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

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

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

<table>
<thead>
<tr>
<th>Types</th>
<th>Mechanisms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Matrix</td>
<td>Diffusion Through a matrix or membrane</td>
</tr>
<tr>
<td>Reservoir/Membrane</td>
<td>Chemical reaction – erosion or cleavage</td>
</tr>
<tr>
<td>(Hybrids)</td>
<td></td>
</tr>
<tr>
<td>Osmotic Pumps</td>
<td>Solvent activation Osmotic pump or polymer swelling</td>
</tr>
</tbody>
</table>
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

Polymer film (membrane)
Drug dissolved or dispersed in polymer

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

Adapted from Langer, Science, 249, 1990
Biodegradable Systems

- Implants for release of anticancer drugs
- Lupron Depot®
  - Injectable microspheres
  - Once per month injection
  - Prostate cancer, fertility treatment, early puberty
- Malaria vaccine
Rate Control: Solvent Activation

Drug dissolved in polymer

Drug dispersed in polymer

Swollen Polymer from which drug has been released

Swelling allows drug to migrate more easily

Osmotic pressure causes water to penetrate, forming pores and releasing drug

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