Week 6
Particle Based Drug Delivery Systems

References
General Drug delivery problems

- High dose
- High frequency of dose
- Systemic toxicity
- Patient discomfort
Plasma Drug concentration profile

- Plasma drug concentration as a function of time (first increasing, then decreasing)
- Minimum effective level and maximum safe level; drug above or below the limit causes material wastage and increased risk

![Graph showing plasma drug concentration profile with time on the x-axis and plasma drug concentration on the y-axis. Key points include max. limit, controlled release, and min. limit.]
Techniques to achieve sustained release

- Slowly dissolve coatings made of cellulose or other materials
- Addition of substances which could complex to a drug and decrease its solubility
- Use of compressed tablets
- Employment of emulsions / suspensions

Problems still persist.....
What are the problems?

- Amount of drug released depends on patients conditions
- Other environmental effects
- Repeated dosage still necessary
History of drug delivery

- In the 1950’s, incorporating drugs into solid polymers done for agricultural products
- In the mid-1960’s, extended to medical products. During this decade, silicone rubber tubing used predominately as the polymer
- In the 1970’s, other solid polymers like EVAc and hydrogels used
Advantages of controlled polymeric delivery system

- Drug level maintained in a therapeutic range
- Harmful side effects reduced
- Drugs with short half-life protected
- Less expensive
- Less wastage of drug
- Drug administration may be improved in under privileged areas
Disadvantages of controlled polymeric delivery system

- Toxicity or lack of biocompatibility
- Harmful by-products if biodegradable
- Surgical operations for implantation
- Pain caused by the implant
- Sometimes expensive
Types of Controlled Drug Release Polymeric System

A) Diffusion controlled system
B) Chemically controlled system
C) Swelling controlled system
D) Magnetically controlled system
A) Diffusion controlled system

- Diffusion-controlled systems are the most widely used drug delivery systems
- Have been formulated in two basic configurations
  Reservoirs and Matrices
Reservoir systems

- Drugs are surrounded by polymer films
- Diffusion of the drug through the polymer is the rate limiting step
  - E.g., Membranes, capsules, liposomes, hollow fibres
- Polymers used
  - silicone rubber, hydrogels, EVAc
- Disadvantage
  1) generally non-biodegradable
  2) surgical removal
  3) rapid release
  4) more expensive
Reservoirs systems
Can achieve zero-order kinetics

Time 0

Time t
Matrix systems

- Drug uniformly distributed in polymer
- Rate limiting step - diffusion
- Release characteristics not generally zero order
- Solution of Fick’s eqn. for transient diffusion show drug release rate for most conventional release examples to be proportional to square root of 1/t
Matrix systems

Drug dispersed in polymer

Time 0

Time t
B) Chemically controlled system

- Bioerodible system
  - Drug distribution same as in the matrix
  - Polymer phase degrades with time & releases drug

- Pendant chain system
  - Drug chemically bound to polymer backbone chain
  - Released by hydrolytic or enzymatic cleavage
Chemically controlled system

Drug dispersed in polymer

Time 0

Time t

Fig. Bioerodible system
**Biodegradable Polymer**

- Degrades by a hydrolytic process
- **Heterogeneous degradation**
  - Occurs at the carrier surface
  - Constant degradation rate
  - Chemical integrity retained by undegraded portion
- **Homogeneous degradation**
  - Random cleavage throughout the polymer bulk
  - Molecular weight decrease steadily
  - At critical molecular weight, solubilization and mass loss occurs
Chemically controlled system

Polymer backbone
Drug bonded with polymer backbone

\[ \text{Drug} + \text{Polymer} \]

Enzyme / Hydrolysis

Fig: Pendant chain system
C) Swelling controlled system

- By employing glassy/rubbery state polymers-macromolecular relaxation associated with the transition
- Drug dissolved or dispersed in polymer (glassy state) - no diffusion
- Dissolution medium penetrates the matrix and swells the backbone
- Glass transition temperature lowered below the experimental temperature
- Swollen polymer in rubbery state - drug diffusion occurs
D) Magnetically controlled system

- Drug and small magnetic beads dispersed in polymer matrix
- Upon medium exposure, release like matrix system
- Upon exposure to oscillating external magnetic filed, more release rate
- Selection of implant polymers based on biocompatibility & toxicity testing
Polymers used in drug release

A) Hydrophilic
B) Hydrophobic
C) Biodegradable
Hydrophilic polymers

Variety of reservoir and monolithic devices prepared from swollen cross-linked hydrophilic polymers

Eg.

PHEMA - poly (2-hydroxy ethyl methacrylate)
PNVP - poly (vinyl 2 pyrrolidone)
PVA - poly (vinyl alcohol)
Hydrophobic polymers

These polymers are available as uncross-linked matrices or membranes

Eg.

PDMS- polydimethyl siloxanes

EVAc- ethylene vinyl acetate
Biodegradable polymers

• PLA - polylactic acid
• PLGA - poly (lactic-co-glycolic) acid
• Copolymers of caprolactone and pivalactone
• Copolymers of amino acids and poly(alkyl cyanoacrylates)
• PCPP - poly(bis (p-carboxyphenoxy) propane anhydride)
<table>
<thead>
<tr>
<th>Disease/Treatment</th>
<th>Drug</th>
<th>Polymer</th>
<th>Release Rate</th>
<th>Duration</th>
<th>Implant site</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glaucoma</td>
<td>Pilocarpine</td>
<td>EVAc</td>
<td>20-40 µg/h</td>
<td>1 week</td>
<td>Conjunctiva (eye)</td>
<td>Being marketed commercially</td>
</tr>
<tr>
<td>Birth Control</td>
<td>Progesterone</td>
<td>EVAc</td>
<td>65 µg/day</td>
<td>1 year</td>
<td>Uterus</td>
<td>Being marketed commercially</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Insulin</td>
<td>EVAc</td>
<td>100 µg/day</td>
<td>1 month</td>
<td>Subcutaneous</td>
<td>Has undergone rat trials</td>
</tr>
<tr>
<td>Dental caries</td>
<td>Fluoride</td>
<td>Poly-2-hydroxyethyl methacrylate</td>
<td>Variable</td>
<td>6 months</td>
<td>Back teeth</td>
<td>Clinical trials</td>
</tr>
<tr>
<td>Anticoagulation</td>
<td>Heparin</td>
<td>Poly-2-hydroxyethyl methacrylate</td>
<td>Variable</td>
<td>Variable</td>
<td>General</td>
<td>In vitro</td>
</tr>
<tr>
<td>Cancer (Prostate)</td>
<td>Testosterone</td>
<td>Silicone</td>
<td>1 year</td>
<td></td>
<td>Subcutaneous</td>
<td>Clinical trials</td>
</tr>
</tbody>
</table>
Starting from Classical Fickian diffusion

\[
\frac{\partial C_i}{\partial t} = D_i \frac{\partial^2 C_i}{\partial x^2}
\]

(I) Infinite coefficient of matter transfer on surface

\( C_i = C_i^\circ \) at \( t = 0 \), for all \( x \); \( C_i = \text{constant} \) at \( t > 0 \), \( x = 0, L \)

Solve for \( C_i (x, t) \)

Integrate over \( L \) to get \( Q_t \). On further simplification yields

\[
\frac{Q_t}{Q_T} = \frac{4}{L} \left( \frac{D_i t}{\pi} \right)^{0.5}
\]

for \( Q_t / Q_T \leq 0.5 \)

\[
\frac{Q_T - Q_t}{Q_T} = \frac{8}{\pi^2} \exp \left( -\frac{\pi^2 D_i t}{L^2} \right)
\]

for \( Q_t / Q_T \geq 0.55 \)
Starting from Classical Fickian diffusion

\[ \frac{\partial C_i}{\partial t} = D_i \frac{\partial^2 C_i}{\partial x^2} \]

(II) Finite coefficient of matter transfer on surface

\[ C_i = C_i^o \text{ at } t = 0, \text{ for all } x \]

\[ t > 0 \quad - D_i \left. \frac{\partial C_i}{\partial x} \right| = h \left( C_s - C_e \right) \quad x = \pm L \]

Solve for \( C_i(x, t) \)
Integrate over thickness to get $Q_t$. On further simplification yields

$$\frac{Q_T - Q_t}{Q_T} = \sum_{n=1}^{\infty} \frac{2 N^2}{\beta_n^2 \left( \beta_n^2 + N^2 + N \right)} \exp \left( -\frac{\beta_n^2 D_i t}{L^2} \right)$$

Where $N$ is a dimensionless number

$$N = \frac{L h}{D_i}$$

and

$\beta_n$s are the positive roots of

$$\beta \times \tan \beta = N$$
Solvent Casting Method

- **EVAc, methylene chloride in the ratio 1:9**
  - Sieved IgG → EVAc solution
  - Poured into glass petri dish (precooled at -70°C)
  - Kept at -70°C, 10 minutes
    - Transferred to -20°C, 2 days
    - Kept under mild vacuum, 2 days

- **Square slabs cut off**
  - Carbon adhesive tape covered on one side
  - Submerged in EVAc 2 mins
  - Tape removed, dried under mild vacuum, 24 hrs
  - Coated slab matrices

- **Release study**
Solvent Casting Method

1. EVAc, methylene chloride in the ratio 1:9
2. Sieved IgG + EVAc solution
3. Extrusion into cold ethanol
4. After 24 hrs, EtOH replaced
5. Vacuum dried-4hrs

Microspheres
Double Emulsion Method

1. **Polymer-DCM Solution**
2. **Protein Solution**
3. **Ultra Sonication**
4. **Primary Emulsion (W/O)**
5. **Add to PVA in Water & Mix**
6. **Secondary Emulsion (W/O/W)**
7. **Solvent Evaporation**
8. **Filtration and Drying**
Spray Dried Microspheres

- Inlet temperature
- Polymer concentration
- Pump feed rate
- Aspirator ratio
- Compressed air flow rate
- Drug loadings
Microsphere surface morphology using different polymer solution concentrations

Degradation of microspheres

Modulation of release by PEG


small discs (diameter = 5mm, thickness = 1mm)  

large discs (diameter = 13mm, thickness = 1mm)