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
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 EVAe 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

Drug\textsubscript{bond}\textsubscript{Polymer} \rightarrow \text{Enzyme / Hydrolysis} \rightarrow \text{Drug} + \text{Polymer}

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
Swelling controlled system

Drug dissolved in polymer

Swollen polymer

Time 0

Time t
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>Glaucama</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

\( C_i = C_i^0 \) 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 simplication yields

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

for \( \frac{Q_t}{Q_T} \leq 0.5 \)

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

for \( \frac{Q_t}{Q_T} \geq 0.55 \)
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

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

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

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

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

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
Transfered 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 into EVAc solution
3. Extrusion into cold ethanol
4. After 24 hrs, EtOH replaced
5. Vacuum dried-4hrs
6. Microspheres
Double Emulsion Method

PROTEIN SOLUTION

POLYMER-DCM SOLUTION

ADD TO PVA IN WATER & MIX

SECONDARY EMULSION (W/O/W)

SOLVENT EVAPORATION

Filtration and Drying

ULTRA SONICATION

PRIMARY EMULSION (W/O)
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


Degradation of microspheres

Modulation of release by PEG

small discs (diameter = 5mm, thickness =1mm)    large discs (diameter =13mm, thickness = 1mm)