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Responsive polymeric delivery systems ☆

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ABSTRACT

This paper discusses the state of the art in a relatively new approach in the field of controlled drug delivery–responsive polymeric drug delivery systems. Such systems are capable of adjusting drug release rates in response to a physiological need. The fundamental principles of externally and self-regulated delivery systems are examined. Special attention is paid to specific clinical settings such as diabetes, presenting the advantages and disadvantages of different approaches.

Contents

1. Introduction

While newer and more powerful drugs continue to be developed, increasing attention is being given to the methods by which these active substances are administered. A new development, polymeric controlled drug delivery, has evolved from the need for prolonged and better control of drug administration. In conventional drug delivery, the drug concentration in the blood rises when the drug is taken, then peaks and declines. Since each drug has a plasma level above which it is toxic and below which it is ineffective, the plasma drug concentration in a patient at a particular time depends on compliance with the prescribed routine. The controlled-release devices, which are

Abbreviations: AIBN, azobisisobutyronitrile; Con A, concanavalin A; DMA, *N*, *N*-dimethylaminoethylmethacrylate; EE, ethinylestradiol; EVAc, ethylenevinylacetate; HCG, human chronic gonadotropin; HEA, hydroxyethylacrylate; HEMA, hydroxyethylmethacrylate; IVGTT, intravenous glucose tolerance test; LCST, lower critical solution temperature; MBAAm, methylenebisacrylamide; MMA, methylmethacrylate; NIPAAm, *N*-isopropylacrylamide; PAH, *para*-aminohippuric acid; PHEMA, poly(2-hydroxyethylmethacrylate); PMMA, poly(methylmethacrylate); PVA, poly(vinyl alcohol); QA, quinaldic acid; RIA, radioimmunoassay; SAPG-insulin, phenyl-α-D-glucopyranoside insulin; SHBG, sex-hormone-binding globulin; TEGDMA, tetraethyleneglycoldimethacrylate; TMS, trimethylsilystyrene; 5-FU, 5-fluorouracil.

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already available commercially, can maintain the drug in the desired therapeutic range with just a single dose, localize delivery of the drug to a particular body compartment, which lowers the systemic drug level, reduces the need for follow-up care, preserves medications that are rapidly destroyed by the body, and increases patient comfort and/or improves compliance.

The basic approach that drug concentration–effect relationships are significantly invariant as a function of time in man has led to the development of constant rate drug delivery systems. Nevertheless, there are a number of clinical situations where such an approach may not be sufficient. These include the delivery of insulin for patients with diabetes mellitus, antiarrhythmics for patients with heart rhythm disorders, gastric acid inhibitors for ulcer control, nitrates for patients with angina pectoris, as well as selective β-blockade, birth control, general hormone replacement, immunization, and cancer chemotherapy. Recent studies in the field of chronopharmacology indicate that the onset of certain diseases exhibit strong circadian temporal dependency. Thus, drug delivery patterns can be further optimized by pulsed or self-regulated delivery, adjusted to the staging of biological rhythms.

In recent years several research groups have been developing responsive systems which would more closely resemble the normal physiological process in which the amount of drug released can be affected according to physiological needs. The responsive polymeric delivery systems can be classified as open- or closed-loop systems. Open-loop control systems are those in which information about the controlled variable is not automatically used to adjust the system inputs to compensate for the change in the process variables, while in closed-loop control systems the controlled variable is detected and as a result the system output is adjusted accordingly. In the controlled drug delivery field, open-loop systems are known as pulsed or externally regulated and the closed-loop systems as self regulated. The externally controlled devices apply external triggers for pulsed delivery such as: magnetic, ultrasonic, thermal, and electric; while in the self-regulated devices the release rate is controlled by feedback information, without any external intervention. The self-regulated systems utilize several approaches as rate-control mechanisms: pH-sensitive polymers, enzyme-substrate reactions, pH-sensitive drug solubility, competitive binding and metal concentration-dependent hydrolysis.

This review will be limited to polymeric responsive delivery systems. Therefore it will not cover important work that uses liposomes, electronic sensors, pumps or microencapsulation of living cells.

2. Externally regulated delivery systems

Delivery systems in which the drug release rates can be activated by an external stimuli are still largely experimental. The mechanisms include magnetism, ultrasound, temperature changes, electrical effects, and irradiation.

2.1. Magnetically modulated systems

Previous studies demonstrated that insulin and other molecules could be continuously released by embedding the hormone in a carrier such as ethylenevinylacetate copolymer (EVAc) [1]. In vitro studies were then conducted characterizing the critical parameters affecting release rates [2]. This information was utilized to design single subcutaneous implants of EVAc-insulin which decreased the glucose levels of diabetic rats for 105 days [3]. The next step in designing a delivery system for use in diabetes was to develop a system which will be capable of releasing insulin at a higher rate upon demand. In vitro studies were conducted showing that EVAc-protein matrices containing magnetic beads exhibit enhanced release rates when placed in an oscillating external magnetic field [4–7]. Recent in vivo studies [7] showed that when polymeric matrices containing insulin and magnetic beads are implanted in diabetic rats, glucose levels can be repeatedly decreased on demand by application of an oscillating magnetic field.

The systems consist of drug powder dispersed within a polymeric matrix together with magnetic beads. One method of formulating this system is to add approximately 50% of the drug–polymer mixture to a glass mold, which has been cooled to −80°C using dry ice. The magnetic particles are added followed by the remaining drug-polymer mixture [5]. In addition to the experimental polymer matrices containing both magnets and insulin, controls including polymer matrices which contained a magnet but no insulin, and which contained insulin but no magnet were made.

When a polymer matrix containing insulin and the magnet was implanted into a diabetic rat [7], the blood glucose level fell from over 400 mg% to nearly 200 mg%. In the absence of the magnetic field, the blood glucose level, remained near this value over the 51-day implantation period. However, every time the magnetic field was applied, the blood glucose level decreased (Fig. 1). The average decrease for the three rats in the experimental group which were triggered a total of 26 times was 29.4%. The difference in glucose changes between the experimental group and the controls (14 rats, 97 triggers) was highly significant (Fig. 2). These results were confirmed by an insulin radioimmunoassay (RIA).

Recently Saslawski et al. [8,9] evaluated a different formulation for in vitro magnetically triggered delivery of insulin based on alginate spheres. In a typical experiment, ferrite microparticles (1 μ) were dispersed in 1.3 ml of sodium alginate aqueous solution (1.5 wt.%). Insulin powder (100 mg) was then added under stirring until homogenization. The ferrite insulin suspension was added dropwise, using a 1-ml syringe to a 15-ml calcium chloride aqueous solution (1.5 wt.%). The obtained alginate spheres were further crosslinked using either a 2 wt.% aqueous solution of poly(L-lysine) or 5% poly(ethylene imine).

The factors that are critical in controlling the release rates in these systems can be characterized by two main groups: (1) magnetic field characteristics; and (2) mechanical properties of the polymer matrix. It was found that the extent of release enhancement increases as the magnetic-field amplitude rises [5]. When the frequency of the applied field was increased from 5 to 11 Hz the rate of release of bovine serum albumin (BSA) from EVAc copolymer matrices rose in a linear fashion. Saslawski et al. [9] investigated the effect of magnetic-field frequency and repeated-field application on insulin release from alginate matrices and found that with repeated applications inverse effects can occur: high frequencies gave a significant release enhancement for the second magnetic field application, after which the enhancement level decreased due to the faster depletion at these frequencies.

The mechanical properties of the polymeric matrix also affect the extent of magnetic enhancement [6]. For example, the modulus of elasticity of the EVAc copolymer can be easily altered by changing the vinylacetate content of the copolymer. The release-rate enhancement induced by the magnetic-field increases as the modulus of elasticity of EXJAc decreases [6]. A similar phenomenon was observed for the crosslinked alginate matrices: higher release rate enhancement for less rigid matrices [9]. Edelman et al. [10] also showed that enhanced release rates observed in response to an electromagnetic field (50 G, 60 Hz) applied for 4 min were independent of the duration of the interval between repeated pulses.

2.2. Ultrasonically modulated systems

Kost et al. [11–14] suggested the feasibility of ultrasonic controlled polymeric delivery systems in which release rates of substances can be repeatedly modulated at will from a position external to the delivery system. Both bio-erodible and non-erodible polymers were used as drug carrier matrices. The bioerodible polymers evaluated were polyglycolide, polylactide, poly(bis(*p*-carboxyphenoxy)alkaneanhydrides and their copolymers with sebacic acid. The releasing agents were *p*-nitroaniline, *p*-aminohippurate, bovine serum albumin and insulin.

Enhanced polymer erosion and drug release were observed when the bioerodible samples were exposed to ultrasound. The systems

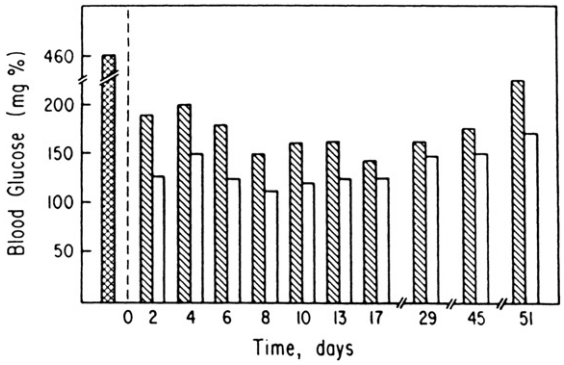

Fig. 1. Results of triggering experiment on a rat with an implant containing magnet and insulin. Before triggering: hatched area, after triggering: unhatched area [7].

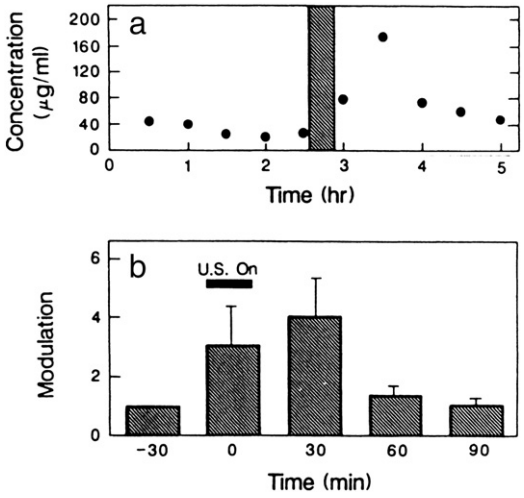

Fig. 3. (a) Para-amino hippuric acid (PAH) concentration in the urine of Sprague–Dawley rats as a function of time before, during, and after a 20-min exposure to ultrasound (hatched area). (b) Modulation vs. time expressed as a mean and standard deviation of four experimental rats. (Modulation was defined as the ratio of PAH concentration during and after the ultrasound (U.S.) exposure to the mean of the PAH concentration before the exposure.) The implants were PCPP/SA copolymers (20:80) loaded with 10% PAH [13].

response to the ultrasonic triggering was rapid (within 2 min) and reversible. The enhanced release was also observed in non-erodible systems exposed to ultrasound where the release is diffusion dependent. Release rates of zinc bovine insulin from ethylenevinylacetate copolymer matrices were 15 times higher when exposed to ultrasound compared to the unexposed periods. It has also been demonstrated that the extent of enhancement can be regulated by the intensity, frequency or duty cycle of the ultrasound [13].

To assess the effect of ultrasonic energy on the integrity of the releasing molecules, insulin samples were evaluated by high pressure liquid chromatography. No significant difference was detected between insulin samples exposed to ultrasound and unexposed samples, suggesting that the ultrasound is not degrading the releasing molecules [13].

Recent studies have suggested the feasibility of in vivo ultrasound mediated drug release enhancement [13]. Implants composed of polyanhydride polymers loaded with 10% *para*-aminohippuric acid (PAH) were implanted subcutaneously in the back of catheterized rats. When exposed to ultrasound, a significant increase in the PAH concentration in urine was detected (Fig. 3). Rat's skin histopathology of the ultrasound treated area after an exposure of 1 h at 5 W/cm^2, did not reveal any differences between treated and untreated skin.

It was proposed [13] that cavitation and acoustic streaming are responsible for this augmented degradation and release. In experiments conducted in a degassed buffer, where cavitation was minimized, the observed enhancement in degradation and release rates was much smaller. It was also considered that several other parameters (temperature and mixing effects) might be responsible for the augmented release due to ultrasound. However, experiments were conducted which suggested that these parameters were not significant. A temperature rise of only 2.5° was recorded in the samples during the triggering period. A separate release experiment done at 40°C instead of at 37°C showed that the rate increase was below 20%. To evaluate the ultrasound effect on the diffusion boundary layer, release experiments were performed under vigorous shaking. The increase of the release rates due to shaking were always below 20%. Therefore it was concluded that the effect of the ultrasound on the augmented release cannot be due to mixing or temperature only [13,14].

Similar phenomena were observed by Miyazaki et al. who evaluated the effect of ultrasound (1 MHz) on the release rates of 5-fluorouracil (5-FU) [15] and bovine insulin [16] from ethylenevinyl alcohol copolymer matrices and reservoir-type drug delivery systems. When diabetic rats receiving implants containing insulin were exposed to ultrasound (1 W/cm^2 for 30 min) a sharp drop in blood glucose levels was observed after the irradiation indicating a rapid rate of release of insulin in the implanted site. The authors speculate that the ultrasound caused increasing temperature in the delivery system, which may facilitate diffusion [15].

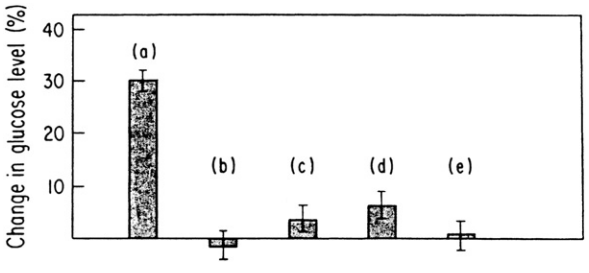

Fig. 2. Mean percentage glucose decrease for diabetic rats containing experimental devices and four groups of controls. These are shown with the standard error of the mean. There are 17 rats total: at least three in each of the five groups. The number of data points (*N*) for each bar is the number of triggers over all rats in the group. (a) Experimentals (*N*=26); (b) diabetic rats with insulin implants without magnets (*N*=35); (c) diabetic rats with implants containing magnets but no insulin (*N*=17); (d) diabetic rats without implants (*N*=18); and (e) healthy rats without implants (*N*=27) [7].

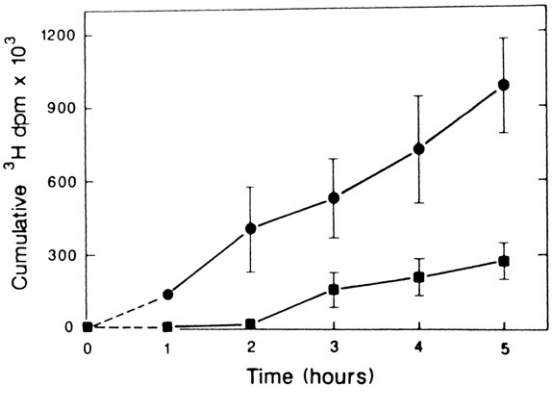

Fig. 4. Rats' cumulative radioactive secretion after topical application of 20 ml of saturated solution of D-mannitol containing 20 μCi D-[^{3}H]mannitol. (●) Ultrasound (US) treated rats; *N*=4 (1.5 W/cm^2 CW, 3 min). (■) Control rats; no US; *N*=12. Values are mean±S.E.M. [20].

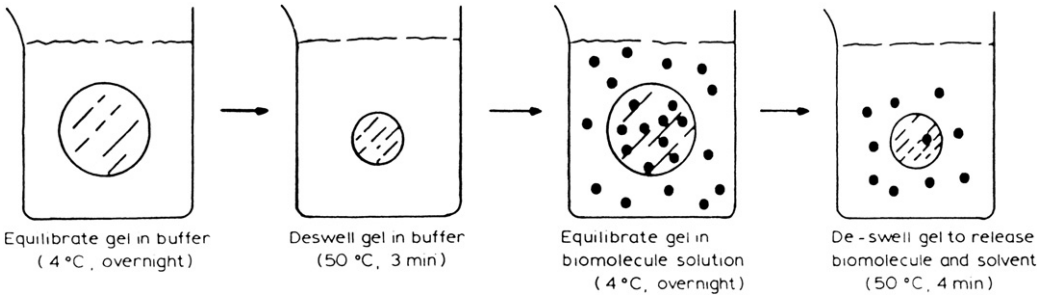

Fig. 5. Schematic of protocol for studying release of biologically active molecules using thermally reversible poly(NIPAAm) hydrogels [27].

Ultrasound was also evaluated as an enhancer for drug delivery through the skin. Skauen and Zentner [17] and recently Tyle and Agrawala [18] reviewed the topic of phonophoresis defined as the movement of drugs through living intact skin and into soft tissue under the influence of an ultrasonic perturbation [17]. Studies performed in our laboratories on the effect of ultrasound on implantable drug delivery devices provided the impetus to conduct studies to evaluate the systemic effect of ultrasound on drug permeation through the skin and explore its applicability as transdermal drug delivery enhancer or trigger when needed [19,20].

The effect of therapeutic range ultrasound (1 MHz) on skin permeation of D-mannitol, insulin and physostigmine was studied in rats and guinea pigs [20]. Ultrasound nearly completely eliminated the lag time usually associated with transdermal delivery of drugs. 3–5 min of ultrasound irradiation (1.5 W/cm^2 continuous wave or 3 W/cm^2 pulsed wave) increased the transdermal permeation of insulin and mannitol in rats by 5- to 20-fold within 1–2 h following ultrasound application (Fig. 4). Ultrasound treatment also significantly increased the inhibition of cholinesterase during the first hour after application in both physostigmine-treated rats and guinea pigs, while in controls no significant inhibition of cholinesterase could be detected.

2.3. Thermoresponsive delivery systems

Thermoresponsive hydrogels such as *N*-substituted polyacrylamide have recently been of interest in the field of controlled drug delivery [21]. The thermosensitive hydrogels can be classified into two groups based on the origin of thermosensitivity in aqueous swelling [22,23]. The first is based on polymer-water interactions, especially specific hydrophobic–hydrophilic balancing effects and the configuration of side groups. The other is based on polymer–polymer interactions in addition to polymer–water interactions [24].

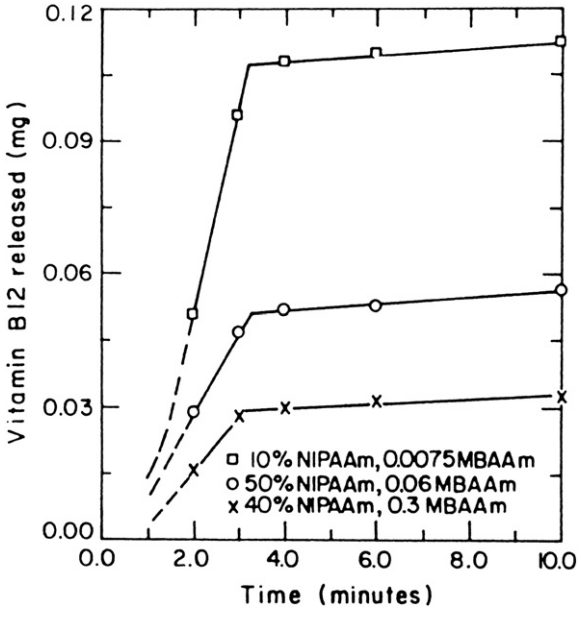

Fig. 6. Amount of vitamin B12 released per gram of polymer in the gel, on heating poly(NIPAAm) hydrogels from 4 to 50°C, as a function of time [27].

Okahata et al. [25] reported release changes induced by temperature changes from surface-modified nylon capsules. Semipermeable nylon capsules were prepared from ethylenediamine and terephtaloylchloride or 1,10-decanedicarbonylchloride by interfacial polymerization with trimesoylchloride as a crosslinking agent. NaCl-loaded capsules were transferred to dodecane solutions of dialkyl surfactant in order to introduce an amphiphilic bilayer on the capsule membrane. Remarkable permeability changes induced by temperature changes were observed at the phase transition temperature, in contrast to the uncoated capsules. The nylon capsules were also grafted with poly(alkylacrylamide) to impart thermoselective permeation [26].

Hoffman et al. [27,28] synthesized hydrogels based on *N*-isopropylacrylamide (NIPAAm) or *N*-isopropylacrylamide-methacrylic copolymers crosslinked with methylene-bis-acrylamide (MBAAm), which exhibit a lower critical solution temperature (LCST). The authors studied the absorption and release of vitamin B12, myoglobin and chymotrypsin. Gel disks were deswelled in water at 50°C for 4 min, placed in vitamin B or protein solution, and incubated at 4°C overnight. After incubation the gel was rinsed in cold buffer solution and then deswelled in buffer solution at 50°C for 4 min, after which the gel was removed and the release kinetics in buffer was determined (Fig. 5). All of the gels absorbed and released vitamin B12. Only certain of the gels could both absorb and release myoglobin while none of the gels was able to absorb chymotrypsin. Fig. 6 shows two regions of vitamin B12 release kinetics: initially a rapid release, followed by a slower release on heating the hydrogels from 4 to 50°C. The first region is attributed by the authors to the release of pore water near the surface along with the vitamin B12 dissolved in it. As the surface shrinks it represents an increasing resistance to transport out of the gel. The quick response of the gel surface to temperature changes may be utilized as an on–off switch for drug release (temperature changes prevent drug release due to instant surface shrinking).

A pulsatile indomethacin release pattern was found to be regulated by temperature changes between 20°C and 30°C due to the reversible swelling properties of copolymers of *N*-isopropylacrylamide and butylmethacrylate [29] (Fig. 7).

Recently, Bae et al. [22] reported on insulin permeability through thermo sensitive hydrogels based on poly(*N*-acryloylpyrolidine) and its copolymers with styrene or 2-hydroxyethylmetacrylate crosslinked by ethyleneglycoldimethacrylate The crosslined poly(*N*-acryloylpyrolidine) homopolymer exhibited thermosensitivity in water swelling, with weak mechanical strength, which restricted its practical application to diffusion experiments. The incorporation of a hydrophobic monomer into the polymer improved the mechanical strength and lowered the overall swelling level as well as the thermosensitivity. Insulin permeation through the copolymers can be regulated by changing the membrane composition and temperature. The permeability was mainly affected by the degree of hydration, regardless of chemical

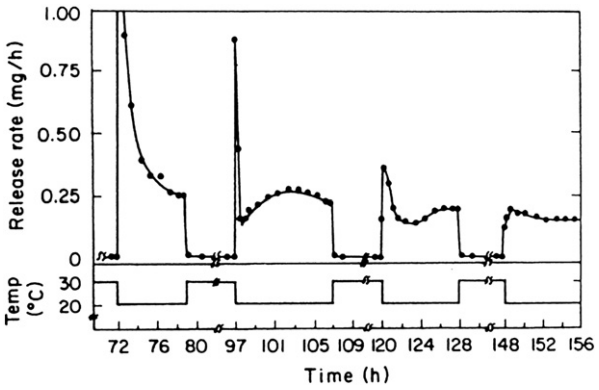

Fig. 7. Pulsatile release rate of indomethacin in response to a stepwise temperature change between 20°C and 30°C in PBS (pH 7.4) [21].

composition and temperature. The rate of insulin permeation through poly(hydroxyethylmethacrylate) increased with an increase in temperature. In contrast the rate of insulin permeation through poly(*N*-acryloylpyrolidine) copolymers increased with a decrease in temperature.

2.4. Electrically controlled delivery systems

Transmembrane solute flux can be modulated by the action of an applied electric field on the membrane and/or directly on the solute. The electrophoretic migration of a charged macrosolute within a hydrated membrane results from the combined response to the electrical forces on the solute and its associated counterions in the adjacent electrolyte solution [30]. Grimshaw et al. [31] have recently demonstrated four distinct electrochemical and electromechanical mechanisms for selective controlled transport of proteins and neutral solutes across hydrogel membranes: (1) electrically and chemically induced swelling of a membrane to alter the effective pore size and permeability; (2) electrophoretic augmentation of solute flux within a membrane; (3) electroosmotic augmentation of solute flux within the membrane; and (4) electrostatic partitioning of charged solutes into charged membranes.

Pasechnik et al. [32] reported an increase in the effective pore radius of ultrafiltration membranes due to electrodynamic effects. Burgmeyer and Murray [33] observed changes in the ionic permeability of polypyrrole redox membranes using a voltage-controlled electrochemical reaction. Bhaskar et al. [34] affected the permeability of liquid crystalline membranes to small organic solutes, applying transmembrane electric fields, which caused a phase change by alignment of the polymeric molecules. Electric fields can cause changes in membrane ionization states affecting membrane hydration and permeability. Eisenberg and Grodzinsky [35] altered the restricted diffusion of sucrose through collagen membranes via electrodiffusion (effect of the electric field on concentration profiles within the membrane), producing flux changes up to 25%. Nussbaum and Grodzinsky [36] demonstrated reversible changes in the uniaxial swelling of PMMA membranes via electrodiffusion control of intramembrane ionic strength. Weiss et al. [37] produced a 16-fold increase in the permeability of similar PMMA membranes to 10 kDa dextran by using the electrolysis reaction at a platinum cathode to alter bash pH and, hence, membrane hydration. Osada [38] induced the release of pilocarpine into the surrounding solution when a DC electric field of 6 V/cm was applied to PMMA gels incorporated with pilocarpine.

Application of an electric field across a hydrated polyelectrolyte membrane, such as PMMA, gives rise to a net force on the space charge in the fluid phase, which contains an excess of counterions over coions; this force is transfered to the solvent, resulting in electrosmotic fluid flow relative to the solid membrane matrix. Grodzinsky arid Grimshaw [30] observed a volume flux of 1.2×10^{-6} m/s at the direction of the current across 3.1 cm^2 PMMA membranes, when the membrane was exposed to pH 7 at a transmembrane current density of 320 A/cm^2. The flow ceased when the current was shut off, and reversed direction when the direction of current was reversed. The same membrane at pH 3 showed a negligible volume flux when the current was applied (Fig. 8). The presence of electroosmotic flow at pH 7 and not at pH 3 reflects the dependence of membrane fixed charge on pH. Electroosmotic transport of water therefore can enhance or oppose the diffusive transport of a neutral or charged solute [30]. With charged membranes and charged solutes, an application of an electric field can result in control of solute flux by a combination of the electrophoretic and electroosmotic mechanisms.

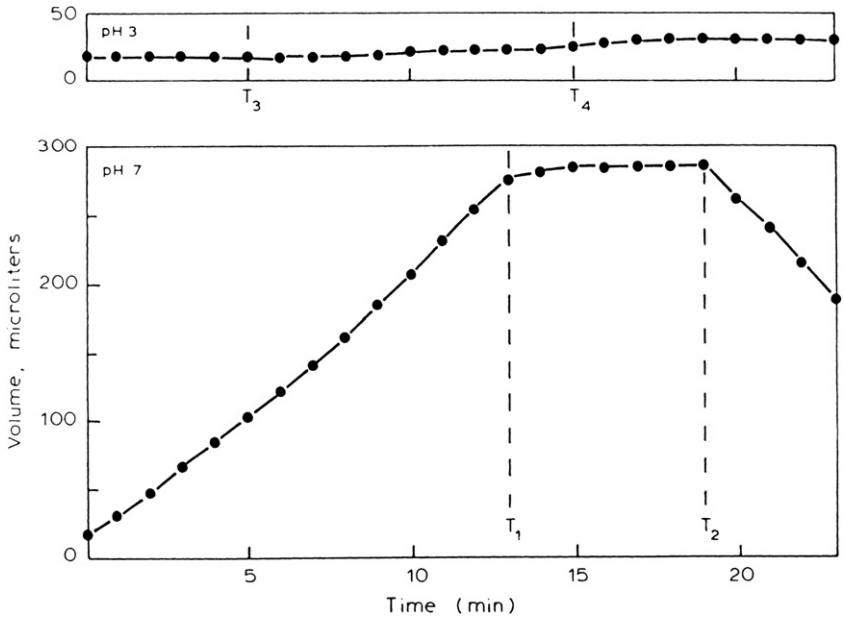

Fig. 8. Cumulative volume of water transported by electroosmosis across a PMAA membrane with an area of 3.1 cm^2. At pH 7 (bottom) a current density of +320 A/m^2 was initially applied across the membrane from the upstream to downstream bath. The current was removed at time T_1 and reversed (−320 A/m^2) at time T_2. At pH 3 (top) +320 A/m^2 was applied starting at time T_3 and removed at time T_4 [30].

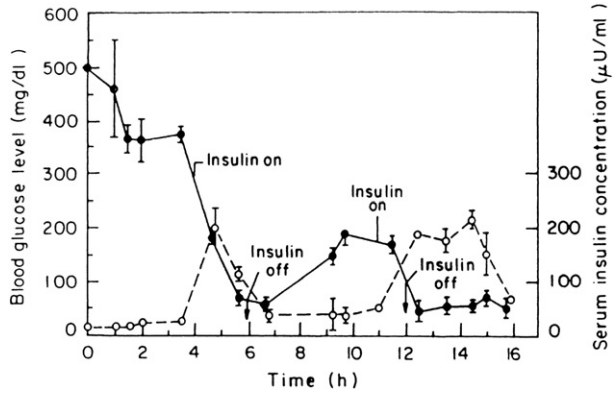

Fig. 9. Results of the administration of insulin to alloxan diabetic rabbits by intermittent iontophoresis over a period of 16 h. A drug reservoir containing 300 units of activity (U) of regular porcine insulin was placed on the animals. No current was applied for 4 h, then a current of 0.7 mA was applied for 5 h, then no current was applied for 5 h, then a current of 0.7 mA was applied for 1 h, then no current was applied for 4 h (●) blood glucose level; (○) serum insulin concentration. All experimental values represent the mean±standard error of the mean of three evaluations using one animal [49].

D'Emanuele and Stainforth et al. [39,40] proposed a drug delivery device which consists of a polymer reservoir with a pair of electrodes placed across the rate limiting membrane. By altering the magnitude of the electric field between the electrodes the authors proposed to modulate the drug release rates in a controlled and predictable manner. A linear relationship was found between current and propanolol HCl permeability through poly(2-hydroxyethylmethacrylate) (PHEMA) membranes crosslinked with ethylene glycol (1% v/v). Buffer ionic strength as well as electrode polarity were found to have a significant effect on the drug permeability.

A different approach to electrochemically controlled release is based on polymers which bind and release bioactive compounds in response to an electric signal. The polymer has two redox states, only one of which is suitable for ion binding. Drug ions are bound in one redox state and released from the other. The attached electrodes serve to switch the redox states and the amount of current passed can control the amount of ions released [41].

The mechanisms described for electrically controlled membrane permeability are of current interest in the field of electrically controlled or enhanced transdermal drug delivery (e.g. iontophoresis) [42–44]. Over the past 60 or more years, the principles of iontophoresis have been applied for localized drug delivery to muscles and joints. Recently, there has been a great emphasis on iontophoretic systemic drug delivery [45–48]. Fig. 9 demonstrates the results of the administration of insulin to alloxan-diabetic rabbits by iontophoresis using a current of 0.4 mA for 2 h and a reservoir containing 300 units of porcine insulin [49].

Current/voltage conditions for the iontophoretic application [50] should: (1) be sufficiently high to provide a desired delivery rate; (2) not produce any harmful effects on the skin including a permanent alteration in the skin permeability; (3) establish a quantitative relationship between the flux and applied current/voltage; and (4) maintain constancy of the current/voltage during the experimental period. In addition, the drug should be electrochemically stable.

Recently, in order to overcome charge build up, irritation and burning of the skin in the area of prolonged continuous current electrode application, a pulsed current approach was evaluated. In this approach the current was turned on and off in short intervals. Using the pulsed current iontophoresis the skin can tolerate much higher voltage and current conditions [50].

2.5. Other stimuli that regulate drug release

Miyazaki et al. [51] investigated the effect of microwave irradiation on the release of 5-fluorouracil which was incorporated into ethylenevinylalcohol copolymer. When exposed to release medium the delivery systems released the drug at a constant rate. Upon exposure to microwave irradiation the drug was released at a higher rate. Release rates returned to baseline levels when the microwave irradiation was discontinued.

Mathiowitz and Cohen et al. [52–57] described photochemically controlled delivery systems, prepared by interfacial polymerization of polyamide microcapsules, For this purpose, azobisisobutyronitrile (AIBN), a substance that photochemically emanates nitrogen gas, was incorporated in a microcapsule reservoir-type delivery system. The pressure build-up in the capsule, due to the release of nitrogen under exposure to light, caused immediate rupture of the microcapsule's wall and release of the contents.

3. Self-regulated delivery systems

Self-regulated delivery systems [58–61] are closed-loop controlled devices in which the release rates are adjusted by the system, in

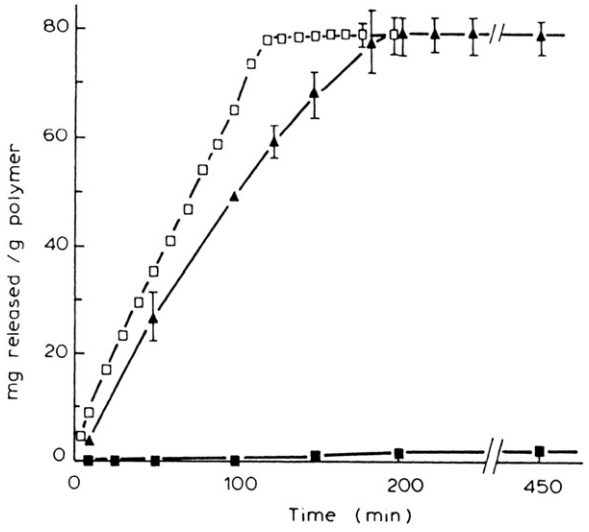

Fig. 10. Kinetics of caffeine release from 8% (w/w) loaded gel disks into citrate buffer at 25°C. (□) pH 3 (▲) pH 5, (■) pH 7 [71].

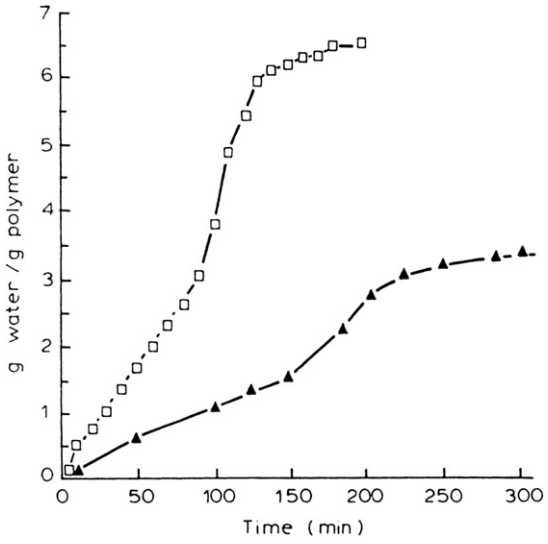

Fig. 11. Kinetics of water sorption into 8% (w/w) caffeine loaded disks placed in citrate buffer of 25°C. (□) pH 3, (▲) pH 5 [71].

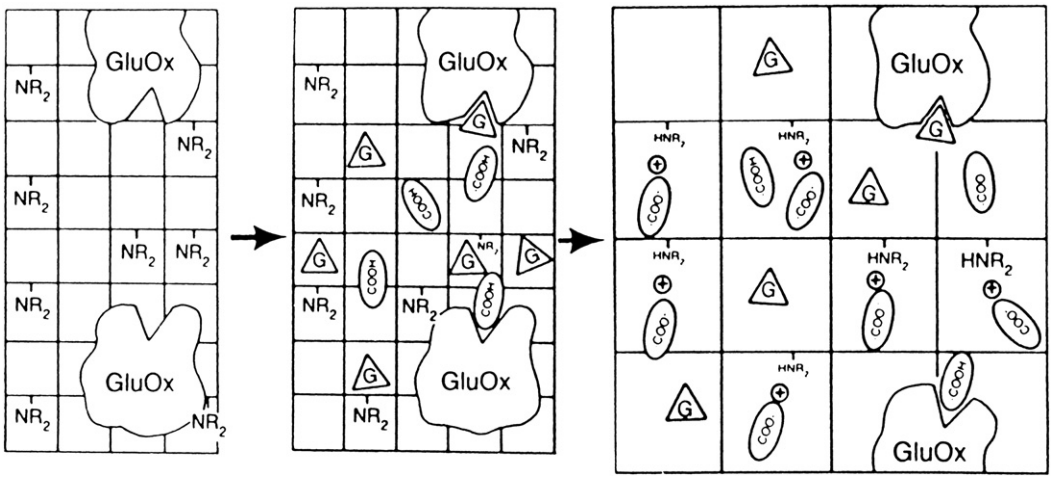

Fig. 12. Schematic representation of mechanism of action of glucose sensitive membranes [85].

response to feedback information, without any external intervention, e.g. delivery of insulin in response to glucose levels in the blood.

3.1. pH and ionic strength responsive drug delivery based on polymer swelling

The pH range of fluids in various segments of the gastrointestinal tract may provide environmental stimuli for responsive drug release. Fildes [62] has developed a membrane to bypass the rumen of the cow but which allows release of its drug in the cow's fourth stomach. The polymeric membrane is highly impermeable at pH 7, the rumen pH, but swells at pH 4, which is the fourth stomach's pH.

Studies by several research groups [30,63–77] have been performed on polymers containing weakly acidic or basic groups in the polymeric backbone. The charge density of the polymers depends on pH and ionic composition of the outer solution (the solution into which the polymer is exposed). Altering the pH of the solution will cause swelling or deswelling of the polymer. Polyacidic polymers will be unswollen at low pH, since the acidic groups will be protonated and hence unionized. With increasing pH, a polyacid polymer will swell. The opposite holds for polybasic polymers, since the ionization of the basic groups will increase with decreasing pH. Thus drug release from reservoir or matrix devices made from these polymers will display release rates that are pH dependent [37,78–81].

Fig. 10 displays release kinetics of caffeine from methylmethacrylate (MMA) *N*,*N*-dimethylaminoethylmethacrylate (DMA) copolymer (MMA/DMA 70/30) matrices at pH 3, 5 and 7 [71]. Caffeine was loaded into gels by swelling them in 50/50 (v/v) water/tetrahydrofuran solutions containing caffeine. After the drug diffused into the swollen gels, they were removed from the solution and dried overnight in an oven at 60°C. The gels, after removal of the crystalline caffeine from the surface, were transferred to a desired buffer or dried and stored. As can be seen the release is nearly zero order and increases with decreasing pH. Fig. 11 shows the kinetics of water sorption (swelling) during the release process. The swelling of the matrices was measured simultaneously with the release kinetics for the same gels as in Fig. 10. The authors propose that the release, as water sorption, are mediated by a moving front mechanism. Drug molecules are assumed to be almost completely immobilized in the dry, glassy polymer matrix. As the swelling front passes a given drug molecule, the latter finds itself in the swollen rubbery polymer phase, through which it may diffuse to the outer solution. Assuming the drug molecule can diffuse much faster than the polymer swells, drug release should follow almost precisely the swelling front [73].

Siegel et al. [82] also evaluated the effect of buffer pK_a and concentration on swelling kinetics of MMA/DMA copolymers and found that swelling rate increases as the pK_a of the buffer increases (fraction of unionized buffer increases), or as the buffers concentration increases. The suggested explanation is based on Donnan exclusion, that retards the entry of protons into the swollen, charged outer layer of the gel. This in turn retards proton transport to the swelling (moving) front. Unionized buffer acids, can move freely in the charged layer. Thus the buffer acids function as proton carriers which shuttle protons to the front, where they can then release the protons charging up the polymer at the front, and permitting swelling to continue. Therefore the swelling process will be faster when more unionized acid is available.

Klier and Peppas [83] suggested complex forming hydrogels sensitive to pH, and buffer concentration, based on graft copolymers of polymethacrylic acid–ethylene glycol. In acidic media, the poly(methacrylic acid) was protonated and formed hydrogen-bonded complexes with the poly(ethylene glycol) chains, creating relatively hydrophobic structures with a low degree of swelling and low permeability to hydrophilic solutes. Upon neutralization, the complexes were dissociated and the resulting polyelectrolyte gel exhibited a high degree of swelling and solute permeability (solvent fraction exceeded 95% at basic pH conditions and were in the range of 25% in acidic conditions).

Several authors evaluated the effect of more than one stimulus such as chemical (pH or buffer ionic strength) and electrical stimuli [30] or pH and thermal stimuli [78].

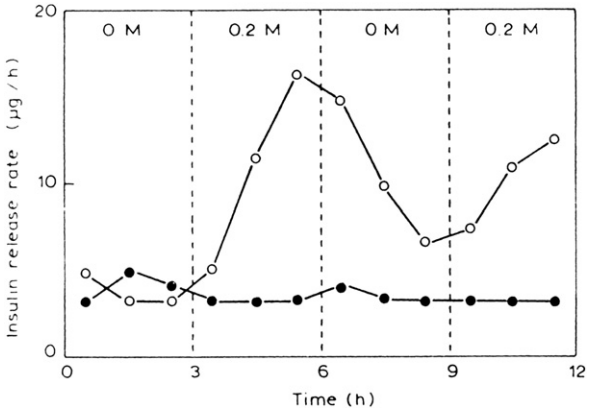

Fig. 13. Effect of glucose concentration of insulin release from glucose-responsive polymer capsule at 30°C. (○) with glucose oxidase and (●) without [95].

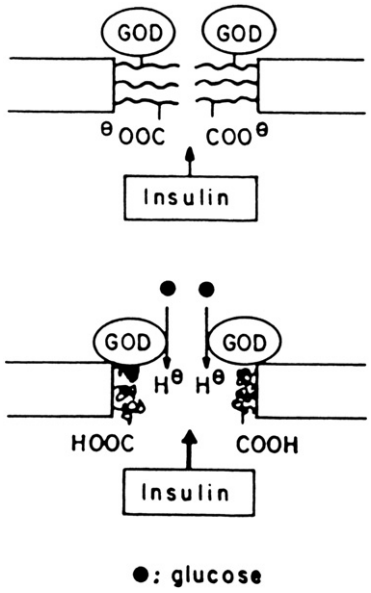

Fig. 14. Principle of controlled-release system of insulin: glucose oxidase. Above: in the absence of glucose, the chains of poly(acrylic acid) grafts are rod-like, lowering the porosity of the membrane and suppressing insulin permeation. Below: in the presence of glucose, gluconic acid produced by glucose oxidase protonates the poly(acrylic acid), making the graft chains coil-like and opening the pores to enhance insulin permeation [98].

3.2. Glucose-responsive insulin delivery

In order to develop glucose sensitive insulin delivery systems, several approaches have been devised.

3.2.1. Immobilized glucose oxidase in pH-sensitive polymers

The systems consist of immobilized glucose oxidase in a pH-responsive polymeric hydrogel, enclosing a saturated insulin solution. As glucose diffuses into the hydrogel, glucose oxidase catalyzes its conversion to gluconic acid, thereby lowering the pH in the microenvironment of the membrane and causing swelling (Fig. 12).

This approach is currently under investigation by several groups: Horbett and coworkers [84–89] immobilized glucose oxidase in a crosslinked hydrogel made from *N*,*N*-dimethylaminoethylmethacrylate (DMA), hydroxyethylmethacrylate (HEMA) and tetraethylene glycol dimethacrylate (TEGDMA). Membranes were prepared at −70°C by radiation polymerization, previously shown to retain the enzymatic activity [90]. To obtain sufficient insulin permeabilty through the gels, porous HEMA–DMA gels were prepared by polymerization under conditions which induce a separation into two phases during polymerization: one phase rich in polymer and the other rich in solvent plus unreacted monomer. When gelation occurs after the phase separation, the areas where the solvent–monomer phase existed become fixed in place as pores in the polymer matrix. The authors used more dilute monomer solution in order to obtain porous gels. The pore diameter was observed to be typically 1–10 μm [88].

The rate of insulin permeation through the membranes was measured in the absence of glucose in a standard transport cell; then glucose was added to one side of the cell to a concentration of 400 mg% (400 mg/100 ml) while the permeation measurement was continued. The results indicated that the insulin transport rate is enhanced significantly by the addition of glucose. The average permeability after addition of 400 mg% glucose was 2.4–5.5 times higher than before glucose was added. When insulin permeabilities through the porous gels were measured in a flowing system in which permeabilities were measured with fluid flowing continuously past one side of the membrane no effect of glucose concentration on insulin permeabilities could be detected. The authors believe that inappropriate design of the membranes used in the experiments is the explanation for their lack of response to glucose concentration. A high amine concentration in the copolymer is expected to eliminate the response, by buffering any pH changes, which otherwise would be established in the system by substrate turnover. In the non-flow through standard transport cells, gluconic acid can accumulate to concentrations high enough to overcome the amine's buffering and produce a large pH decrease in the membrane [89].

A mathematical model describing these glucose responsive hydrogels demonstrates two important points [88,89]: (1) progressive response to glucose concentration over a range of glucose concentrations can be achieved only with a sufficiently low glucose oxidase loading; otherwise, depletion of oxygen causes the system to become insensitive to glucose; and (2) a significant pH decrease in the membrane, with resultant swelling, can be achieved only if the amine concentration is sufficiently low that pH changes are not prevented by the buffering of the aniines.

Ishihara et al. [91–95] investigated two approaches for glucose responsive insulin delivery systems: one approach is similar, to that investigated by Horbett et al. [84]. The polymers were prepared from 2-hydroxyethylacrylate (HEA)-*N*,*N*-dimethylaminoethylmethacrylate (DMA) ,4-trimethylsilystyrene (TMS), by radical polymerization of the corresponding monomers in DMF. The mole fractions of HEA, DMA and TMS in the copolymer were 0.6, 0.2 and 0.2, respectively. Membranes were prepared by solvent casting. Capsules containing insulin and glucose oxidase were prepared by an interfacial precipitation method using gelatin as an emulsion stabilizer. The average diameter of the

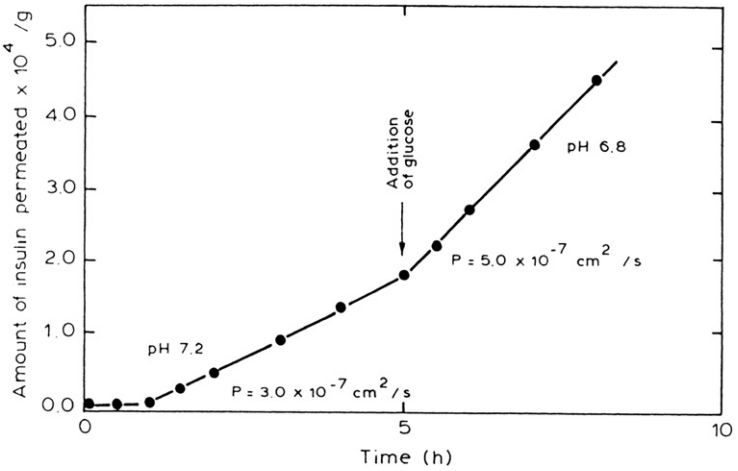

Fig. 15. Permeation of insulin through poly(acrylic acid) grafted membrane in 0.1 M Tris–HCl-buffered solution. The concentration of added glucose is 0.2 M [98].

polymer capsules obtained was 1.5 mm [94,95]. The water content of HEA–DMA–TMS copolymer membranes increased with a decrease in the pH of the medium. An especially drastic change was observed in the pH range of 6.3 to 6.15. The permeation of insulin through the copolymer membrane increases in response to pH decreases. The permeation rate of insulin at pH 6.1 was greater than that at pH 6.4 by about 42 times. The permeation of insulin through the copolymer membranes was very low in buffer solution without glucose. Addition of 0.2 M glucose to the upstream compartment induced an increase in the permeation rate of insulin. When glucose was removed, the permeation rates of insulin gradually returned to their original levels.

Fig. 13 shows the release profile of insulin from polymer capsules containing insulin and glucose oxidase. The release rate of insulin depends on glucose concentration; low rates were observed in the absence of glucose, while the release gradually increased when the capsules were exposed to 0.2 M glucose [95].

The other approach proposed by Ishihara et al. [92] is based on a glucose oxidase immobilized membrane and a redox polymer having a nicotinamide moiety. The device consists of two membranes. One membrane with the immobilized glucose oxidase acts as a sensor for glucose and forms hydrogen peroxide by an enzymatic reaction; the other membrane is a redox polymer having a nicotinamide moiety which controls the permeation of insulin by an oxidation reaction with the formed hydrogen peroxide. The oxidation of the nicotinamide group increases hydrophilicity and therefore should enhance the permeability to water soluble molecules such as insulin. The results showed relatively small increases in insulin permeability.

Iwata et al. [96,97] pretreated porous poly(vinylidene fluoride) membranes (average pore size of 0.22 μm) by air plasma and subsequently acrylamide was graft polymerized on the treated surface. The polyacrylamide was then hydrolyzed to poly(acrylic acid). In the pH range of 5–7, grafted poly(acrylic acid) chains are solvated and dissolved, but cannot diffuse into the solution phase because they are grafted to the porous membrane. Thus they effectively close the membrane pores. In the pH range of 1–5, the chains collapse and the permeability increases. To achieve the sensitivity of the system toward glucose, glucose oxidase was immobilized onto a poly(2-hydroxyethylmethacrylate) gel.

Ito et al. [98], adopted the approach proposed by Iwata et al. [97], using a porous cellulose membrane with surface-grafted poly(acrylic acid) as a pH-sensitive membrane. By immobilization of glucose oxidase, onto the poly(acrylic acid)-grafted cellulose membrane, it became responsive to glucose concentrations (Fig. 14). Fig. 15 shows the change in permeability of insulin through poly(acrylic acid)-grafted cellulose membranes following the addition of 0.2 M glucose to the buffered solution. The permeation coefficient after glucose addition was approximately 1.7 times that before addition of glucose. The authors suggest to improve the proposed system (sensitivity of insulin permeability to glucose concentrations) by modification of the graft chain: density, length, and size or density of pores.

Siegel and coworkers [73,99,100] are investigating the feasibility of an implantable 'mechanochemical' pump which functions by converting changes in blood glucose activity into a mechanical force which pumps insulin out of the device. The device consists of three chambers (Fig. 16): chamber I contains an insulin solution, chamber II contains aqueous fluid, while chamber III consists of a pH-sensitive polymer with immobilized glucose oxidase that expands when glucose level rises. The expansion of the polymer in chamber III is the driving

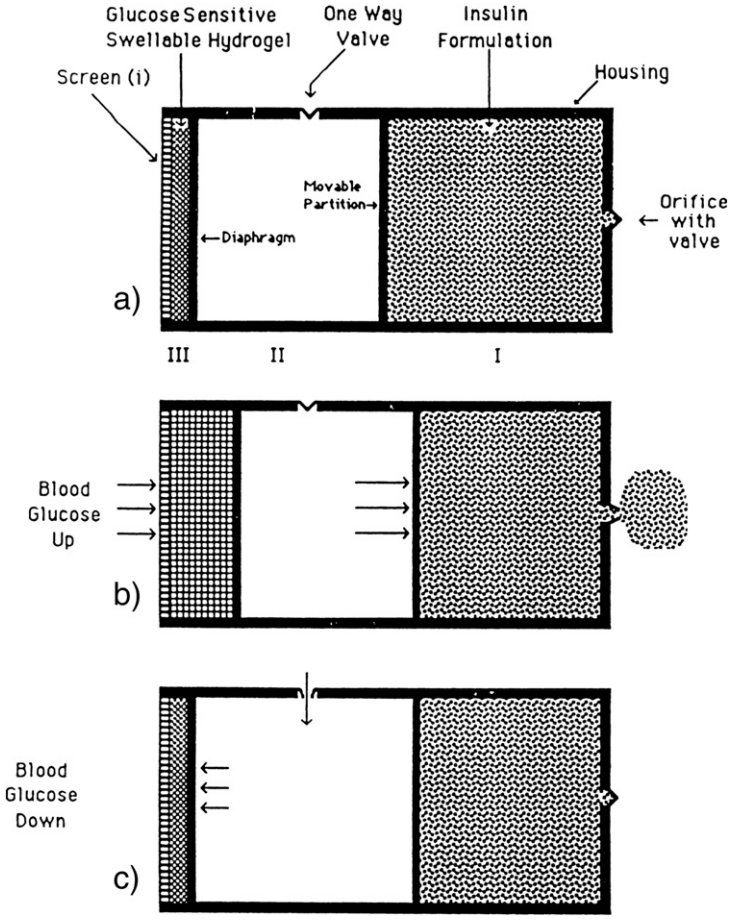

Fig. 16. Proposed mechanochemical insulin pump [73].

force of the suggested glucose sensitive pump. Chamber I is separated from the environment by a one-way valve which opens when pressure in the pump exceeds that of the environment. Chamber II communicates with body fluids through a one-way valve which opens when the pressure inside the pump is less than that of the surrounding medium. Chamber III communicates with body fluids through a rigid screen which passes small molecules but excludes large molecules such as plasma proteins. Chambers II and III are separated by an elastomeric diaphragm, while chambers I and II are separated by a movable partition. Mathematical modeling of the osmotic pressure generated and requirements for the mechanical properties of the diaphragm separating chambers I and II were discussed [99].

Heller et al. [101,102] suggested a system in which insulin is immobilized in a pH-sensitive bioerodible polymer and this system was allowed to interact with a hydrogel containing immobilized glucose oxidase. When glucose diffuses into the hydrogel and is oxidized to gluconic acid, the resultant lowered pH triggers enhanced polymer degradation and release of insulin from the polymer in proportion to the concentration of glucose.

The response of the pH-sensitive polymers synthesized as shown in Fig. 17 containing 10 wt.% insulin to pH pulses was rapid. Insulin was rapidly released when the pH decreased from 7.4 to 5.5. Insulin release was shut off rapidly when the pH increased. The authors are studying factors that are important in designing a hydrogel containing immobilized glucose oxidase. Fig. 18 shows weight loss of polymer disks containing 10 wt.% insulin exposed to an aqueous solution of glucose oxidase and catalase, following the addition of varying concentrations of glucose.

Glucose-dependent insulin release was proposed by Langer and coworkers [103,104] based on the fact that insulin solubility is pH dependent. Insulin was incorporated into ethylenevinylacetate (EVAc) copolymer matrices in solid form. Thus, the release was governed by its dissolution and diffusion rates. Glucose oxidase was immobilized to sepharose beads which were incorporated along with insulin into EVAc matrices. When glucose entered the matrix, the produced gluconic acid caused a rise in insulin solubility and consequently enhanced release. To establish this mechanism in the physiological pH of 7.4, the insulin was modified by three additional lysine groups so that the resultant isoelectric point was 7.4. In vitro and in vivo studies demonstrated the response of the system to changes in glucose concentration. In the in vivo experiments a catheter was inserted into the left jugular vein, and two polymer matrices containing insulin and immobilized enzyme were implanted subcutaneously in the lower back of diabetic rats. Serum insulin concentrations were measured for different insulin matrix implants. A 2 M glucose solution was infused, 15 min into the experiments, through the catheter. Rats which received trilysine insulin–glucose oxidase matrices showed a 180% rise in serum insulin concentration which peaked at 45 min into the experiment. Control rats which received matrices containing no insulin, or insulin but no glucose oxidase, or diabetic rats without implants showed no change in serum insulin.

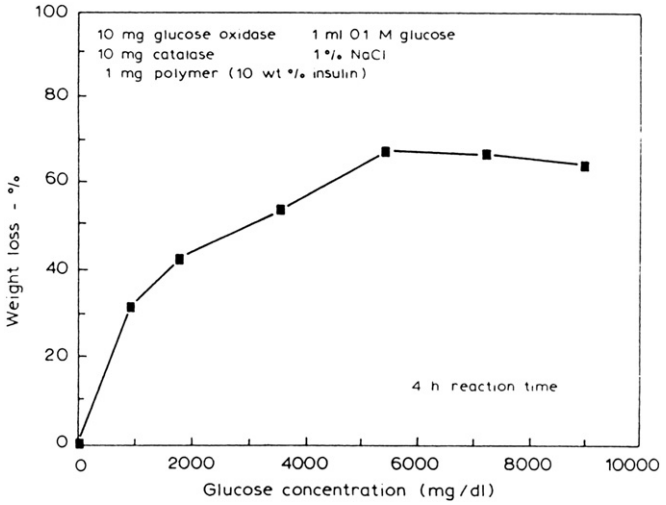

Fig. 18. Polymer erosion as a function of glucose concentration [101].

3.2.2. Competitive binding

The basic principle of competitive binding, first presented by Brownlee and Cerami [105,106] suggests the preparation of glycosylated insulins which are complementary to the major combining site of carbohydrate binding proteins such as Concanavalin A (Con A). Con A is immobilized on sepharose beads. The glycosylated insulin, which is biologically active is displaced from the Con A by glucose in response to, and proportional to, the amount of glucose present which competes for the same binding sites. Kim et al. [107–113] found that the release rate of insulin also depends on the binding affinity of an insulin derivative to the Con A and can be influenced by the choice of saccharide group in glycosylated insulin. By encapsulating the glycosylated insulin-bound Con A with a suitable polymer that is permeable to both glucose and insulin, the glucose influx and insulin efflux would be controlled by the encapsulation membrane (Fig. 19).

It was found [109] that the glycosylated insulins are more stable against aggregation than commercial insulin and are also biologically active. The functionality of the intraperitoneally implanted device was tested in pancreatectomized dogs by an intravenous glucose tolerance test (IVGTT). The effect of an administered 500 mg/kg dextrose bolus on blood glucose level was compared with normal and pancreatectomized dogs without an implant. Fig. 20 shows the results of this study [110]. In addition the blood glucose profile for a period of 2 days demonstrated that a diabetic dog, implanted with the self-regulating insulin delivery system, was capable of maintaining acceptable glucose levels (50–180 mg/100 ml) for the majority of the experiment (40 h). Recent studies [112,113] analysed the phenyl-α-D-glucopyranoside insulin (SAPG-insulin), its immune response in rats and in vitro release characteristics.

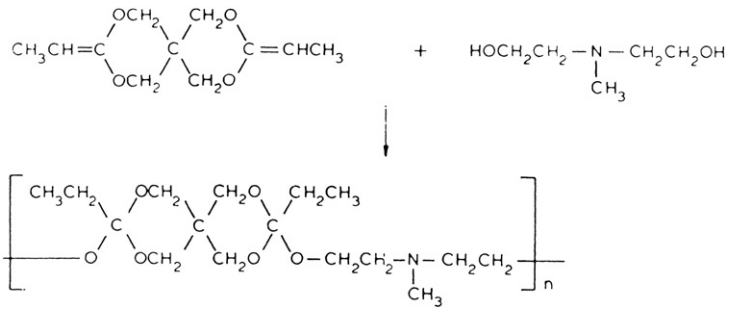

Fig. 17. Synthesis of pH-sensitive poly(orthoester) [101].

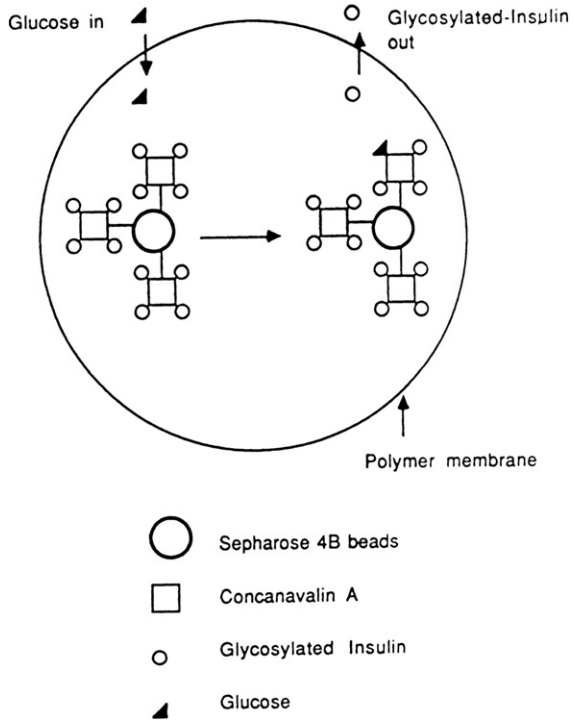

Fig. 19. Scheme of self-regulating insulin delivery based on competitive binding [110].

3.3. Urea-responsive delivery

Heller and Trescony [114] were the first to attempt using immobilized enzymes to alter local pH and thus cause changes in polymer erosion rates. The proposed system is based on the conversion of urea to NH_4HCO_3 and NH_4OH by the action of urease. As this reaction causes a pH increase, a polymer that is subjected to increased erosion at high pH is required. The authors suggested a partially esterified copolymer of methylvinylether and maleic anhydride. This polymer displays release rates that are pH dependent. The polymer dissolves by ionization of the carboxylic acid group [115].

Fig. 21 shows release of hydrocortisone from a disk composed of *N*-hexyl half ester of methylvinylether and maleic anhydride surrounded by a hydrogel containing urease immobilized by glutaraldehyde crosslinking. Although the device has no therapeutic relevance, it established the feasibility of creating self-responsive delivery system.

Ishihara et al. [116,117] suggested a non-erodible system based on a similar idea. The system was comprised of a pH-sensitive membrane, by copolymerizing 4-carboxyacrylanilide with methacrylate, sandwiched within a membrane containing urease immobilized in free radically crosslinked *N*,*N*-methylenebisacrylamide. The permeation of a model substance (1,4-bis(2-hydroxyethoxy)benzene varied with the urea concentration in the external solution.

3.4. Other responsive systems

Membrane-controlled devices responsive to the concentration of external amines and amino acids were prepared by polymerizing 2-hydroxyethylmethacrylate and then reacting the polymer with 3,5-dinitrobenzenoylchloride to attach 3,5-dinitrobenzoate groups to the polymer [118]. Upon addition of amine substances to the external solution a charge-transfer complex forms which increases the degree of swelling and thus the permeability of the membrane. The authors found that permeation of methyl orange through the membrane was proportional to the triethylamine concentration; the permeation rate returned to its original value when triethylamine was removed from the solution.

A different approach is based on hapten-antibody interactions [60,102,119]. In these systems the enzyme is covalently bound to a trigger molecule which is also the hapten for the antibody. While the covalently attached hapten is bound by the antibody, the activity of the attached enzyme is suppressed by steric hindrance of the active site. The appearance of a free hapten molecule's will result in competitive binding to the antibody in proportion to the hapten molecule's concentrations. The exposure of the active site of the enzyme serves as a trigger for responsive drug delivery.

An example of such a system is a responsive delivery system for the narcotic antagonist naltrexone. It has been found that it is possible to maintain drug addicted subjects on a dose of an opiate antagonist such as naltrexone [120]. The naltrexone displaces the opiate from its receptor sites, thus neutralizing the opiate effect. (Because

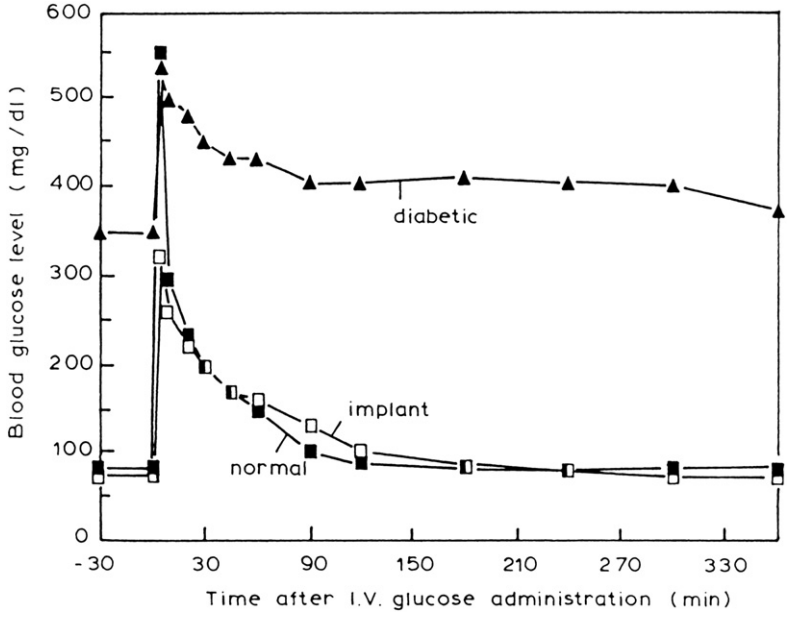

Fig. 20. Peripheral blood glucose profiles of dogs administered bolus dextrose (500 mg/kg) during an intraveneous glucose tolerance test. Blood glucose levels at $t=-30$ min show the overnight fasting level 30 min prior to bolus injection of dextrose [110].

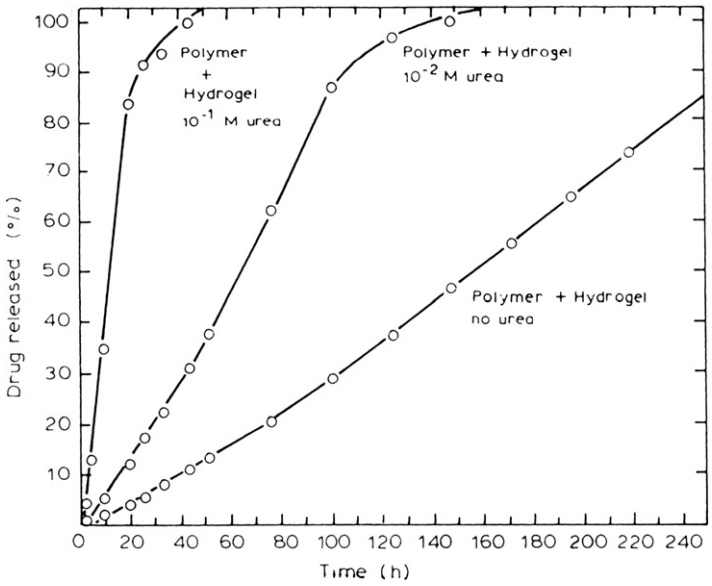

Fig. 21. Hydrocortisone release from the *N*-hexyl half ester of methylvinylether and maleic anhydride disks coated with immobilized urease, in the presence and absence of external urea, 35°C, pH 6.25, hydrocortisone loading 10 wt.% [114].

heroin administration results in rapid appearance of morphine the hapten in the proposed system can be morphine.)

When the enzyme-morphine conjugate is complexed with the morphine antibody, it sterically inhibits access of the enzyme substrate to the enzyme active site. In the presence of free morphine, the complex can dissociate and thus cause activation of the enzyme [121]. Initial work done by Heller et al. [60,122,123] was done with the enzyme, lysozyme, and a partially deacetylated chitin hydrogel prepared by crosslinking the partially deacetylated chitin with glutaraldehyde. As degradation of partially deacetylated chitin with a lysozome-morphine conjugate was slow, recent experiments were based on the enzyme, amylase acting on acidic starch hydrogels [60]. The device contains three separate components. One is a pH-sensitive bioerodible polymer capable of releasing naltrexone. The polymer erodes at physiological pH and therefore releases the drug, but at lower pH it is stable and no drug is released. The second component is an enzyme-degradable hydrogel that surrounds the bioerodible polymer (first component) with a low pH environment so that no degradation of the pH-sensitive polymer occurs. The third component is a reversible inactivated enzyme that in its active state is capable of degrading the hydrogel, exposing the bioerodible polymer to the physiological pH. The device responds to opiate diffusion into the device, which activates the degradation of the protective hydrogel, and therefore triggers the diffusion of naltrexone from the polymer. In order to prevent the release of enzymes and antibodies to the environment, the device is encapsulated in a membrane permeable to naltrexone and opiate, but impermeable to larger molecular weight enzymes or antibodies. Polymers that have been demonstrated to be stable at low pH values are partially esterified copolymers of methylvinylether and maleic anhydride.

Pitt et al. [119] proposed utilizing the hapten–antibody interaction to suppress enzymatic degradation and permeability of polymeric reservoirs or matrix drug delivery systems. Their delivery device (Fig. 22) consists of naltrexone contained in a polymeric reservoir or dispersed in a polymeric matrix configuration. The device is coated by covalently grafting morphine to the surface. Exposure of the grafted surface to antibodies to morphine results in coating of the surface by the antibodies, a process that can be reversed by exposure to exogenous morphine. The presence of the antibodies on the surface or in the pores of the delivery device will block or impede the permeability of naltrexone in a reservoir configuration or enzyme catalyzed surface degradation and concomitant release of the drug from a matrix device. Fig. 22 also illustrates a second example of the proposed mechanism for responsive release of a contraceptive agent. The b-subunit of human chorionic gonadotropin (HCG) is grafted to the surface of the polymer, which is then exposed to antibodies to β-HCG. The appearance of HCG in the circulatory system (indication of pregnancy)

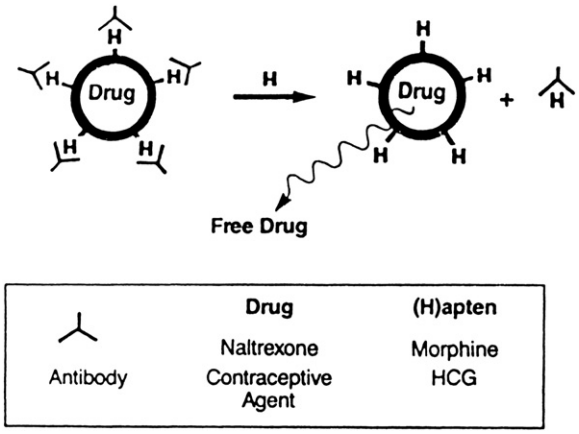

Fig. 22. Responsive release based on reversible antibody binding to haptens attached to the surface of permeable or biodegradable polymers. (Antibody binding is reversed by the appearance of a trigger molecule which is competitive hapten [119].)

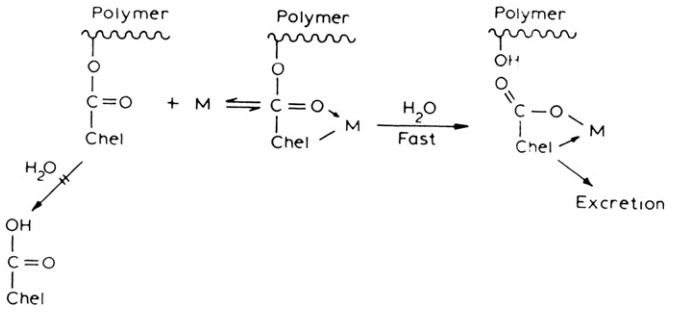

Fig. 23. Concept of a self-regulated delivery system for metal chelators, based on metal promoted hydrolysis of carboxylic esters [119].

will cause release of a contraceptive drug (The HCG competes for the polymer-bound antibodies to HCG and initiates release of the contraceptive drug.)

Pitt et al. [59,119] also proposed a hypothetical reversible antibody system based on the ability of ethinylestradiol (EE) to stimulate biosynthesis of sex-hormone-binding-globulin (SHBG). High serum levels of EE stimulate the production of SHBG, which increases the concentration of SHBG bound to the polymer surface and reduces the EE release rate. When the EE serum level falls, the SHBG level falls, as does binding of the SHBG to the polymer surface, producing an automatic increase in the drug release rate.

The polymers evaluated by Pitt and coworkers for covalent attachment of haptens were poly(ethylenevinylacetate) copolymers for reservoir devices and hydroxylated polyester urethanes where the release is enzymatic degradation dependent. The polymers were prepared from ϵ-caprolactone and δ-valerolactone, lightly crosslinked with 1,6-hexanediisocyanate. The residual hydroxyl groups of the elastomer were shown to be suitable sites for hapten derivatization by treatment with chloroacetic anhydride. Biodegradability studies of the crosslinked polymers were conducted by implanting films subdermally in rabbits, and measuring weight loss and dimensional changes with time. No weight loss was observed after 4 weeks of implantation. These results were in contrast with the immediate and rapid surface erosion of polymers prepared from ϵ-caprolactone and δ-valerolactone crosslinked with bis-2-2-(ϵ-caprolactone-4-yl) propane in which weight loss was detected within 2 weeks and increased thereafter in an approximately linear fashion [124].

Pitt et al. [119,125] also reported on the self-regulated delivery of drugs which function by chelation. These include certain antibiotics and drugs for the treatment of arthritis, as well as chelators used for the treatment of metal poisoning. The concept presented in Fig. 23 is based on the ability of metals to accelerate the hydrolysis of carboxylate or phosphate esters and amides by several orders of magnitude. Attachment of the chelator to a polymer chain by a covalent ester or amide link serves to prevent its premature loss by excretion and reduces its toxicity. In the presence of the specific ion, a complexing with the bound chelating agent will take place, followed by metal-accelerated hydrolysis and subsequent elimination of the chelated metal. Measurement of the rates of hydrolysis of poly(vinyl alcohol) coupled with quinaldic acid chelator (PVA–QA) in the presence of Co (II), Zn(II), Cu(II) and Ni(II) confirmed that it is possible to retain the susceptibility of the esters to metal-promoted hydrolysis in a polymer environment, even in solid state when the polymer matrix is sufficiently hydrated that diffusion of the metal ion and metal chelate is not rate limiting [125].

4. Concluding remarks

The pharmaceutical industry has gone through several evolutionary stages starting with the introduction of antibiotics in the 1930s and 1940s to the development of drugs produced by genetic engineering techniques today. During the last two decades, polymeric controlled drug delivery has become an important area of research and development. In this short time, a number of systems displaying constant or decreasing release rates have progressed from the laboratory to the clinic and, in some cases, commercial products. Polymer systems for controlled release of such drugs as nitroglycerin, scopalamine, pilocarpine, antibiotics, birth control drugs, and anti-cancer drugs are either in late stage clinical trials or are available clinically. Although these polymeric controlled delivery systems are advantageous compared to the conventional methods of drug administration they are insensitive to the changing metabolic state. In order to control the physiological requirements of the specific drugs more closely, responsive mechanisms must be provided. The approaches discussed in this article represent attempts conducted over the past decade to achieve pulsatile release. It should be pointed that these drug delivery systems are still in the early developmental stage and much research will have to be conducted for such systems to become practical clinical alternatives. Critical considerations are the biocompatibility and toxicology of these multi-component polymer-based systems, the response times of these systems to stimuli, the ability to provide practical levels of the desired drug, and addressing necessary formulation issues in dosage or design (e.g. shelf life, sterilization, reproducibility). A key issue in the practical utilization of the externally triggered release systems (i.e. magnetic, ultrasound, etc.) will be the design of small portable units that the patient can easily use. Ideally, such systems could be worn by the patient, such as a wristwatch-like system, and it could be either pre-programmed to go on and off at specific times or the patient could turn it on when needed. A critical issue in the development of self-regulated systems such as those containing enzymes or antibodies, are the stability and/or potential leakage and possible immunogenicity of these bioactive agents. While the successful development of responsive polymer delivery systems will be a significant challenge, the considerable pharmacological benefit these systems could potentially provide, particularly given ongoing research in pharmacology and chronobiology which may provide new insights on the desirability and requirements for pulsatile release, should make this an important and fruitful area for future research.

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