Controlled Release

Introduction and Background

Topics

- Definitions
- Classifications of CR Systems
  - Rate control, physical form
- Design considerations
- Routes of administration
- Review of mass transfer

Definition of Controlled Release

- A system that:
  - Delivers an agent at a controlled rate for an extended time
  - Might localize drug action by spatial placement near where it is needed
  - Might target drug action by using techniques to deliver drug to a particular cell type

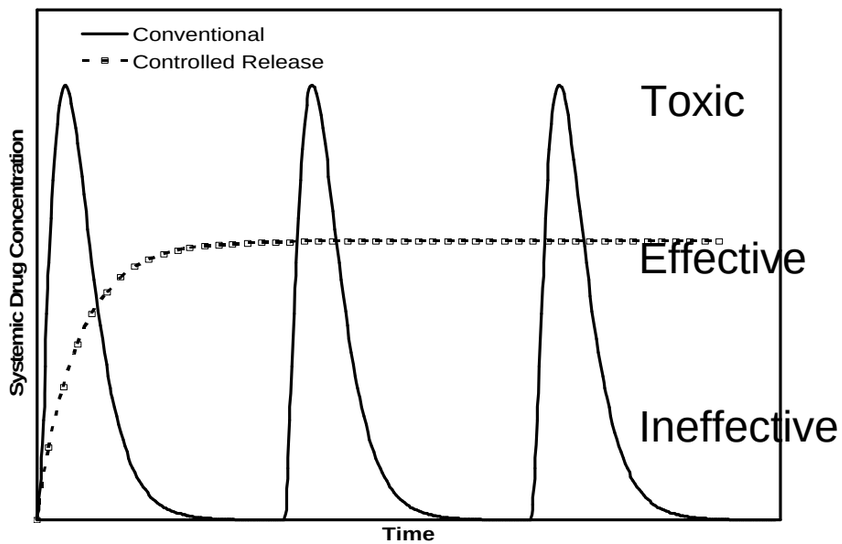
Controlled Release Agents

- In nature (?)
  - Oxygenation of blood
  - Transport of nutrients and waste through cell membranes
  - Transport and evaporation of water (sweat) to control body temperature
- Engineered systems (?)
  - Drugs
  - Biocides
  - Fragrances

Controlled Release vs. Sustained Release

- Controlled drug delivery
  - Well-characterized and reproducible dosage form
  - Controls entry to the body according to the specifications of the required drug delivery profile
    - rate and duration of delivery are designed to achieve desired concentration
- Sustained Release
  - Release of drug is extended in time
  - Rate and duration are not designed to achieve a particular profile.

Controlled Release vs. Conventional



- CR
  - Drug Concentration rises quickly to effective level.
  - Effective concentration is maintained for extended time

- Conventional
  - Periodic administration
  - Non-specific administration
  - High systemic concentrations can be toxic, causing side effects or damage to organs
  - Low concentrations can be ineffective

Disadvantages of Conventional Delivery

(Brainstorm)

- Inconvenient
- Difficult to monitor
- Careful calculation necessary to prevent overdosing
- Large amounts of drug can be “lost” when they don’t get to the target organ
- Drug goes to non-target cells and can cause damage
- Expensive (using more drug than necessary)

Advantages of Controlled Release

(Brainstorm)

- Reproducible rate, prolonged delivery
- Less frequent administration
  - Better patient compliance
  - Increased convenience
- Reduced side effects because effective C is maintained
- Targeting can eliminate damage to non-target organs
- Less drug used
- Re-patenting without new drug development

Challenges to Controlled Release

- Cost of formulation – preparation and processing
- Fate of controlled release system if not biodegradable
- Biocompatibility
- Fate of polymer additives, e.g., plasticizers, stabilizers, antioxidants, fillers

Polymer Systems for Controlled Release

- Classified by
  - Type of device
  - Rate controlling mechanism

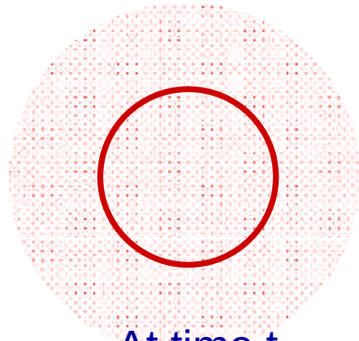
Types	Mechanisms
Matrix	Diffusion Through a matrix or membrane
Reservoir/Membrane	Chemical reaction – erosion or cleavage
(Hybrids)	
Osmotic Pumps	Solvent activation Osmotic pump or polymer swelling

Matrix Systems

- Drug is physically blended with the polymer
  - Dissolved or dispersed
- This is the simplest and cheapest device

At t=0

Polymer matrix contains uniformly dissolved or dispersed drug

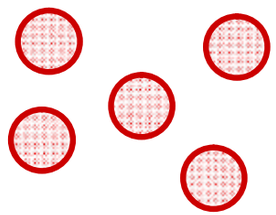


At time t

Drug is being released by some rate-controlling mechanism

Reservoir Systems

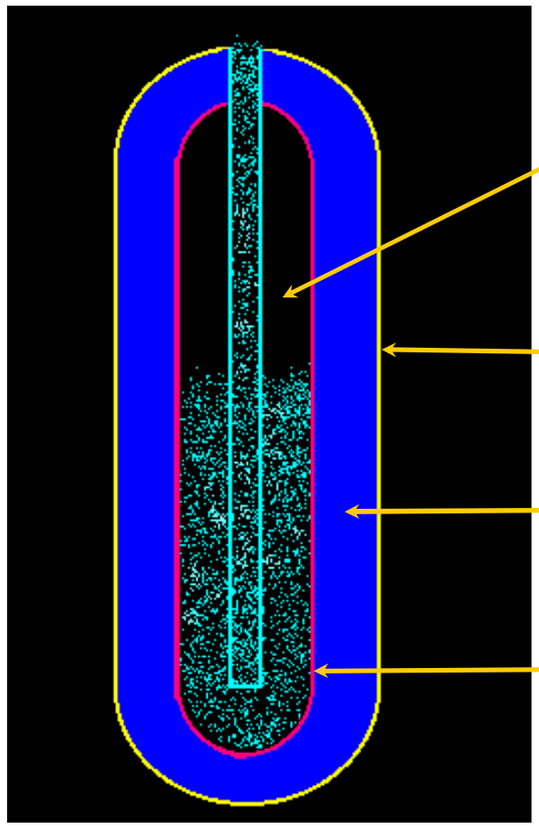
- With or without a rate-controlling membrane
- Geometric Form
  - Microbead – thin polymer coating around particles or droplets
  - Microtube – polymeric hollow fiber



Microbeads

Microtube

The Osmotic Pump

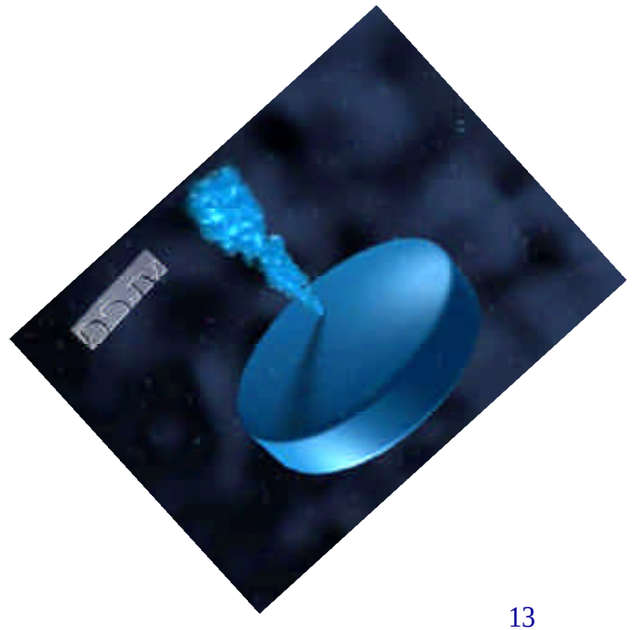


Reservoir containing drug

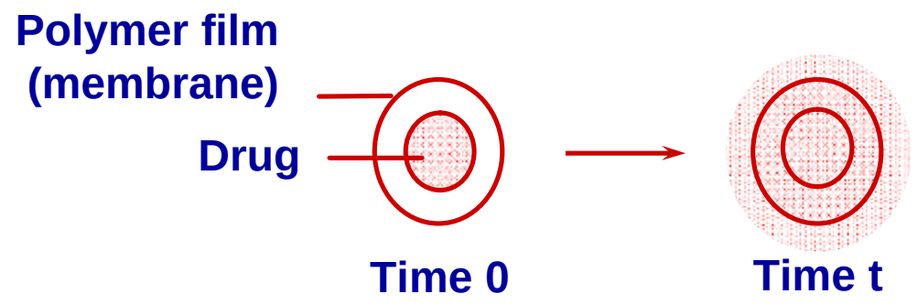
Rigid semipermeable membrane

Osmotic agent

Flexible impermeable wall

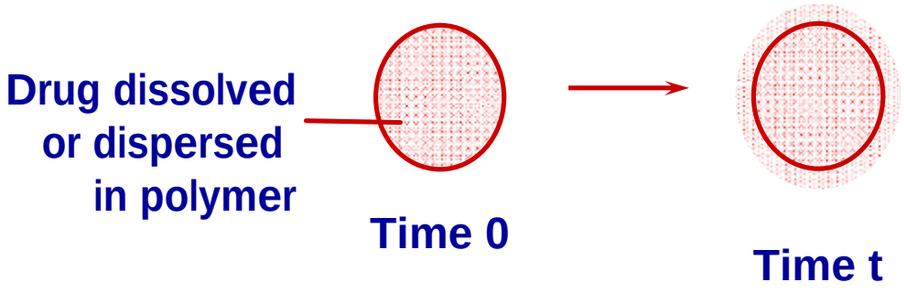


Rate Control: Diffusion



Membrane System

Drug surrounded by polymer film or membrane



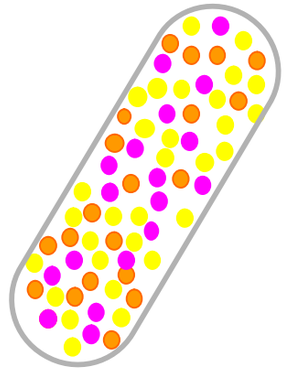
Matrix System

Drug is distributed uniformly throughout polymer

Adapted from Langer, Science, **249**, 1990

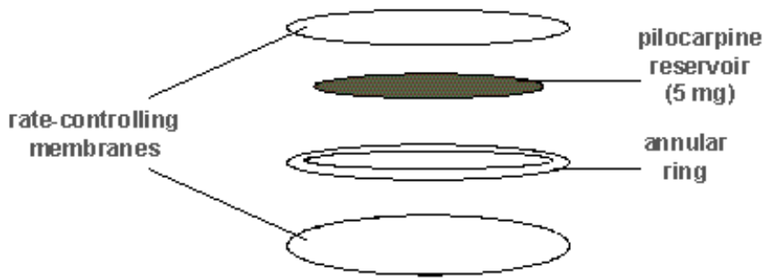
Diffusion Systems

Contac® 12 Hour Cold Capsules

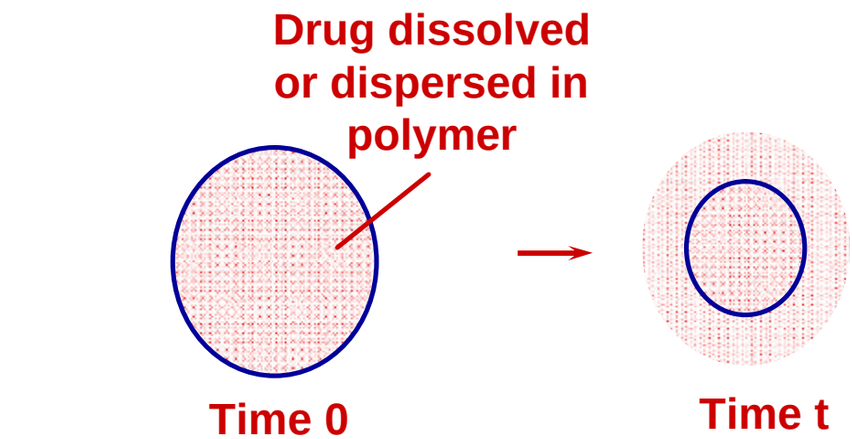


Nocoderm® Patch

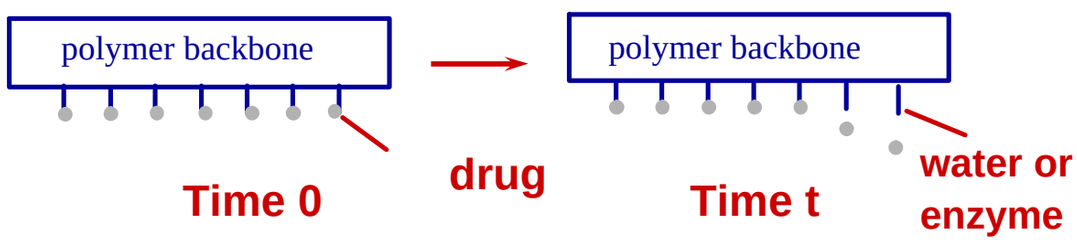
Ocusert®
(Pilocarpine for Glaucoma)



Rate Control: Chemical Reaction



Degradation of polymer



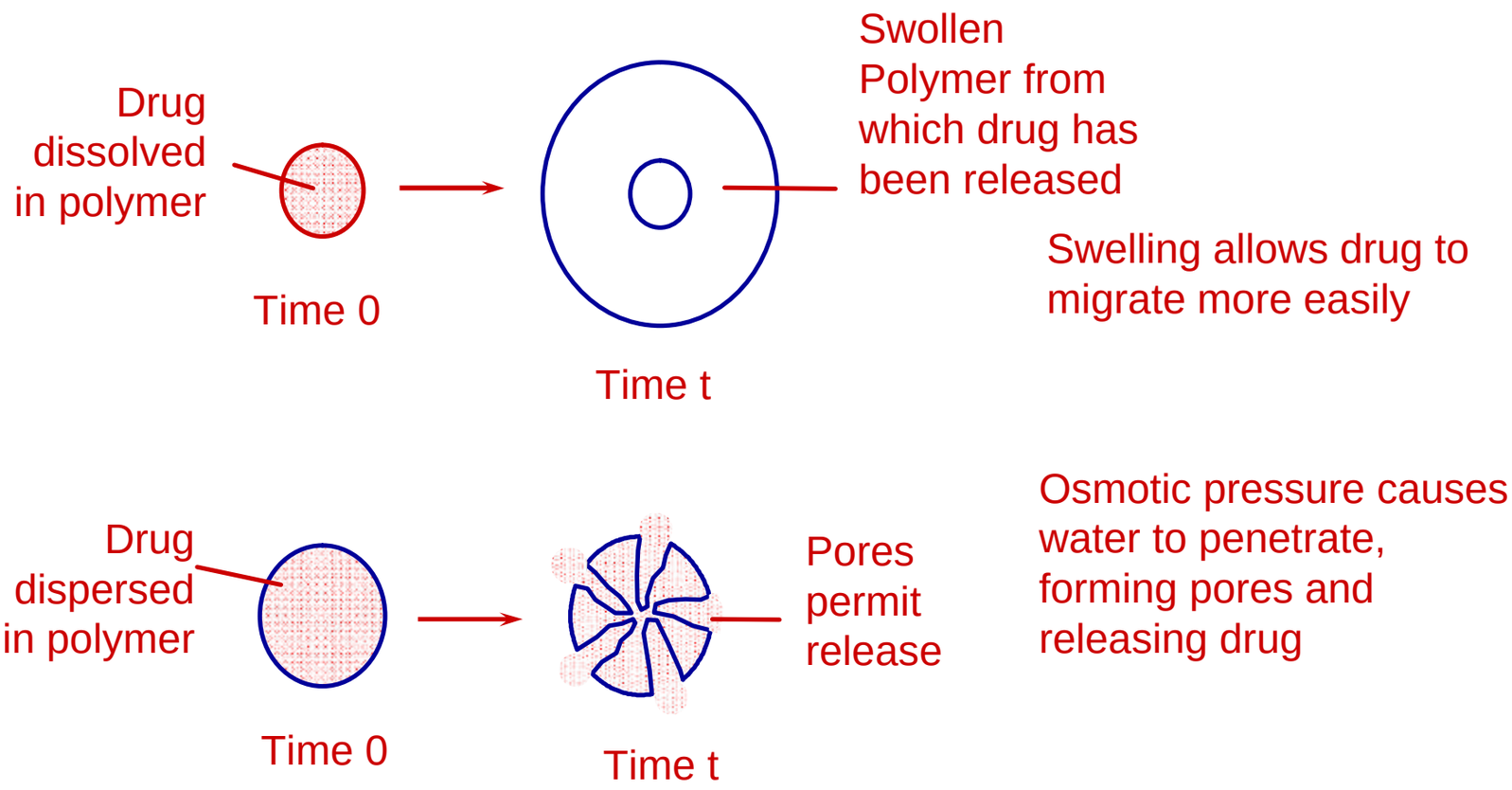
Cleavage of drug from polymer backbone

Adapted from Langer, Science, **249, 1990**

Biodegradable Systems

- Implants for release of anticancer drugs
- Lupron Depot®
  - Injectable microspheres
  - Once per month injecton
  - Prostrate cancer, fertility treatment, early puberty
- Malaria vaccine

Rate Control: Solvent Activation



Adapted from Langer, Science, **249**, 1990

Design Considerations

- Basic components
  - Active agent
  - Polymer
- Polymer design considerations (?)
  - Physical properties
    - Glass transition temperature
    - Diffusion characteristics
  - Compatibility with active
  - Stability – must not decompose in storage
  - Biocompatibility of polymer and degradation products
  - Ease of formulation and fabrication
  - Mechanical properties are stable when drug is added
  - Cost

Design considerations

- Agent
  - Physicochemical properties
    - Stability
    - Solubility
    - Partitioning
    - Charge
    - Protein binding propensity

Design Considerations

- Route of delivery
- Target sites
  - Desired site for efficacy
  - Sites to avoid to minimize side effects
- Type of therapy
  - Acute or chronic – rate and duration
    - e.g., 1 yr contraceptive implant vs. antibiotic for acute infection
- Patient condition
  - Cognative ability and memory
  - Physical condition – ambulatory, bedridden, etc.

Routes of Administration for CR

- Parenteral – outside GI tract
  - Usually refers to injectables
    - Subcutaneous
    - Intramuscular
    - Intraperitoneal
    - Intravenous
- Advantages
  - Bypasses some routes of metabolic clearance
- Disadvantages (?)
  - Painful
  - Inconvenient

Routes of Administration

- Oral
  - Most common route
    - Easy to formulate and manufacture
    - Patient compliance is generally good
    - Inexpensive dosage form
  - Tricky due to environment of GI tract
    - pH degradation
    - Enzymatic degradation
    - Intestinal motility – affects residence time
      - Single patient and patient-to-patient variations
    - Absorption limitations in stomach

Routes of Administration

- Buccal/ Sublingual
  - Thin mucous membrane
  - Rich blood supply
  - Mild pH ~6.0
- Nasal
  - Easy administration
  - Rapid absorption
  - Bypasses certain clearance routes
- Rectal
  - No pH or enzymatic degradation as in oral (+)
  - More effective than buccal or sublingual for some drugs (+)
  - Limited absorption (-)
- Pulmonary
  - Large S.A. for absorption

Routes of Administration

- Transdermal
  - Accessible organ, large surface area
  - Avoid first pass metabolism
  - Avoid GI incompatibility of drugs
  - Good patient compliance
  - Transport across skin can be a challenge
- Ocular
  - Localized delivery for eye disorders
  - Good absorption for many drugs
  - Loss of drug in tears