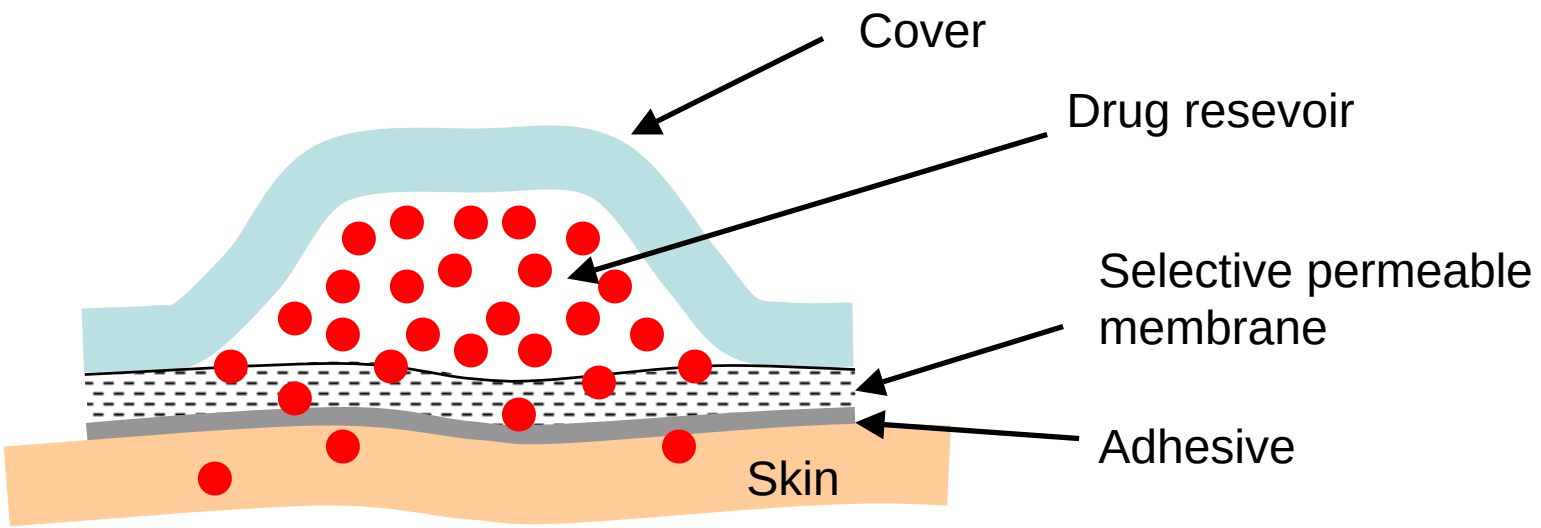
(E. Wintermantel / S.-W. Ha, 2002)

- Encapsulation of the drug in one or more membranes
- Application in the body
- Release by diffusion or osmosis
  - within the membrane oversaturated drug concentration
  - release with zero-order kinetics as long as the concentration gradient is constant

Membrane Systems

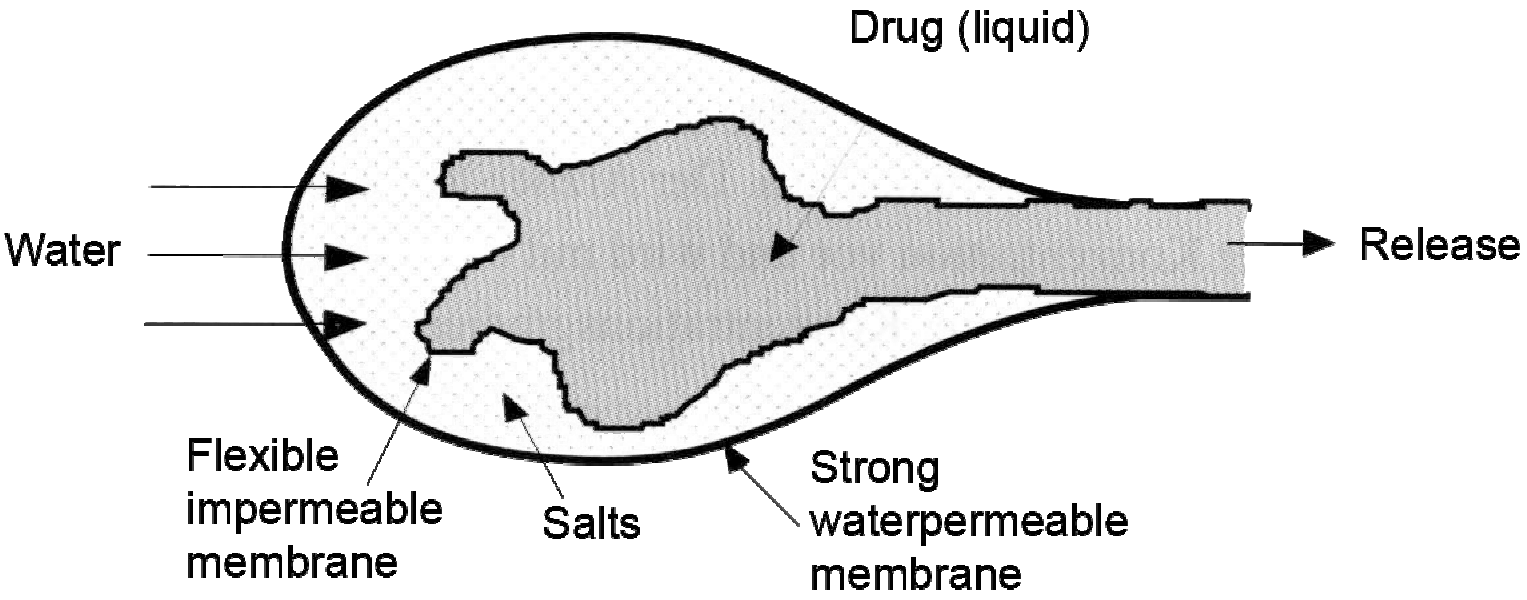
Transdermal Therapeutical Systems (TTS)

- Cover membrane: Al, PE
- Microporous selective permeable membrane: ethylene vinyl alcohol (EVOH)



Membrane Systems

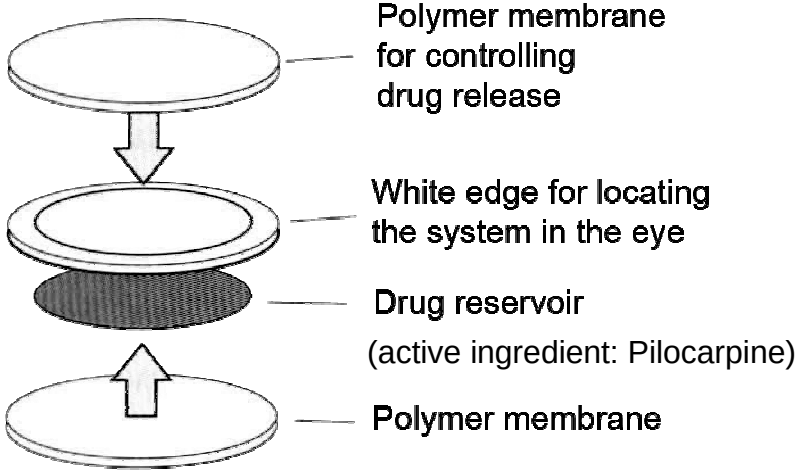
Osmotic Pump

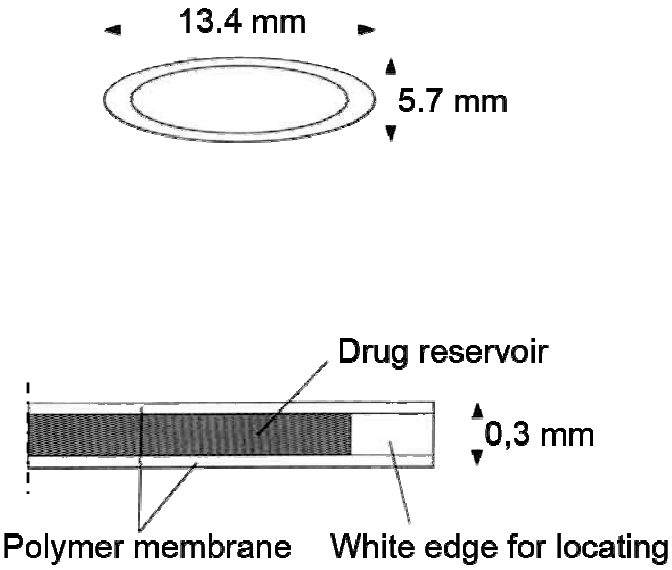


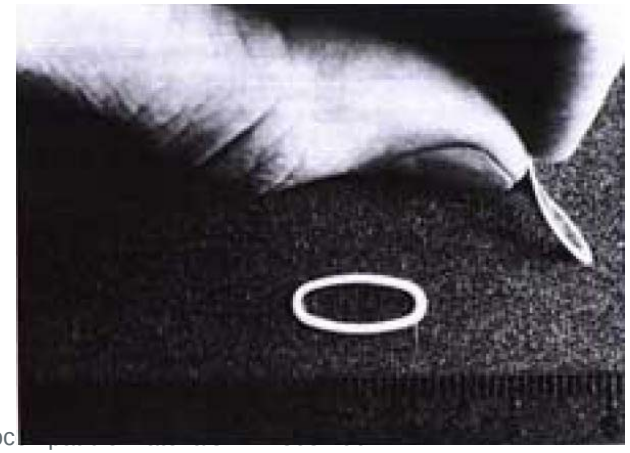
(E. Wintermantel / S.-W. Ha, 2002)

Membrane Systems

Ocular Therapeutic System (e.g. Ocusert®)

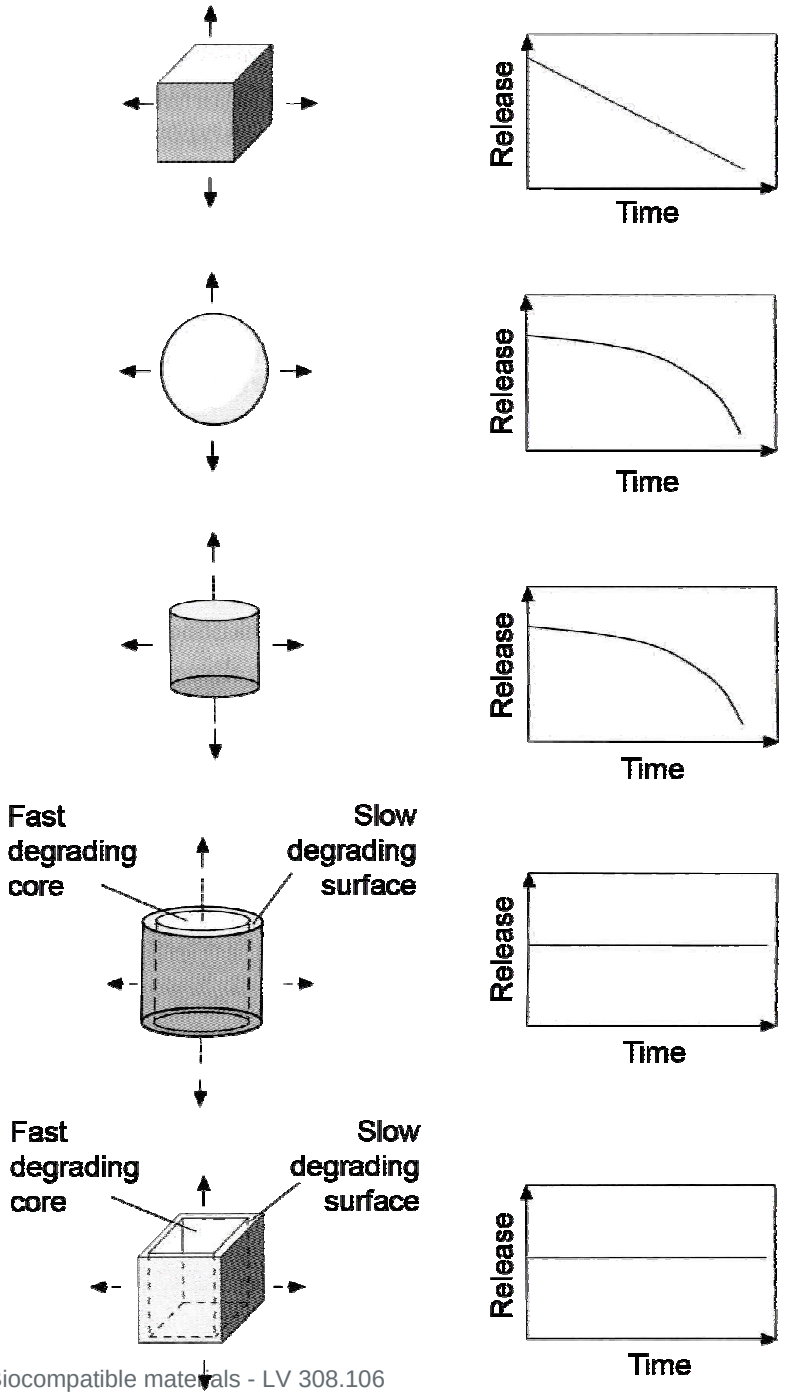






Matrix Systems

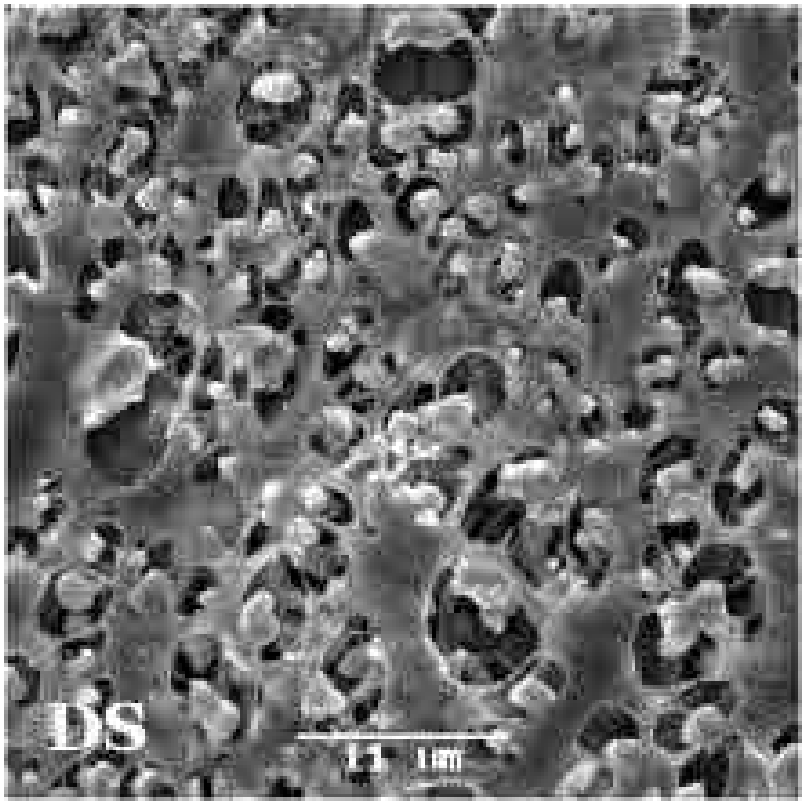
- The drug is dissolved or dispersed in the polymer and diffuses through the polymer matrix in the surrounding tissue
  - Non-porous matrix: diffusion along or between the polymer segments
  - No zero-order release kinetics:
    - relatively fast release of the drug situated at the matrix surface
    - Retarded drug release from the volume
- Zero-order release kinetics:
  - Development of biodegradable or swellable polymers:
    - Release rate depends on the degradation rate of the polymer
      - hydrolytic (PGA, PLA, PVA ...) or enzymatic (PHB) degradation
      - Geometry



Influence of Geometry on Release Rate

(E. Wintermantel / S.-W. Ha, 2002)

PLA-Calcium Phosphate Composite



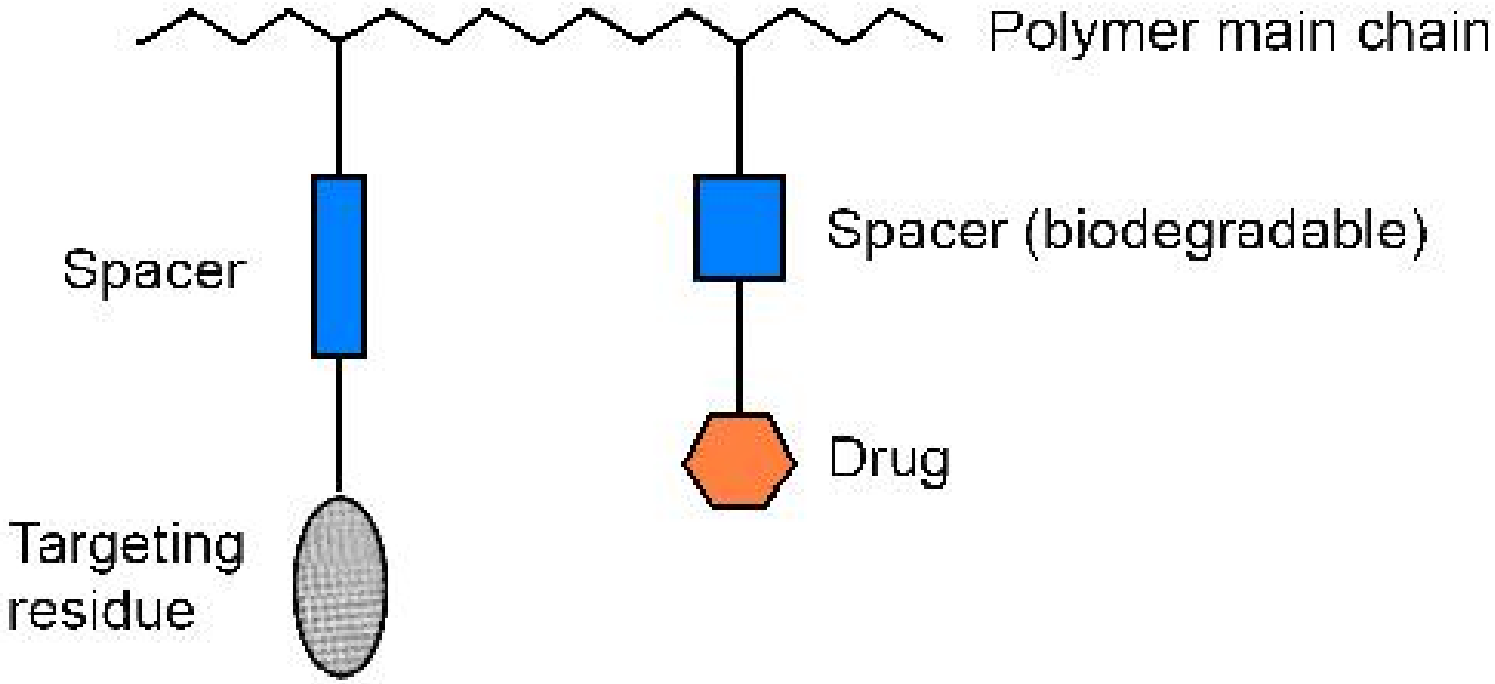
Incorporation of fillers leads to a more homogeneous degradation

Application of composites is preferred for bone therapies

Carrier Systems

- Chemical bonding of the drug on branches of a degradable or biological inert main chain
- High drug content (up to 80 mass-%)
- Advantages
  - Higher specificity due to the higher availability of the drug on the desired site
  - Longer action duration
  - Higher therapeutic efficiency
- Requirements
  - Hydrophilic for a solubility in water
  - Functional groups for a covalent bonding of the drug
  - biodegradable spacer: determined release rate on a specific site
  - specific localisation by specific functional groups (targeting residue) that allow a cell-specific absorption by receptor-connected pinocytosis

Carrier Systems

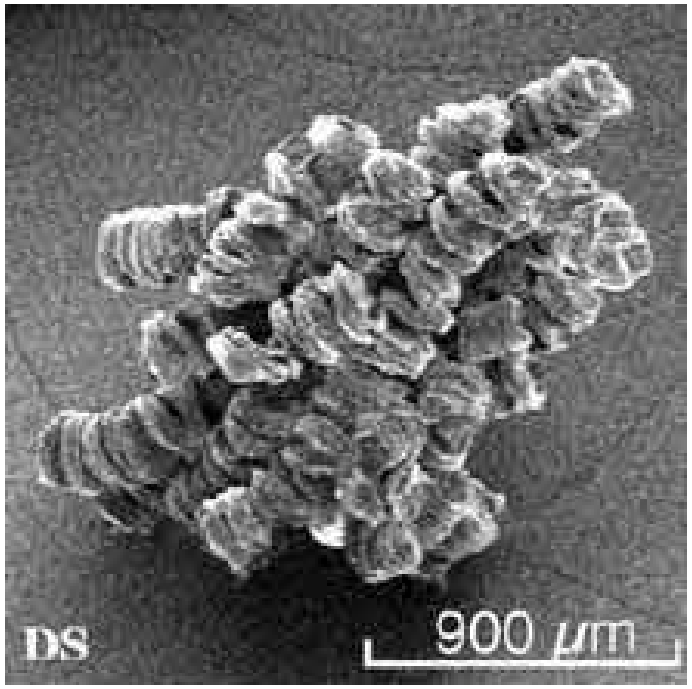


Cell specific absorption

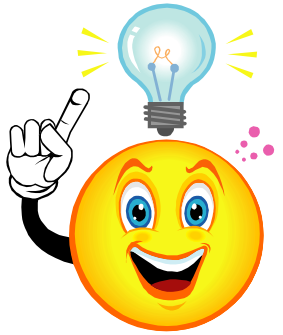
Systems: dextran, polyethylene glycol, N-(2-hydroxypropyl) methacrylamide (HPMA) copolymers, polyaspartic acids ...

(from E. Wintermantel / S.-W. Ha, 2002, modified)

Particle Carrier, Fabricated by CO_2-Foaming



Lessons learned



- Implants for the blood circulatory system
  - Materials for prosthetic devices (sealants, valves, stents, grafts) and corresponding requirements
  - Advantages and disadvantages
- Wound dressings and suture materials
  - Requirements on wound dressings in view of the healing
  - Design and types of wound dressings in modern wound management
  - Degradable and nondegradable suture materials
  - Skin adhesives
- Controlled drug delivery systems
  - Types of drug release systems and their mode of action
  - Materials for drug delivery systems