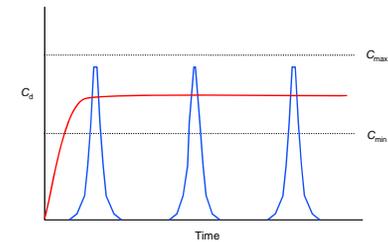


Chapter 12 Modulated Drug-Delivery Systems

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)

Pulsatory Drug Release



Recombinant Protein Drugs

Protein	Company	Use
Tissue plasminogen activator	Genentech	acute myocardial infarction
Erythropoietin	Amgen	renal failure anemia
Interferon- α	Genentech	hepatitis C
Interferon- α -2a	Hoffman La Roche	hairy cell leukemia and AIDS-related Kaposi's sarcoma
Interferon- α -2b	Schering-Plough	hairy cell leukemia, AIDS-related Kaposi's sarcoma, and genital warts
Human growth hormone	Genentech Lilly	growth stimulus
Insulin	Lilly	diabetes
Haemophilus B conjugate vaccine type B	Praxis Biologics	prophylaxis against haemophilus influenza

Drug Delivery of Proteins

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

Routes for Insulin Delivery

- Insulin has been delivered primarily by injection**
- Alternative routes
 - Ophthalmic
 - Nasal
 - Buccal
 - Oral
 - Pulmonary**
 - Transdermal
 - Rectal

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).

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



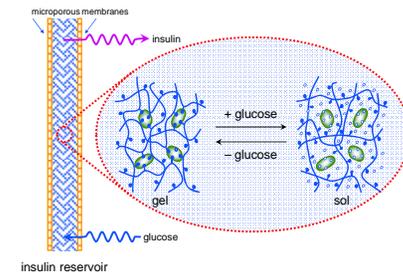
Insulin Delivery Approaches

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

Requirements

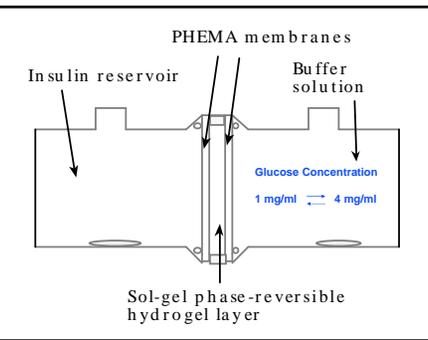
- Glucose-sensing ability
 - Information processor
 - Glucose concentration → Insulin dose
 - Actuator
 - Insulin delivery & Automatic shut-off
- Size and Shape

Sol-Gel Phase Reversible System

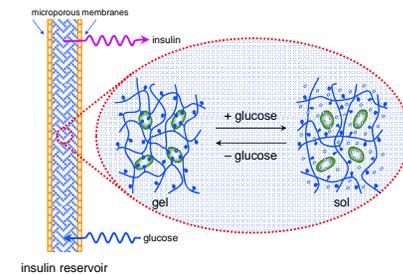


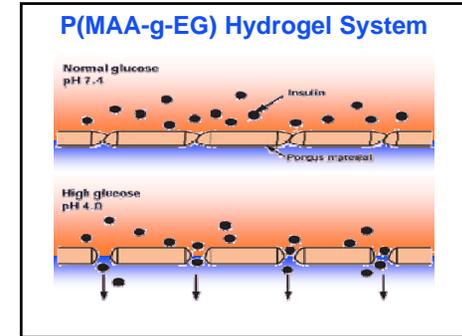
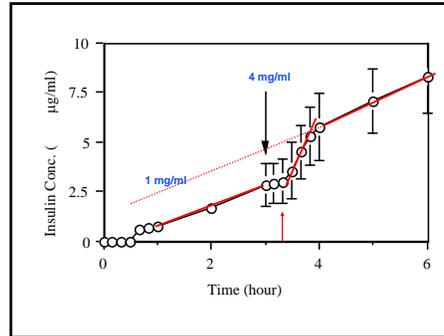
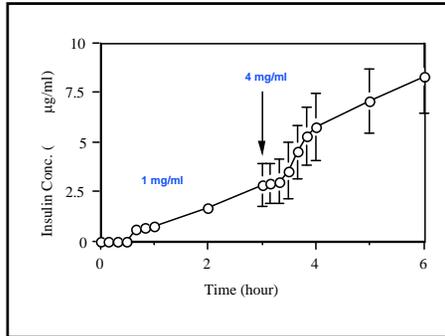
Sol-Gel Phase Reversible System

- 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.



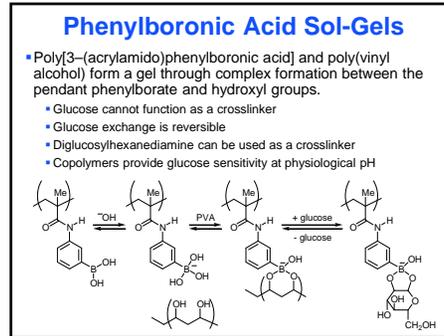
Sol-Gel Phase Reversible System





P(MAA-g-EG) Hydrogel System

- An insulin-containing reservoir within a hydrogel membrane of poly(methacrylic acid-g-poly[ethylene 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.

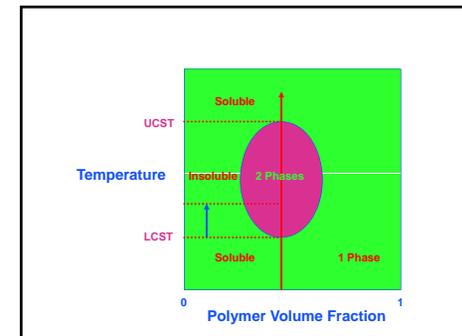
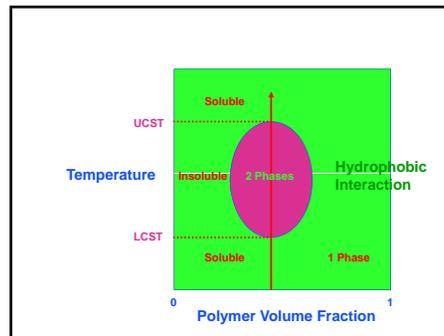


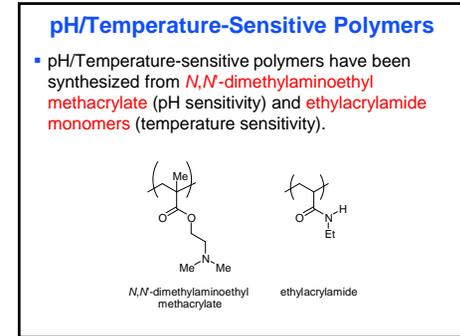
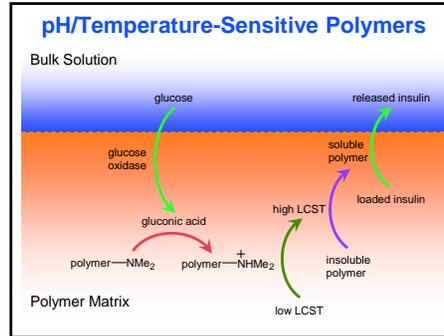
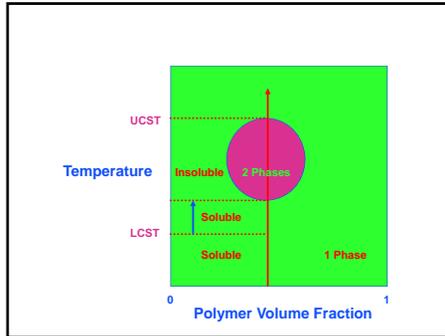
Erodible Matrix Systems

- 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

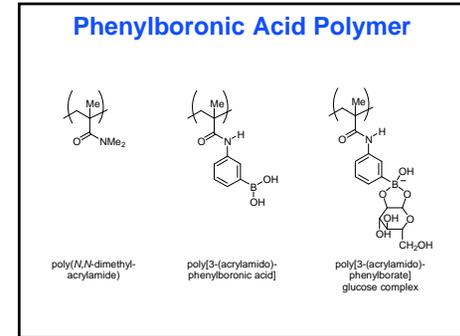
- Some polymers made from hydrophobic monomers precipitate from aqueous solutions upon a temperature increase.
- Precipitation (phase separation) occurs rather dramatically by a minute temperature increase at a certain temperature.
- The temperature that induces polymer precipitation (phase separation) 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.



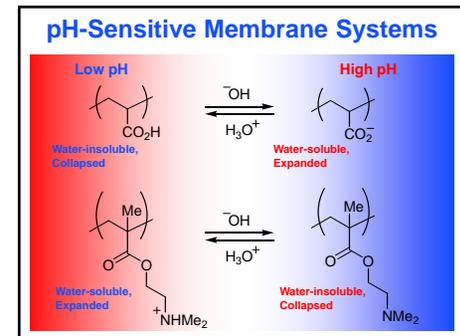
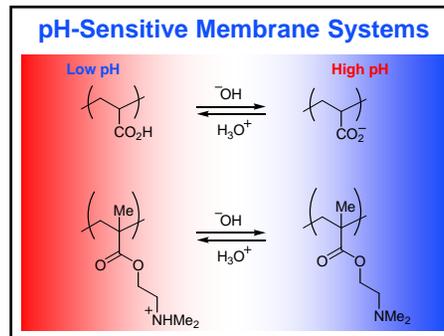


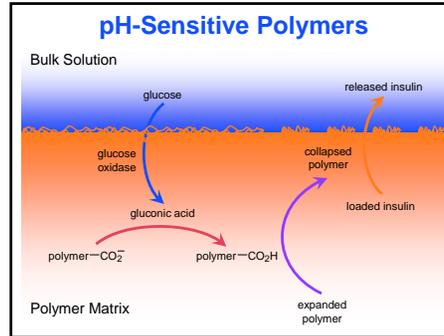
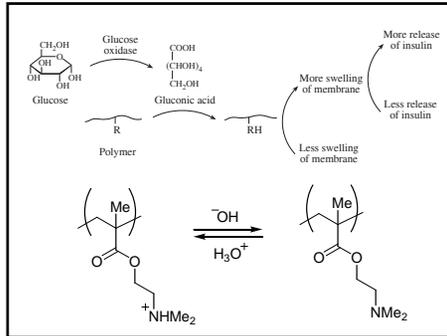
- ### pH/Temperature-Sensitive Polymers
- The LCST increases as the polymer becomes ionized (lower pH).
 - At a given temperature, the insoluble polymer matrix becomes water soluble as the pH of the environment becomes lower.
 - For use in insulin release, gluconic acid generated by glucose oxidase protonates 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.



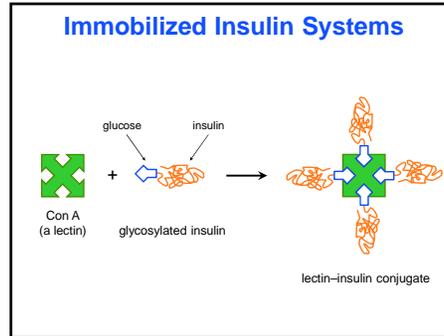
- ### pH-Sensitive Membrane Systems
- Membranes made of crosslinked polyelectrolytes (*i.e.*, with ionizable groups) display large differences in swelling properties depending on the pH of the environment.
 - When a polymer is charged, it becomes more water soluble.
 - Crosslinked polymers swell more 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.



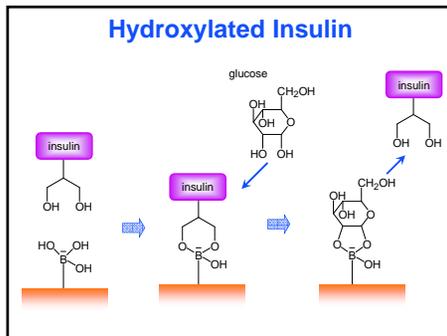


- ### Insulin Release
- PDAEM membranes have been used to entrap glucose oxidase and thus release more insulin as the glucose concentration increases.
 - Polyanionic membranes (e.g., poly(methacrylic acid-co-butyl methacrylate)) has been used to immobilize glucose oxidase.
 - At physiological pH, the 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.

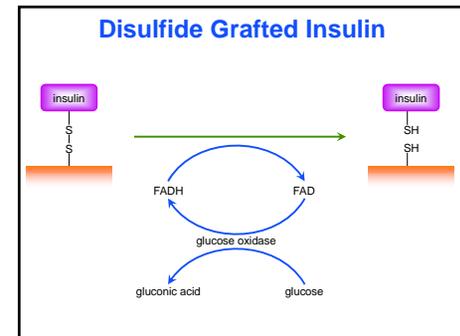
- ### Immobilized Insulin Systems
- Insulin molecules are attached to a support or carrier through specific interaction which can be interrupted by glucose itself.
 - Chemically modified insulin with glucose attached to a tether.
 - The tethered glucose binds to concanavalin A
 - Free glucose competes 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



- ### 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.



Immobilized 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