12 MODULATED DRUG-DELIVERY SYSTEMS

I. NECESSITY FOR NEW CONTROLLED-RELEASE DOSAGE FORMS

While drug delivery at zero order is highly desirable for most drugs, there are many other circumstances in which zero-order drug delivery does not result in the optimum drug action. For example, insulin delivery does not have to be, and maybe should not be, zero-order. As shown in Figure 12.1, pulsatile delivery of insulin depending on the glucose level in the blood is required rather than the delivery of a constant amount of insulin regardless of the glucose concentration in the blood. Pulsatile release, which is designed to mimic natural biorhythms, is inherently a better mode of delivery for certain drugs. Some drugs are known to provide maximal efficacy if given in a pulse pattern. The killing power of antimicrobial and anticancer drugs is thought to rely on the peak blood levels, and continuous low doses may select for resistant strains of bacteria or cancer cells (Check, 1984). It is also desirable to deliver in a pulsatile fashion for peptide vaccines. The initial peak of vaccine can be followed later by a booster of the same or a different vaccine.

In treating certain diseases, following the daily rhythm, known as circadian, is proven to be quite important. Many physiological functions exhibit prominent rhythmic changes, and the onset of some diseases is

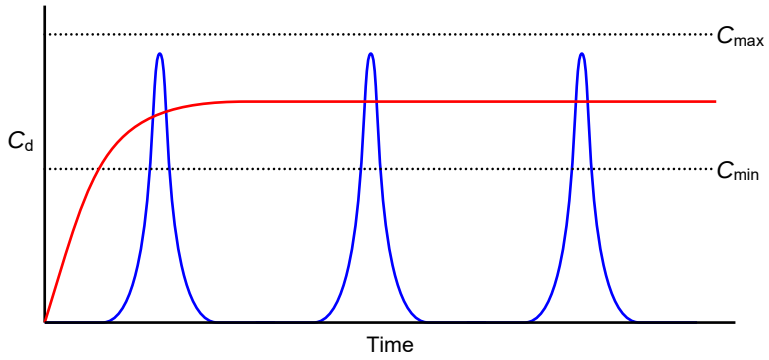


Figure 12.1 Two different profiles of the drug concentration in blood (C_d) obtained from zero-order release (dotted line) and modulated release (solid line) from the dosage forms. C_{max}: maximum safe drug concentration; C_{mim}: minimum effective drug concentration.

known to depend strongly on circadian temporal rhythm. For example, gastric acid secretion rate is high in the evening hours and low in the morning hours (Moore *et al*.,1969). Myocardial infarction, sudden cardiac death, thrombotic stroke, and arterial embolism show a strong circadian rhythm with a morning peak and an evening trough (Berner & Kydonieus, 1996). This suggests that the chronobiological aspects of the pathophysiology of the disease can be applied better management of patients.

In addition to the need of non-traditional delivery modes, many new peptide and protein drugs require unique delivery systems. Table 12.1 lists examples of recombinant protein drugs approved by FDA or under development. While the advances in biotechnology resulted in getting new drugs, especially peptide and protein drugs, onto the market, actually getting them into patients is proven to be quite challenging. As mentioned before, the delivery of peptide and protein drugs can not be achieved using the technologies used for the low molecular weight drugs. One factor that adds to the difficulty in the delivery for protein drugs is that proteins, in general, are usually not very stable and have a tendency to adsorb to solid surfaces. The adsorption may result in conformational changes causing

Table 12.1 Recombinant Protein Drugs Approved by FDA or Under Development

Protein Drug	Company	Indication
Tissue plasminogen activator	Genentech	acute myocardial infarction
Erythropoeitin	Amgen	renal failure anemia
Interferon-α	Genentech	hepatitis C
Interferon-α2a	Hoffman La Roche	hairy cell leukemia and AIDS-related Kaposi's sarcoma
Interferon-α2b	Schering-Plough	hairy cell leukemia, AIDS-related Kaposi's sarcoma, and genital warts
Human growth hormone	Genentech and Lilly	
Insulin	Lilly	diabetes
Hepatitis B virus vaccine	SmithKline Beecham, Merck, and Lilly	prophylaxis against hepatitis B
Haemophilus B conjugate vaccine type B	Praxis Biologics	prophylaxis against haemophilus influenza
Factor VIII	Cutter Biological	hemophilia
Granulocyte-macrophage factor	Amgen, Genetics Institute & Sandoz, Hoechst-Roussel & Immunex, and Schering Plough	regeneration of immune colony-stimulating system in AIDS, cancer
Muromonab-CD3	Ortho	kidney transplant rejection
Superoxide dismutase	Biotechnology General & Brystol-Myers Squibb, Chiron & Pharmacia, Sterling Drug & Enzon	acute myocardial infarction, organ transplantation
Epidermal growth factor	Chiron	corneal repair.
Atrial peptide	California Biotechnology & Wyeth-Ayerst	congestive heart failure.
CD4 protein	Genentech	AIDS, AIDS-related complex.
Interleukin-2	Cetus	renal cell carcinoma.
Monoclonal antibodies	Cetus, Centocor, Pfizer, Xoma	gram negative sepsis, treatment of graft vs host disease.

the loss of bioactivity. Furthermore, the surface adsorption may begin an aggregation process of the protein drugs. For example, when basic fibroblast growth factor (BFGF) was delivered from the conventional matrix polymer-based release device, 99% of BFGF activity was lost. The loss came during the course of device fabrication through adsorption to the polymer surface and denaturation of encapsulated growth factor. Thus, the formulation of peptide and protein drugs requires consideration of additional factors such as prevention of surface adsorption, denaturation, etc.

Drug delivery systems that deliver necessary amounts of drugs on demand (*i.e.*, in accordance with the biological needs) and stop until required again at a later time are known as "modulated drug delivery systems" or "self-regulated drug delivery systems." (Other commonly used names for these devices are signal-responsive, signal-receptive, signal-sensitive, signal-triggered, or on-demand drug-delivery systems). Of the many drugs requiring modulated drug-delivery systems, insulin presents the most difficult challenges. The timing of insulin delivery and the amount of delivered insulin must be precise. The amount of delivered insulin is determined by the glucose level in the blood, and this requires use of a glucose sensor. The insulin release must stop once the glucose level is reduced. Thus, the modulated insulin delivery system need to have the abilities to measure the glucose level, to control the amount of insulin, to release insulin within several minutes of glucose level increase, and to shut off insulin release. Combining all these abilities in one controlled release dosage form presents ultimate challenges, and for this reason modulated drug-delivery systems will be described using insulin delivery as a model system.

II. SELF-REGULATED INSULIN-DELIVERY SYSTEMS

A. ROUTES FOR INSULIN DELIVERY

As shown in Figure 12.1, the choice of the route of administration affects the design parameters of insulin delivery systems. Insulin has been delivered primarily by injection. Because of the inconvenience of multiple, daily injection, many investigators have examined other more convenient, noninvasive ways of insulin delivery. Other routes of insulin delivery examined so far are ophthalmic, nasal, buccal, oral, pulmonary, transdermal, and rectal routes. While the possibilities have been shown for the insulin delivery through these routes, the total amount of insulin delivered is quite low and most often permeation enhancers were required. More importantly, the reliability or the reproducibility of insulin delivery by those routes is very low. For this reason, the daily injection still remains the method of choice for insulin delivery. Implantable insulin delivery devices may be viable candidates if they can deliver insulin for long periods of time to make up for the disadvantages of implantation.

B. Approaches of Insulin Delivery

Table 12.2 provides various approaches used or studied for modulated insulin delivery.

Each system described in Table 12.2 has its advantages and limitations. Regardless of which system is to be used, however, the development of a long-term self-regulating insulin delivery system should consider the two most important requirements: glucose-sensing ability and an automatic shut-off mechanism. Depending on an approach, the insulin-delivery mechanism as well as the size and shape of the device will change.

Studies have shown that somatic cell gene therapy offers a feasible approach to modulated insulin delivery. Cells can be engineered to secrete insulin upon glucose stimulation and such cells might serve as surrogates for islets in insulin dependent diabetes mellitus. The gene therapy, however, will not be practical in the near future. Transplanted pancreas provides continuous source of insulin and autoregulatory features, but the transplanted pancreas tends to cause problems of immune rejection. Furthermore, there is a significant shortage of pancreas to be transplanted. A bioartificial pancreas (or hybrid bioartificial membrane pancreas) is a system that contains isolated islets of Langerhans protected against immune rejection by an artificial membrane permeable to glucose and insulin, but not to lymphocytes and immunoglobulins. The islet cells can be placed inside of microcapsules, hollow fibers, or between two flat ultrafiltration membranes. The bioartificial pancreas presents probably the best closed loop (continuous glucose monitoring with feedback control) insulin therapy. Although the approach is promising, the problems related to the long-term survival of the encapsulated islet cells and the biocompatibility of the device have to be solved.

Intensified insulin therapy for diabetes requires three or more injections daily. The use of an external or an implantable insulin pump is an alternative approach to conventional insulin therapy. Advances in computer-chip technology make it possible to prepare a pump which is programmed to deliver very precise dosages with adjustable delivery rate with time. The hurdles in the development of clinically useful implantable pumps are miniaturization of the device and improving the biocompatibility of the device. Implantable-pump system can be divided into closed-loop and

Table 12.2 Approaches for Modulated Insulin Delivery

Gene therapy
Transplanted pancreas
Bioartificial pancreas (Transplanted islet cells)
Pump Systems
Closed loop pump system
Open loop pump system
Polymeric Delivery Systems
Sol-gel phase-reversible system
Erodible matrix system
pH-sensitive membrane system
Immobilized insulin system

open-loop pump systems. In a closed-loop system, glucose levels are continuously monitored and the insulin release is accordingly adjusted. In an open-loop system, however, glucose levels are not monitored since there are no glucose sensors in the systems. The closed-loop pump system, which can monitor and respond to tiny fluctuation of glucose levels, would potentially prevent many of the complications of diabetes. Closed loop insulin therapy certainly represents one of the best possible approachs to insulin replacement. For this approach to be clinically useful, however, a glucose sensor that is effective for long-term *in vivo* applications has to be developed. The sensitivity of implanted glucose sensors deteriorates rapidly owing to the surface fouling by protein adsorption and cell adhesion. MiniMed™ Implantable Pump (MiniMed Technologies, Inc.: Sylmar, CA) is an example of implantable insulin pumps (open-loop system). The device is a disk with 8.1 cm in diameter and 1.9 cm thick, weighing 220 g with a full reservoir (Saudek *et al*., 1996). The free-floating tip of a 12-cm catheter delivers 400 U/mL of regular human insulin, stabilized with a surfactant additive (Grau & Saudek, 1987), into the abdominal cavity. Refill of the implantable insulin pump can be performed transcutaneously with a syringe approximately every 4–12 wk, depending on insulin requirement. Insulin can be delivered in preprandial boluses on top of a continuous basal rate delivery (Saudek *et al*., 1996). The implantable insulin pump is currently about six times more expensive than conventional multiple daily injections and the biocompatibility issue of the implantable devices has to be solved.

The implantable polymeric insulin delivery system ranges from a simple, continuous baseline insulin release systems to the complicated feedback controlled-release systems. Chemical feedback occurs between intracorporal glucose and insulin release from a reservoir, which may or may not be refillable. The following section describes new concepts of designing implantable polymeric devices. While no approach has been advanced enough to develop a clinically usable device, new concepts provide a basis for further advances in modulated insulin delivery systems.

C. POLYMERIC INSULIN DELIVERY SYSTEMS

1. Sol-Gel Phase Reversible System

Hydrogels can be made to undergo sol-gel phase transformations depending on the glucose concentration in the environment. Preparation of glucose-sensitive phase-reversible hydrogels demands two fundamental requirements: glucose-specificity and reversible crosslinking (*i.e*., physical crosslinking). A highly specific interaction between glucose and concanavalin A (Con A) was used to form physical crosslinks between glucose-containing polymer chains. Since Con A exists as a tetramer at physiological pH and each subunit has a glucose binding site, Con A can function as a crosslinking agent for glucose-containing polymer chains. Because of the non-covalent interaction between glucose and Con A, the formed crosslinks are reversible (Figure 12.2). Individual free glucose molecules can compete with the polymer-attached glucose molecules. Thus, the

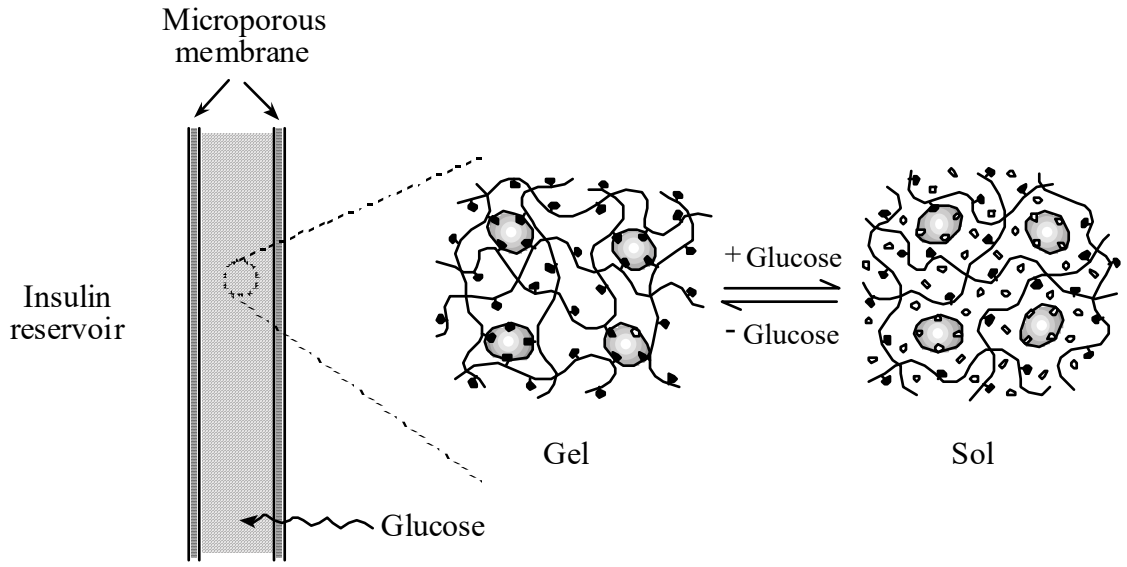


Figure 12.2 Sol-gel phase-transition of a glucose-sensitive hydrogel. Large circles represent Con A, a glucose-binding protein. Small closed and open hexagons represent a polymer-attached glucose and a free glucose, respectively.

maintenance of the cross-links depends on the relative concentration of free glucose in the environment. The gel is formed by mixing glucose-containing polymers with Con A in the absence of external glucose. In the presence of elevated glucose levels in solution, however, the gel becomes a sol (*i.e*, the gel dissociate into a solution). The sol-gel phase transition is reversible. It has been shown that diffusion of insulin through a solution (sol) is an order of magnitude faster than that through a hydrogel (gel), and that insulin release can be controlled as a function of the glucose concentration in the environment.

Glucose-sensitive phase-reversible hydrogels can also be prepared without using Con A. Polymers having phenylboronic groups (*e.g*., poly[3-(acrylamido)phenylboronic acid] and its copolymers) and polyol polymers (*e.g*., poly(vinyl alcohol)) form a gel through complex formation between the pendant phenylborate and hydroxyl groups (Figure 12.3). Glucose, having pendant hydroxyl groups, competes with polyol polymers for the borate groups. Since glucose is monofunctional (*i.e*., has only one binding site for the borate group), it can not function as a crosslinking agent as polyol polymer does. Thus, as the glucose concentration increases, the crosslinking density of the gel decreases and the gel swells to release more insulin. With higher glucose concentrations, the gel becomes a sol. The glucose exchange reaction is reversible, and borate-polyol crosslinking is reformed at a lower glucose concentration. Instead of long chain polyol polymers, shorter molecules, such as diglucosylhexanediamine, can be used as a crosslinking agent. Since the phenylboronic acid gel is sensitive to glucose only at alkaline conditions (pH $\geq$ 9), various copolymers containing phenylboronic acid were synthesized to provide glucose sensitivity at physiological pH.

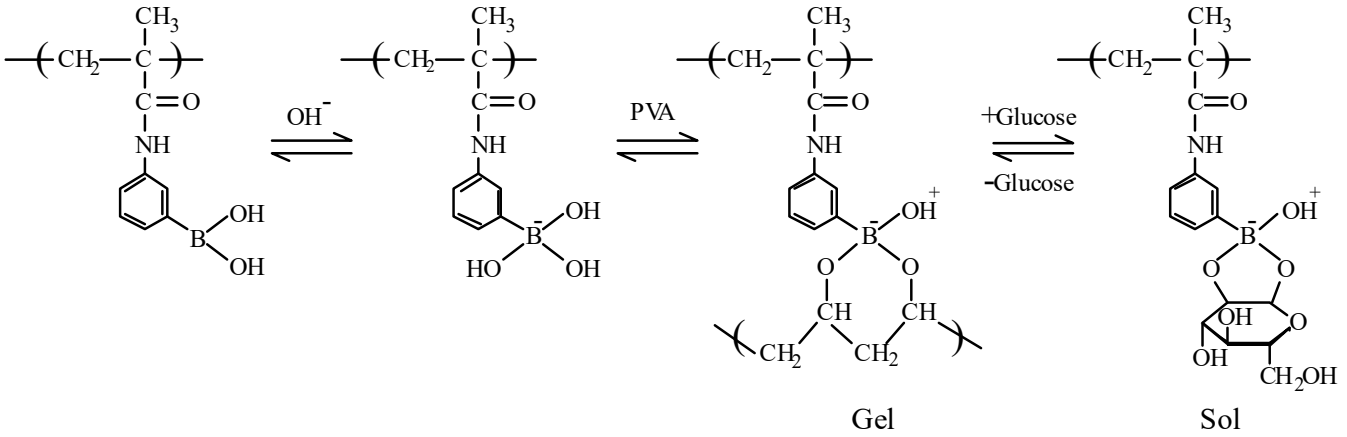
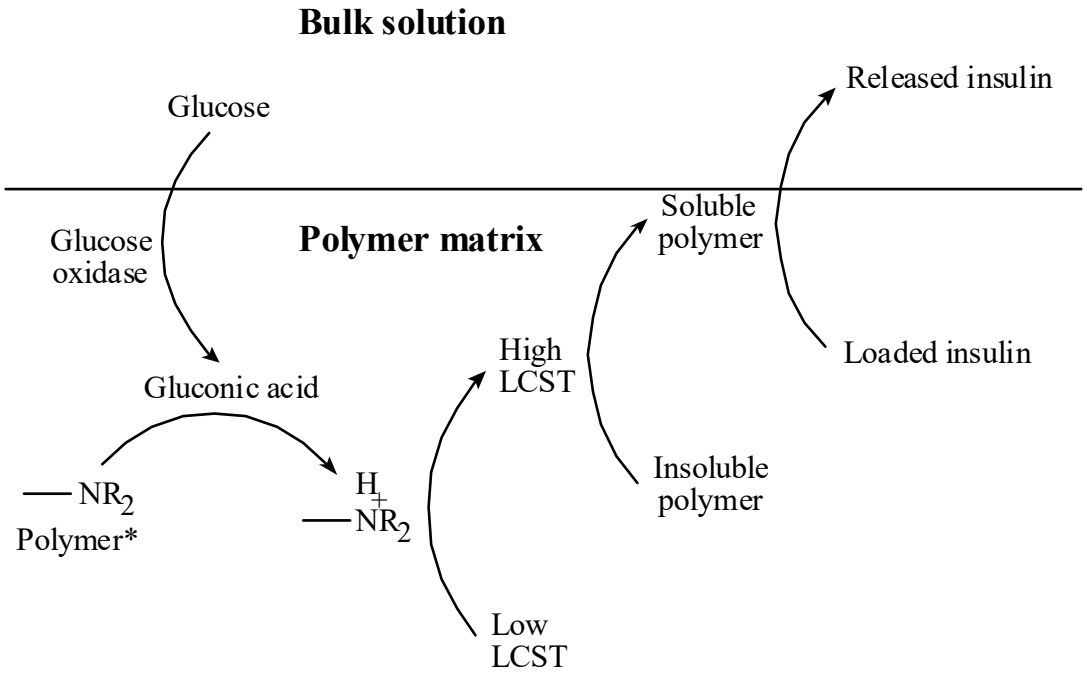


Figure 12.3 Sol-gel phase-transition of a phenylborate polymer. At alkaline pH, phenylborate polymer interacts with poly(vinyl alcohol) (PVA) to form a gel. Glucose replaces PVA to result in transition of a gel to a sol.

2. Erodible Matrix System

Any sol-gel phase-reversible system described above can be used as an erodible matrix system. All the components of the system in the sol state are essentially in the dissolved state, and thus they can be released to the environment in the absence of protecting membranes. During the process of gel to sol transition by the addition of glucose, the incorporated insulin can be released as a function of glucose concentration. There are of course other polymeric systems that can be used in glucose-sensitive erodible insulin delivery.

Most hydrophilic polymers dissolve more upon increase in temperature. On the other hand, some polymers made of relatively hydrophobic monomers precipitate from aqueous solution upon a temperature increase. Precipitation (or phase separation) occurs rather dramatically by a minute temperature increase at a certain temperature. The temperature that induces polymer precipitation (or phase separation) is known as a lower critical solution temperature (LCST). Thus, polymers exist as a homogeneous single-phase solution at temperatures below the LCST, and phase separation occurs when heated to above the LCST. Simply put, polymer does not dissolve at temperatures above the LCST and becomes water-soluble as the temperature decreases below the LCST. pH/temperature-sensitive polymers were synthesized from *N*,*N*″-dimethylaminoethyl methacrylate and ethylacrylamide monomers providing pH sensitivity and temperature sensitivity, respectively. The uniqueness of poly(*N*,*N*″-dimethylaminoethyl methacrylate–co–ethylacrylamide) is that the LCST increases as the polymer becomes ionized (*i.e.*, the pH becomes lower). Thus, the insoluble polymer matrix at a certain temperature becomes water soluble as the pH of the environment becomes lower. This unique property was used for glucose-controlled insulin release as described in Figure 12.4. In the presence of glucose, gluconic acid generated by glucose oxidase, protonates the dimethylamino groups of the polymer. This induces a shift of the LCST to higher temperature for the polymers at the surface of



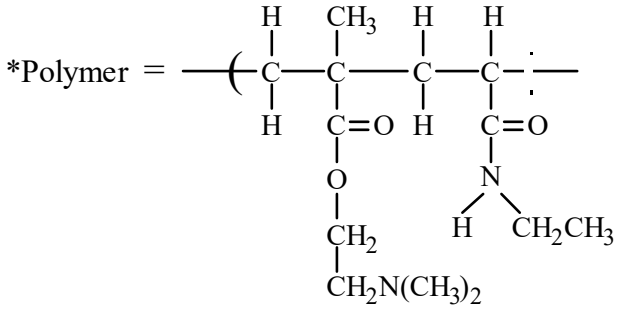


Figure 12.4 Sequence of insulin release from pH/temperature-sensitive polymer matrix. Both glucose oxidase and insulin are loaded inside the matrix. The decrease in pH by gluconic acid results in ionization of the polymer, which in turn increase the LCST. This makes the polymer water-soluble, and erosion of the polymer matrix at the surface releases the loaded insulin.

the insulin-loaded polymer matrix. This leads to the dissolution of the polymer from the surface and thus the release of insulin.

An erodible matrix system based on the shift of the LCST can also be made using polymers containing phenylboronic acid groups. Poly[*N*,*N*′-dimethylacrylamide–co–3-(acrylamido)phenylboronic acid] shifts its LCST in response to changes in glucose concentration. Addition of glucose to such a polymer system can increase the LCST by 15 °C around body temperature. Thus, the system can be designed to become water-soluble in the presence of glucose at the body temperature. Insulin that is loaded inside the polymer can be released as a function of glucose concentration in the environment.

3. pH-sensitive membrane system

Membranes made of crosslinked polyelectrolytes (*i.e.*, polymers with ionizable groups) display big differences in swelling properties depending on the pH of the environment. When a polymer is charged, it dissolves more in aqueous solution. When polymer molecules are crosslinked, the crosslinked network (*i.e.*, a hydrogel) swells more instead of dissolving more. As shown in Figure 12.5, cationic polyelectrolytes, such as poly(*N*,*N*″-diethylaminoethyl methacrylate) (PDAEM), dissolve more, or swell more if crosslinked, at low pH owing to the ionization. On the other hand, polyanions, such as poly(acrylic acid) (PAA), dissolve more at high pH.

Membranes made of PDAEM have been used for self-regulated insulin delivery. Addition of glucose leads to the lowering of pH, which in turn results in ionization and thus swelling of the membrane (Figure 12.6). When a membrane swells, it tends to release more drugs than the membrane in the non-swelled state. Thus, the PDAMEM membrane can be used to deliver insulin as the environmental glucose concentration increases.

Polyanions can also be used for self-regulated insulin delivery. A glucose-sensitive hydraulic flow controller can be designed using a porous membrane system consisting of a porous filter grafted with a polyanion (*e.g.*, poly(methacrylic acid–co–butyl methacrylate)) and immobilized glucose oxidase (Figure 12.7). The grafted polyanion chains are expanded at pH 7 owing to electrostatic repulsion among charges on polymer chains. Glucose oxidase converts glucose to gluconic acid, which lowers the pH and protonates the carboxyl groups of the polymer. Owing to the reduced

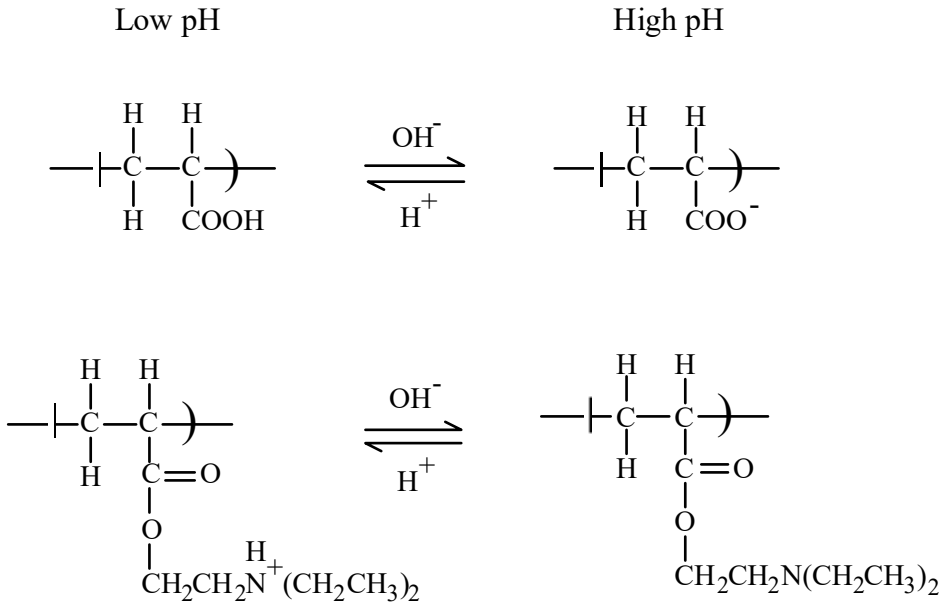


Figure 12.5 pH-dependent ionization of polyelectrolytes. Poly(acrylic acid) becomes ionized at high pH, while poly(*N*,*N*″-diethylaminoethyl methacrylate) becomes ionized at low pH. Ionized polymers dissolve more in aqueous solution. Hydrogels swell more since they are not water-soluble.

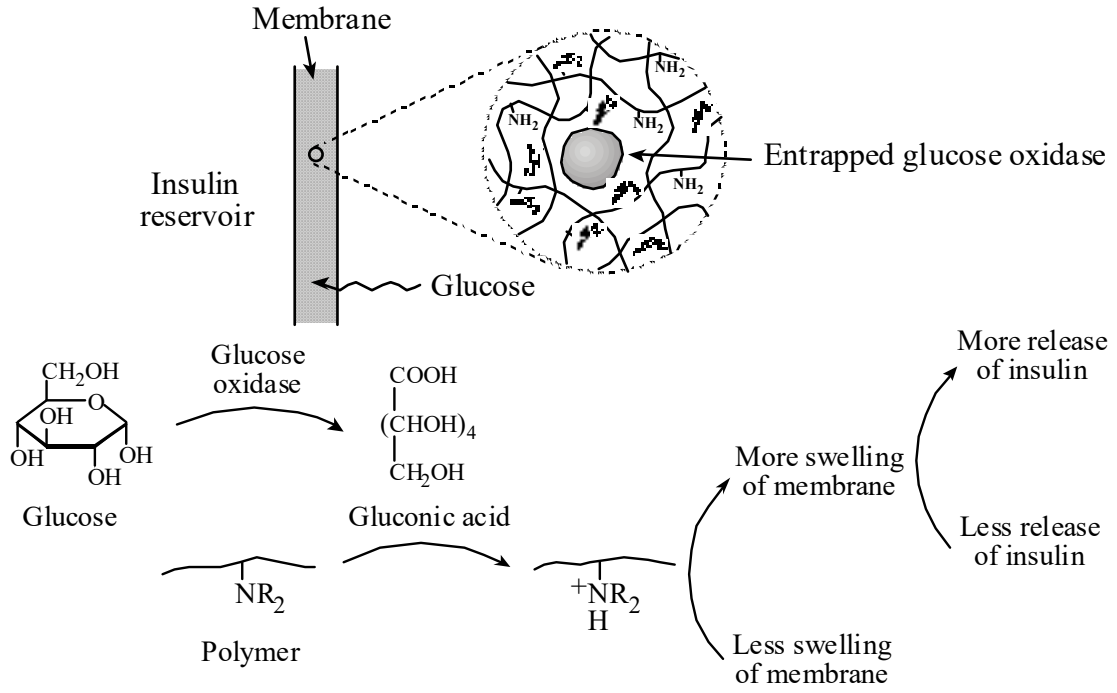


Figure 12.6 Self-regulated insulin release membrane made of poly(N,N"-diethylaminoethyl methacrylate) hydrogel membrane. As glucose enters the membrane, glucose oxidase entrapped inside the membrane transforms glucose into gluconic acid, which in turn reduced the pH of the hydrogel membrane. This makes swelling of the membrane followed by more release of insulin through the membrane.

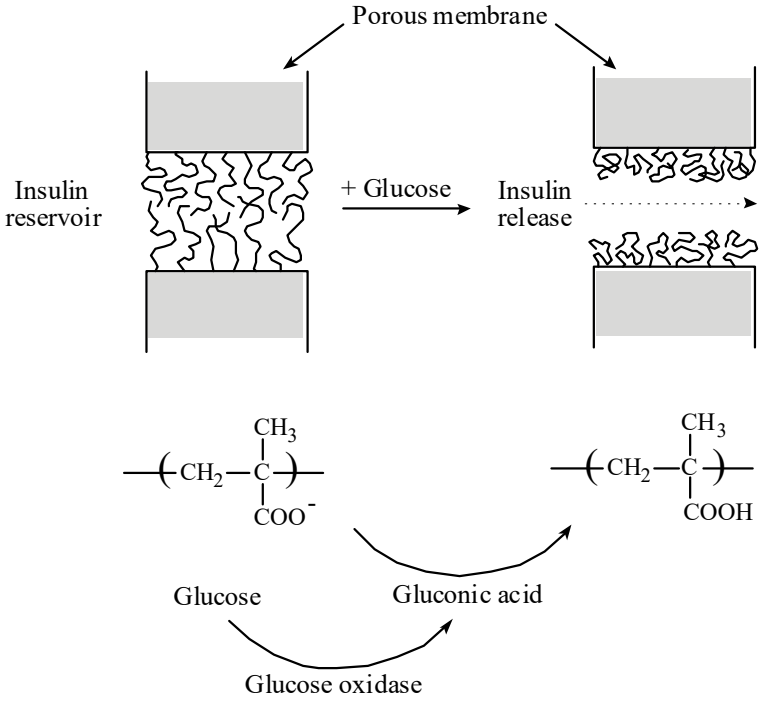


Figure 12.7 Anionic polymer chains grafted to the surface undergo conformational changes in response to pH changes. At physiological pH, poly(methacrylic acid) (PMAA) chains are expanded due to electrostatic repulsion of carboxylate ions. As the pH decreases as a result of gluconic acid formation, the carboxylate groups are protonated and the electrostatic repulsion is reduced. This in turn causes shrinkage of the polymer chains to open pores for insulin release.

electrostatic repulsion, the polyanion chains then collapse (*i.e.*, shrink) and pores of the membrane become open and insulin is released.

4. Immobilized insulin system

In this type of systems, insulin molecules are attached to a support or carrier through specific interactions that can be interrupted by glucose itself. This generally requires introduction of functional groups to insulin molecules. In one approach, insulin was chemically modified to introduce glucose, which has specific binding sites in Con A. The glycosylated insulin-Con A system exploits complementary and competitive binding behavior of Con A with glucose and glycosylated insulin. The free glucose molecules complete with glucose–insulin conjugates bound to Con A, and thus, the glycosylated insulin is desorbed from the Con A in the presence of free glucose (Figure 12.8). The desorbed glucose–insulin conjugates are released to the surrounding tissue, and the studies have shown that the glucose–insulin conjugates are bioactive.

In another approach, insulin was modified to introduce hydroxyl groups so that the hydroxylated insulin can be immobilized by forming complex with phenylboronic acid groups on the support (Figure 12.9). The support can be hydrogel beads made of polymers containing phenylboronic acid (*e.g.*, poly(*m*-methacrylamidophenylboronic acid)). The hydroxylated in-

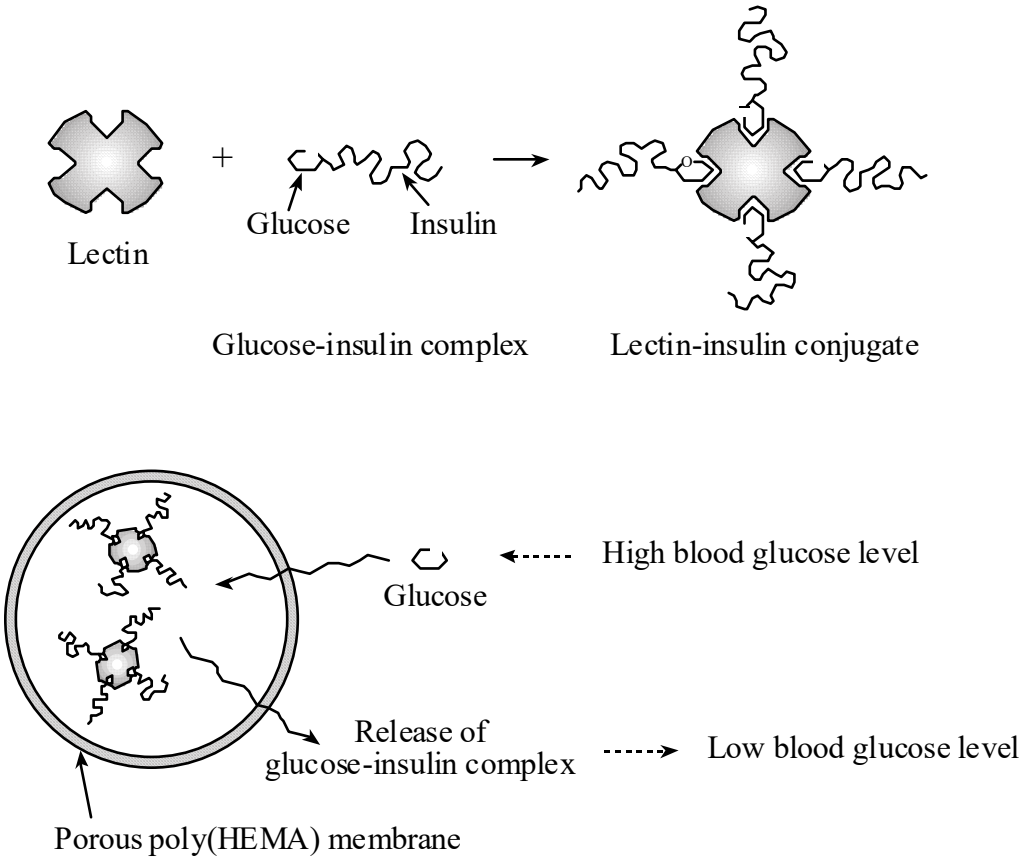


Figure 12.8 Desorption controlled release of insulin from the insulin-Con A complex. In this approach, each insulin molecule is modified with a glucose molecule.

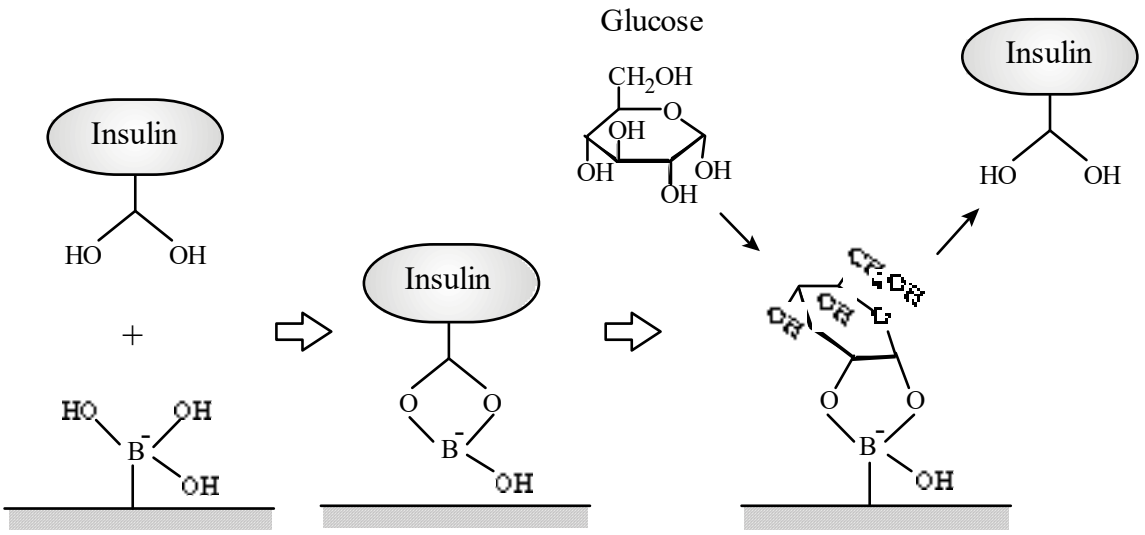


Figure 12.9 Release of hydroxylated insulin from the phenylboronic acid support as a result of displacement by glucose.

sulin can be displaced by the added glucose and the displaced insulin can be released.

Sometimes, insulin can be covalently grafted to the support as shown in Figure 12.10. In this example, insulin is grafted to the support through a disulfide bond. In the presence of glucose, electrons generated by glucose oxidase are transferred to the disulfide linkage via flavin adenine dinucleotide (FAD) to result in reductive cleavage of the disulfide bond. The cleaved insulin is then released to the environment.

While the approaches taken in the immobilized-insulin systems are highly elegant, there is an inherent drawback of this approach. The approach requires chemical modification of insulin to introduce glucose, hy-

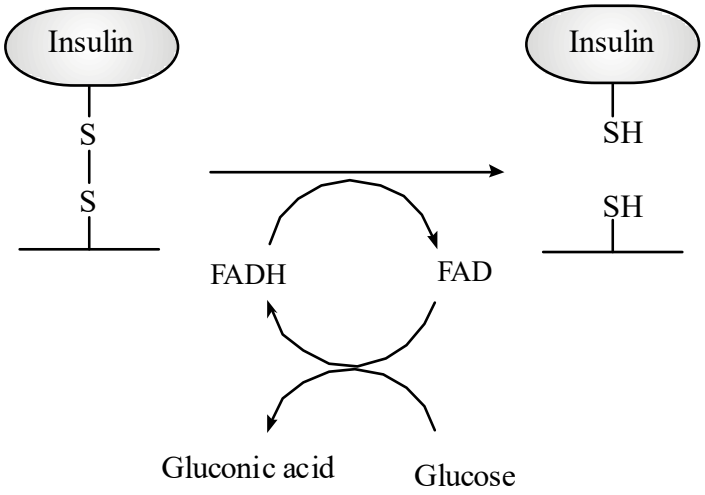


Figure 12.10 Release of immobilized insulin in respond to addition of glucose. The disulfide bond is cleaved by electrons resulting from glucose transformation to gluconic acid by glucose oxidase. This approach requires a coenzyme flavin adenine dinucleotide (FAD).

Table 12.3 Issues to Consider in the Development of Self-Regulating Insulin Delivery Systems

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
Biocompartibility of the device

droxyl, or sulfhydryl group, and this makes insulin a new chemical entity. The chemically modified insulin has to be approved by FDA for human applications.

D. MORE CONSIDERATIONS IN MODULATED INSULIN-DELIVERY SYSTEM DEVELOPMENT

In addition to achieving glucose sensing and autoregulation functions, development of modulated-insulin delivery systems requires consideration of other important factors listed in Table 12.3. To be clinically useful, the device should be able to act as fast as possible, preferably in less than a few minutes after the glucose concentration changes in blood. Since diabetes is a life-long disease, long-term delivery of insulin is desired. This requires an insulin formulation with long-term stability. Insulin molecules tend to precipitate and this may result in irreversible obstructions in the delivery systems. Since long-term self-regulated insulin delivery inevitably demands implantation into the body, the device has to be configured for easy insulin refilling. In addition, insulin delivery systems should be biocompatible (*i.e.*, should not cause any adverse response by the body) and be free of any infection. Development of devices that fulfill all the requirements in Table 12.3 will take years. Considering the fast advances made in the last few decades, however, one can be optimistic that such devices can be developed in our lifetime. Let's keep our fingers crossed.

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