Chapter 12
Modulated Drug-Delivery Systems

Necessity for New Controlled-Release Dosage Forms
- Non-zero-order drug release for optimum drug action
- Pulsatile release may be desired
  - Mimics biorhythms
  - Better mode of delivery for certain drugs (e.g., insulin, antimicrobial, anticancer, peptide vaccines)
- Circadian rhythm is often important
  - Gastric acid secretion
  - Circulatory system (e.g., myocardial infarction, sudden cardiac death, thrombotic stroke, arterial embolism)

Recombinant Protein Drugs

<table>
<thead>
<tr>
<th>Protein</th>
<th>Company</th>
<th>Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tissue plasminogen activator</td>
<td>Genentech</td>
<td>acute myocardial infarction</td>
</tr>
<tr>
<td>Erythropoietin</td>
<td>Amgen</td>
<td>renal failure</td>
</tr>
<tr>
<td>Interferon-α</td>
<td>Genentech</td>
<td>hepatitis C</td>
</tr>
<tr>
<td>Interferon-α-2b</td>
<td>Roche</td>
<td>very cell leukemia, AIDS-related Kaposis's sarcoma</td>
</tr>
<tr>
<td>Interferon-α-26</td>
<td>Schering-Plough</td>
<td>very cell leukemia, AIDS-related Kaposis's sarcoma and genital warts</td>
</tr>
<tr>
<td>Human growth hormone</td>
<td>Genentech</td>
<td>growth stimulus</td>
</tr>
<tr>
<td>Insulin</td>
<td>Lilly</td>
<td>diabetes</td>
</tr>
<tr>
<td>Haemophilus B conjugate vaccine type B</td>
<td>Praxis Biologics</td>
<td>prophylaxis against haemophilus influenza</td>
</tr>
</tbody>
</table>

Drug Delivery of Proteins
- Protein drugs are not very stable
- Proteins tend to adsorb to solid surfaces
  - Adsorption may result in conformational changes
  - Surface adsorption may result in aggregation
- Drug-on-demand delivery
  - Modulated drug delivery system
  - Self-regulated drug delivery system
- Precise timing is often critical

Insulin Delivery Approaches
- Gene therapy
- Transplanted pancreas
- Bioartificial pancreas (transplanted islet cells)
- Pump systems
  - Open loop
  - Closed loop
- Polymeric delivery systems
  - Sol-gel phase-reversible
  - Erodible matrix
  - pH/temperature-sensitive membrane
  - Immobilized insulin

Insulin Delivery Approaches
Gene therapy
- Somatic cells can be engineered to secrete insulin upon glucose stimulation
  - These cells may serve as surrogates for islet cells in insulin dependent diabetes mellitus.

Insulin Delivery Approaches
Transplanted pancreas
- Immune rejection
- Shortages of donor pancreases

Bioartificial pancreas (transplanted islet cells)
- Isolated islets of Langerhans protected against immune rejection by an artificial membrane permeable to glucose and insulin, but not to lymphocytes and immunoglobulins.
- Closed-loop (continuous glucose monitoring with feedback control)

Pulsatory Drug Release

Insulin Delivery Approaches

**Pump systems**
- Insulin pumps (with computer programs)
  - Implantable/External
- Closed-loop systems
  - Glucose levels are continuously monitored
- Open-loop systems
  - No glucose sensor

**Closed-Loop System**
- Can monitor and respond to tiny fluctuations of glucose levels.
- Can potentially prevent many of the complications of diabetes (e.g., retinal eye disease by 76%, nerve disease by 60%, kidney disease by 56%).
- Represents the best-possible approach to insulin delivery.
- A glucose sensor effective for long-term *in vivo* applications must be developed.
  - Sensitivity rapidly deteriorates owing to surface fouling by protein adsorption and cell adhesion.

**MiniMed™ Devices**

**Insulin Delivery Approaches**

**Polymeric delivery systems**
- Sol-gel phase-reversible
- Erodible matrix
- pH/temperature-sensitive membrane
- Immobilized insulin

**Requirements**
- Glucose-sensing ability
- Information processor
  - Glucose concentration → Insulin dose
- Actuator
  - Insulin delivery & Automatic shut-off

**Size and Shape**

**Sol-Gel Phase Reversible System**

- Hydrogels can be made to undergo solution–gel (sol–gel) transformations depending on the glucose concentration in the environment.
  - Glucose-specificity
  - Reversible crosslinking
- A highly specific interaction between glucose and concanavalin A (con A), a protein that binds to carbohydrates, is used to form crosslinks to glucose-containing polymer chains.
  - Con A exists as a tetramer at physiological pH.
  - Each subunit has a glucose binding site.

**Sol-Gel Phase Reversible System**

- Glucose concentration
  - 1 mg/ml
  - 4 mg/ml
- Sol-gel phase-reversible hydrogel layer

**Sol-Gel Phase Reversible System**

- Insulin reservoir
- Buffer solution
- PHEMA membranes
- Glucose Concentration
  - 1 mg/ml
  - 4 mg/ml

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**P(MAA-g-EG) Hydrogel System**

- An insulin-containing reservoir within a hydrogel membrane of poly(methacrylic acid-g-polyethylene glycol) copolymer in which glucose oxidase has been immobilized.
- The surface of the porous membrane contains a series of molecular "gates," which open and release insulin when the hydrogel shrinks at low pH values as a result of the interaction of glucose with glucose oxidase.

**Phenyloboronic Acid Sol-Gels**

- Poly(3-(acrylamido)phenylboronic acid) and poly(vinyl alcohol) form a gel through complex formation between the pendant phenylborate and hydroxyl groups.
- Glucose cannot function as a crosslinker.
- Glucose exchange is reversible.
- Diglucosylhexanediamine can be used as a crosslinker.
- Copolymers provide glucose sensitivity at physiological pH.

**Erodible Matrix Systems**

- Any of the sol-gel phase-reversible systems described previously can be used as an erodible matrix system.
- All of the components of the system in the solution state are essentially in the dissolved state.
- The components can be released to the environment in the absence of protecting membranes.
- Most hydrophilic polymers dissolve more upon increase in temperature.

**Lower Critical Solution Temperature**

- Some polymers made from hydrophobic monomers precipitate from aqueous solutions upon a temperature increase.
- Precipitation (phase separation) occurs rather dramatically by a minute temperature increase at a certain temperature.
- The temperature that induces polymer precipitation (phase separation) is known as the lower critical solution temperature (LCST).
- Polymers exist as homogeneous single-phase solutions below their LCST.
- Phase separation occurs when heated above the LCST.
- The polymer is water soluble below the LCST and water insoluble above the LCST.
**pH/Temperature-Sensitive Polymers**

- The LCST increases as the polymer becomes ionized (lower pH).
- At a given temperature, the insoluble polymer matrix becomes water soluble as the pH of the environment becomes lower.
- For use in insulin release, gluconic acid generated by glucose oxidase protonates the amino groups of the polymer.
  - This induces a shift of the LCST to higher temperatures for the polymer at the surface of the insulin-loaded polymer matrix.

**Phenylboronic Acid Polymer**

- Poly(N,N-dimethylacrylamide-co-3-(acrylamido)phenylboronic acid) shifts its LCST in response to changes in glucose concentration.
  - Addition of glucose can increase the LCST by 15 °C around the body temperature.
  - The system can be designed to become water soluble in the presence of glucose at body temperature.
  - Loaded insulin can be released as a function of glucose concentration.

**pH-Sensitive Membrane Systems**

- Membranes made of crosslinked polyelectrolytes (i.e., with ionizable groups) display large differences in swelling properties depending on the pH of the environment.
  - When a polymer is charged, it becomes more water soluble.
  - Crosslinked polymers swell more instead of dissolving more.
  - Cationic polyelectrolytes (e.g., poly(N,N-dimethylaminoethyl methacrylate) [PDAEM]) dissolve more at low pH.
  - Anionic polyelectrolytes (e.g., poly(acrylic acid) [PAA]) dissolve more at high pH.
**Immobilized Insulin Systems**
- Insulin molecules are attached to a support or carrier through specific interaction which can be interrupted by glucose itself.
  - Chemically modified insulin with glucose attached to a tether.
  - The tethered glucose binds to concanavalin A
  - Free glucose competes with tethered glucose for site on con A
  - Glycosylated insulin is desorbed from con A in the presence of free glucose
  - The glycosylated insulin is bioactive

**Immobilized Insulin Systems**

**pH-Sensitive Polymers**
- Bulk Solution
- Glucose oxidase
- Gluconic acid
- Polymer
- RH
- COOH
- (CHOH)₄
- CH₂OH
- O
- CH₂OH
- OH
- OH
- OH
- OH
- OO
- NHMe₂
- Me
- OH
- H₃O
- H₂O
- Insulin Release
- PDAEM membranes have been used to entrap glucose oxidase and thus release more insulin as the glucose concentration increases.
- Polyanionic membranes (e.g., poly(methacrylic acid-co-butyl methacrylate)) has been used to immobilize glucose oxidase.
  - At physiological pH, the strands expand and hold in the drug
  - When glucose is oxidized to gluconic acid, the pH lowers and the strands collapse (shrink), thus opening the pores and releasing the drug

**Hydroxylated Insulin**
- Insulin has been modified by adding hydroxyl groups.
  - The hydroxylated insulin binds to phenylboronic acid groups on the support.
  - The support can be hydrogel beads made of polymers of phenylboronic acid (e.g., poly[m-(methacrylamido)phenylboronic acid]).
  - The hydroxylated insulin can be displaced by free glucose
  - The displaced insulin is then released from the support

**Disulfide Grafted Insulin**
- Insulin has been grafted to a support through disulfide bonds.
  - In the presence of glucose, glucose oxidase breaks the disulfide linkage via flavin adenine dinucleotide (FAD).
  - The cleaved insulin is then released to the environment.
**Immovilized Insulin Drawbacks**

- Requires chemical modification of insulin
  - Glucose
  - Hydroxyl groups
  - Sulfhydryl groups
- **Modified insulin is a new substance**
- Has been approved by the FDA for human applications

**Considerations**

- Glucose-sensing system with long-term stability
- Autoregulation of insulin release
- Fast and accurate response of the system to the environmental glucose changes
- Stable insulin formulation for long-term delivery
- Device configuration for easy implantation and insulin refilling
- Biocompatibility of the device