REVIEW ARTICLE

Accepted 30 August 2002
Revised 24 July 2002
Received 22 September 2001
Indian J. Pharm. Sci., 2002, 64(6): 515-524

Recent Advances in Modulated Drug Delivery Systems

SUSHAMA TALEGAONKAR*, P. R. MISHRA AND R. K. KHAR
Department of Pharmaceutics, Faculty of Pharmacy,
Hamdard University, Hamdard Nagar, New Delhi-110 062.

Modern therapeutic system has often been criticized for the toxicity associated with the drugs. To minimize this drawback, many researchers have focussed attention towards developing modulated drug delivery systems capable of releasing therapeutic agents in response to physiological requirements. Another class of modulated drug delivery systems are those in which pulsatile release of drugs is triggered by external signals. The former is known as self-regulated or responsive systems while the latter is known as externally regulated or pulsatile delivery systems. This article briefly describes the fundamental principles of various types of pulsatile as well as responsive drug delivery systems. Recent developments in the field of pulsatile systems based on external triggers such as electrical, ultrasound, magnetic and massages have been reported. This article also traces recent research in the field of polymer based temperature-sensitive, pH-responsive, inflammation-responsive and glucose-and other saccharide-sensitive systems; enzyme-based urea-responsive, glucose-responsive and morphine-triggered systems; systems based on antibody interactions, and systems utilizing chelation.

The conventional manner of introducing drugs to patients is inefficient and often leads to toxic side effects. The dramatic advances in controlled and targeted drug delivery system over the past few decades have lead to enormous expectations for treatment of number of complicated ailments with minimum side effects. One class of such systems is Modulated Drug Delivery Systems (MDDS), which generated a lot of excitement in pharmaceutical area. These systems are based on the principle of altering drug release process by sensing physiological events. This approach helps to deliver drug as per requirement i.e. it releases the drug in response to the condition of the patient. This is in contrast to constant-rate drug delivery systems, which aim at maintaining drug concentration in therapeutic range over a desired period.

MDDS are implanted or injected into the body and are capable of releasing drugs in response to certain pre-selected stimuli. Such systems can be broadly classified into two categories, (a) open-loop systems also known as pulsatile or externally regulated, and (b) closed-loop or self-regulated or responsive systems. In the externally regulated devices external triggers such as magnetic, ultrasonic, thermal, electric, electromagnetic irradiation and mechanical stimulation are applied for delivery of drugs. In such systems, the drug is generally released in a burst (pulse) on the application of the external trigger and hence they are also referred to as pulsatile systems. On the other hand, the self-regulated devices utilize feedback information to control the release rate. The self-regulated systems utilize several approaches as rate control mechanism: pH-sensitive polymers, enzyme-substrate reaction, pH-sensitive drug solubility and competitive binding antibody interactions.

*For correspondence

EXTERNALLY REGULATED OR PULSATILE DRUG DELIVERY SYSTEMS

Ultrasonically modulated systems:

Ultrasonication has been employed to modulate repeated release of drug from ultrasonic controlled polymeric

devices. Both bioerodible and nonbioerodible polymers have been used as drug carrier matrices[1]. Miyazaki *et al.*[2] reported the effect of ultrasound (1 MHz) on the release of insulin from ethylene-vinyl alcohol copolymers when employed in matrices and reservoir type drug delivery systems. A sharp drop in blood glucose levels was observed after irradiation, indicating a rapid release of insulin in implanted sites. The latter has been attributed to increased temperature in delivery system due to ultrasound facilitated diffusion.

Over the years many researchers have worked on phonophoresis[3], which involves placing a topical preparation over the affected part of the skin and massaging the area with an ultrasound probe. The possible application of ultrasound in transdermal drug delivery system (TDDS) was studied by Kost *et al.*[3-4] and Leavy *et al.*[5] The characteristic lag time associated with TDDS was nearly eliminated by employing ultrasonication. Merely 3 to 5 min of ultrasound irradiation (1.5 W/cm^2 continuous wave or 3.0 W/cm^2 pulsed wave) was enough to increase transdermal permeation of insulin and mannitol in rats by 5-20 fold within 1-2 h. Miyazaki *et al.*[6] and Bommannan[7] studied permeation of indomethacin and lanthanum nitrate, respectively in rats employing ultrasound. Application of low frequency ultrasound waves to enhance transdermal transport of lidocaine and insulin across hairless mice skin has been reported[8-10]. Enhancement in the transport of various low molecular weight drugs (salicylic acid and corticosterone) as well as high molecular weight proteins (insulin and erythropoeitin) across the human skin *in vitro* and *in vivo*, utilizing a similar technique of low frequency ultrasound, was reported by Mitragotri *et al.*[11,12] Mitragotri *et al.*[13] also evaluated the role played by various ultrasound related phenomena including cavitation, thermal effects, generation of convective velocities and mechanical effects. Lavon and Kost[14] studied the mass transport enhancement by ultrasound in non-erodible polymeric controlled release systems. It was found that drug release rates from polymeric matrices exposed to ultrasound can be controlled by modifying various parameters like ultrasound frequency, molecular weight of incorporated drug and structure of the polymeric matrix (size of pores in network). The effect of continuous wave and pulsed 20 kHz ultrasound on the doxorubicin uptake by HL-60 cells from the phosphate buffered saline solution and pluronic micellar solutions were studied by Marin *et al.*[15] The main factor that effected the drug uptake was ultrasound power density.

Electrically regulated systems:

Electrically regulated systems utilize action of an electric field on a rate limiting membrane or directly on the solute or both to control the drug release. Grimshaw *et al.*[16] reported four different mechanisms for the transport of proteins and neutral solutes across hydrogel membranes:

(1) Electrically-and chemically-induced swelling of membrane to alter the effective pore size and permeability,

(2) Electro-phoretic augmentation of solute flux within a membrane,

(3) Electro-osmotic augmentation of solute flux within a membrane and

(4) Electrostatic partitioning of charged solutes into charged membranes.

Electrically-controlled membrane permeability has also been studied[17,18] for application in the field of electrically-controlled or enhanced transdermal drug delivery (e.g. iontophoresis and electroporation). The effect of electric current on positively charged solute (edrophonium chloride) from crosslinked poly(2-acrylamido-2-methyl propane sulfonic acid-co-n-butylmethacrylate) was studied by Kwon *et al.*[19] The mechanism was explained as fast release of the charged solute from hydrogel following an ion exchange between positive solute and hydroxonium ion. Hsu and Block[20] reported use of anionic gels as vehicles for electrically modulated drug delivery. Agarose and combination of agarose with anionic polymer (PAA, xanthum gum) were evaluated and it was concluded that carbomer (polyacrylic acid) in conjugation with agarose enables the formulator to achieve zero order release with electrical application.

A drug delivery device consisting of a polymer reservoir with a pair of electrodes placed across the rate limiting membrane was proposed by D'Emanuele *et al.*[21] The drug release rate was modulated by altering the magnitude of electric field. The same authors[22] reported that parameters such as buffer ionic strength, drug reservoir concentration and electrode polarity have significant effect over drug permeability. Labhasetwar *et al.*[23] proposed similar approach for cardiac drug delivery modulation. The authors studied a cardiac drug implant in dogs, which was amenable to electric current modulation. Cation exchange membrane was used as an electrically sensitive rate-limiting barrier.

Nakhare *et al.*[24] studied the iontophoretic drug delivery of a non-steroidal antiinflammatory drug (diclofenac sodium) across cellophane membrane, employing a four probe electrode system. The effect of various parameters like on/off

ratio, frequency, applied voltage and pH of the drug solution on the iontophoretic transport of diclofenac sodium was studied. Langkjaer *et al.*[25] have studied the influence of association state and net charge of human insulin analogues on the rate of iontophoretic transport across the hairless mouse skin and the effect of different skin pretreatments on said transport. No flux was observed with anodal delivery probably because of degradation at the Ag/AgCl anode. Wiping the skin gently with absolute alcohol prior to iontophoresis resulted in a 1000 fold increase in transdermal transport of insulin relative to that across untreated skin. The alcohol pretreatment reduced the electrical resistance of the skin, presumably by lipid extraction. Enhanced transdermal delivery of AZT (zidovudine)) using iontophoresis and penetration enhancer across hairless mouse skin was studied by Oh *et al.*[26] The *in vitro* iontophoretic flux from AZT solution increased to about 5-40 fold than that obtained by passive diffusion, depending on the current density. Transdermal delivery of drugs using iontophoresis with cation and anion exchange fibres as controlled delivery vehicles was reported by Jasaki *et al.*[27] Complexation of charged model drugs with ion exchange fibres was studied as a method to achieve controlled transdermal delivery. Drug release from the cation exchange fibre into a physiological saline was found to be dependent on the lipophilicity of the drug.

Sung *et al.*[28] investigated the *in vitro* transport of nelbuphine (NA) and its prodrugs across various skin in order to assess the effects of prodrug lipophilicity on passive as well as iontophoretic permeation. The passive diffusion of NA and its prodrugs increased with the drug lipophilicity. Iontophoresis significantly increased the transport of NA and its prodrugs. Rowland and Chilcott[29] studied the electrostability and electrically assisted delivery of an organophosphate pretreatment (physostigmine) across human skin *in vitro*. This drug was selected as it prevents the degradation of the electrodes. It was concluded that physostigmine did not penetrate the skin when electroporated at a frequency of 0.1 Hz or 10 Hz, but significant amounts were delivered at a frequency of 100 Hz. Iontophoretic and electroporative drug delivery of physostigmine sulphate was found to be buffer dependent, which could be attributed to combination of co-ion competition, mono/di cation ratio and applied charge effect. Use of chitosan gels as a matrices for electrically modulated drug delivery was studied by Ramanathan and Block[30]. The cumulative gel mass loss increased with increase in applied current. The release of the model drug from the gel matrix in the descending order was -benzoic acid, hydrocortisone and lidocaine, which is consistent with the electrokinetically competing forces that are involved in these gels.

Magnetically modulated systems:

One way of fabricating magnetic modulated system is based on the application of oscillating magnetic field, which induces release of drug from elastic polymer containing drug and magnetic beads. This in turn causes pulsatile release of drug in the physiologic milieu, as and when required. It has been demonstrated that insulin could be continuously released by embedding ethylene-vinyl acetate co-polymer, (EVAC)[31]. This principle was also employed to design subcutaneous implants of EVAC-insulin, which decreased glucose levels of diabetic rats for 105 d[32]. *In vivo* studies[33] revealed that, when polymeric beads were implanted in diabetic rats, glucose level could be repeatedly decreased on demand by application of a oscillating magnetic field. This type of systems are generally fabricated by adding 50% of the drug polymer mixture to a glass mould that has been chilled to -80° using dry ice. The magnetic beads are then added followed by remaining drug polymer mixture[34].

The factors that are critical in controlling the release rates in these systems can be characterized by two main groups (a) magnetic field characteristics, and (b) mechanical properties of polymer matrix. The release of drug from such a system depends on the amplitude of the magnetic field. Saslavski *et al.*[35] reported that magnetic field frequency inversely affects the release of drug due to faster depletions. As far as mechanical properties of the polymeric matrix are concerned it has been reported[36,37] that release rate is inversely proportional to modulus of elasticity of EVAC polymer.

Photo-induced systems:

A photoresponsive polymer consists of photoreceptor, usually a photochromic chromophore, and a functional part. The optical signal is captured by the photochromic molecules and then the isomerization of the chromophores in photoreceptor converts it to a chemical signal. Photo-induced phase transition of gels was reported by Mamada *et al.*[38] Copolymer gels of N-isopropylacrylamide and a photosensitive molecule, bis (4-dimethylamino)phenyl)(4-vinylphenyl)methyl leucocyanide, showed a discontinuous volume-phase transition upon ultraviolet irradiation. Suzuki and Tanaka[39] reported on phase transition in polymer gels induced by visible light, where the transition mechanism is due only to the direct heating of the network polymer by light. Photoresponsive degradation of heterogeneous hydrogels

comprising cross-linked hyaluronic acid and lipid microspheres for temporal drug delivery was reported by Yui *et al.*[40] The degradation of cross-linked hyaluronic acid gels was induced by visible light and methylene blue was used as photosensitizer.

The possibilty of active uptake and photo-induced release of the doxorubicin from liposomes incorporating a photoisomerizable lipid was studied by Bisby *et al.*[41] The isomerization on exposure to near-UV light results in change in membrane permeability to solutes. The use of light to stimulate the release of encapsulated compounds from liposomes has recently been reported by Bondurant *et al.*[42] PEG-liposome composed in part of the photosensitive lipid, bis-SorbPC, was so prepared to effectively encapsulate water soluble compounds, which could be released by increasing the permeability upon exposure to ultraviolet light in the presence of oxygen. The photoinitiated destabilization of these PEG-liposomes is probably attributable to the formation of defects in the bilayer during crosslinking of the bis-SorbPC.

Massage-induced systems:

Trubetskoy *et al.*[43] have reported liposome-based externally regulated drug delivery system, in which liposome-encapsulated bioactive molecules can be delivered into the blood in response to simple mechanical action. Subcutaneously injected 200 nm liposomes were trapped in the interstitial space for prolonged time of which up to 40% could be delivered to the blood via lymphatic pathway from the injection site by 5 min manual massage cycle. Modification of liposome surface with polyethylene glycol was found to increase blood localization of liposome-encapsulated drug presumably due to decreasing the uptake of drug carrier by lymph node macrophages.

SELF REGULATED OR RESPONSIVE SYSTEMS

Temperature-sensitive polymer-based systems:

Recently several groups[44-60] have studied responsive drug delivery systems based on temperature-sensitive polymers. Bioactive agents such as drugs, enzymes and antibodies may be immobilized on or within the temperature sensitive polymers. Temperature-sensitive polymers can be classified into two groups based on the origin of the thermosensitivity in aqueous media. The first is based on polymer-water interactions especially specific hydrophobic/hydrophillic balancing effects and the configuration of side groups. Second group is based on polymer-polymer interactions as well as polymer-water interaction. All thermosensitive polymers which are characterised by low critical solution temperature (LCST), usually shrink as the temperature is increased through LCST. Lowering the temperature below LCST results in the swelling of the polymer.

Kurisawa *et al.*[61] have synthesized a thermosensitive copolymer and evaluated its *in vitro* gene transfection efficiency at different incubation temperatures. Jeong *et al.*[62] have studied the drug release from biodegradable injectable thermosensitive hydrogel of PEG-PLGA-PEG triblock copolymers with a specific composition as a free flowing sol at room temperature that becomes a gel at body temperature.

A novel positively thermosensitive, controlled release microcapsule with membrane of nano-sized poly(N-isopropylacrylamide) gel dispersed in ethyl cellulose matrix were studied by Ichikawa and Fukumori[63]. Hinrichs *et al.*[64] have used different thermosensitive polymers as carrier for DNA delivery. In their studies they concluded that copolymers of 2-(dimethylamino)ethyl methacrylate (DMAEMA) and N-isopropylacryl amide (NIPAA) having various monomer ratios and molecular weights can be used as a carrier for DNA delivery. The results of their studies showed that the formation of stable copolymer/plasmid complexes with a size of around 200 nm is a prerequisite for efficient transfection. Transfection effeciency and cytotoxicity are directly proportional to zeta potential.

Needham *et al.*[65] have developed a new thermosensitive liposomal drug delivery system containing doxorubicin for local control of solid tumor. The system was found to be significantly more effective than free drug or current formulations. A positively charged thermosensitive drug release microcapsule (MC) was designed and prepared by Ichikawa and Fukumori[66]. The MC had a core layered with carbazochrome sodium sulfonate particles and a thermosensitive coat composed of an ethylcellulose matrix containing nano-sized thermosensitive hydrogel. This MC demonstrated a positive thermosensitive drug release; the release rate was remarkably enhanced at temperature above a lower gel collapse point of 32°. Sershen *et al.*[67] have reported photothermally modulated drug delivery of methylene blue by composites of thermally sensitive hydrogel and optically active nanoparticles. Copolymers of N-isopropylacrylamide (NIPAAm) and acrylamide exhibit a LCST that is slightly above body temperature. When the temperature of the copolymer exceeds the LCST, the hydrogel collapses causing burst release of the drug. A temperature change is achieved in response to light irradiation by incor-

porating nanoparticles (gold-gold sulphide nanoshells) into poly(NIPAAm-co-Aam) hydrogels that convert light into heat. Recently, Shin *et al.*[68] have reported hybrid nanogel composed of thermosensitive poly(N-isopropyacrylamide) gels and tailored nonporous silica, in which temperature sensitive shrinkage of the polymer induces squeezing of the drug into porous channels, from where it diffuses out slowly.

pH-responsive systems:

pH-sensitization constitute an interesting therapeutic avenue, since certain pathological conditions (e.g. tumor) and cellular compartments (e.g. endosomes) are associated with a relatively acidic pH[69,70]. Studies by several research groups[71-83] have been performed on polymers containing weakly acidic or basic groups in polymeric backbone. Change in the pH of the solution causes swelling or deswelling of the polymer as the charge density of the polymers depends on pH and ionic strength of the outer solution. Thus, the drug release from devices made from these polymers will display release rates that are pH-dependent. Polyacidic polymers will be unswollen at low pH because the acidic groups will be protonated and hence unionized. With increasing pH, polyacid polymers will swell. The opposite holds for polybasic polymers. Siegel *et al.*[84] found that the swelling properties of the polybasic gels get influenced by buffer composition (concentration and pKa). Giannos *et al.*[85] proposed temporally controlled drug delivery systems by coupling pH oscillators with membrane diffusion properties. By changing the pH of solution relative to pKa, a drug may be rendered charged or uncharged. Because only the uncharged form of drug can permeate across lipophilic membranes, temporally modulated delivery profile may be obtained with a pH oscillator in the donor solution.

Bioerodible hydrogels containing azoaromatic moieties were synthesized by Ghandehari *et al.*[86] Hydrogels with lower cross-linking density underwent a surface erosion process and degraded at a faster rate. Hydrogels with higher cross-linking densities degraded at a slower rate by a process where the degradation front moved inward to the centre of the polymers.

Recently Petka[87] used recombinant DNA methods to create artificial proteins that undergo reversible gelation in response to changes in pH and temperature. The protein consists of terminal leucine zipper domains flanking a central, flexible, water soluble polyelectrolyte segments. Ganorkar *et al.*[57] proposed modulating insulin-release profile from pH responsive polymeric beads of acrylic acid and butyl methacrylate of various molecular weights. Studies revealed that the low MW polymeric beads may be used for immediate delivery of protein drugs in the duodenum, the intermediate MW polymeric beads may be used for lower small intestine targeting, while the high MW polymeric beads may be used to target protein drugs predominantly to the colon. Pillay and Fassihi[88] reported crosslinked pellets of sodium alginate bearing diclofenac sodium for pH dependent site specific delivery to gastro-intestinal tract. It is concluded that the proper selection of rate-controlling polymers and their interactive potential for crosslinking is important, and will determine the overall size and shape of pellets, the duration and pattern of dissolution profiles, pH sensitivity, drug loading capacity and mechanism of drug release. Taillefer *et al.*[89] prepared and characterized pH responsive polymeric micelles (PM) consisting of random copolymers of N-isopropylacrylamide methacrylic acid and octadecylacrylate. These PM were used for the delivery of photosensitizing anticancer drug aluminium chloride phthalocyanine (AlClpc). PM loaded with AlClpc were found to exhibit higher cytotoxicity against EMT-6 mouse mammary cells. De Jaeghere *et al.*[90] reported pH sensitive nanoparticles and microparticles made of the poly(methacrylic acid-co-ethylacrylate) copolymer Eudragit containing poorly water soluble HIV-1 protease inhibitor (CGP 70726) for oral delivery. The results showed that bioavailabity of the drug has been improved by using this system. Risbud *et al.*[91] developed a pH-sensitive chitosan/polyvinyl pyrrolidone (PVP) based controlled drug release system for antibiotic delivery (amoxicillin). Porous freeze dried hydrogels exhibited superior pH-dependent swelling properties over non-porous air dried hydrogels. Hydrophobically modified copolymers of N-isopropylacrylamide bearing a pH-sensitive moiety were investigated for the preparation of pH responsive liposomes and polymeric micelles by Leroux *et al.*[92] Release of both a highly water soluble fluorescent contents marker, pyranine, and an amphipathic cytotoxic anti-cancer drug, doxorubicin, from copolymer-modified liposomes was found to be dependent on pH, concentration of copolymer, the presence of other polymers (such as polyethylene glycol) and the method of preparation.

Inflammation-responsive systems:

Yui *et al.*[93] proposed an inflammation-responsive drug delivery system based on biodegradable hydrogels of crosslinked hyaluronic acid. Hyaluronic acid is specifically degraded by hydroxyl radicals which are produced by phagocytic cells such as leukocytes and macrophages locally at inflammatory sites. A biodegradable, inflammation-responsive microsphere system for the intraarticular delivery of

therapeutic proteins was reported by Brown *et al.*[94] Microspheres were synthesized by complex coacervation. Radiolabeled protein release and microsphere degradation were assessed by exposing the microspheres to human synovial fluids (SF) and recombinant gelatinase. Significant (up to 100%) release of encapsulated protein occurred in SF samples with measurable metalloprotease activity while release was minimal in SF with negligible activity.

Glucose and other saccharide-sensitive-polymer based systems:

The preparation of glycosylated insulins, which are complementary to the major combining site of carbohydrate binding proteins such as concanavalin A (Con A) was first suggested by Brownlee and Cerami[95], It was subsequently found that the release rate of insulin was also dependent on the binding affinity of the insulin derivative to Con A and could be influenced by the choice of saccharide group in glycosylated insulin[96-103]. 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 encapsulated membrane. Kokufata *et al.*[104] reported a gel system that swells and shrinks in response to specific saccharides. The gel consists of a covalently cross-linked polymer network of N-isopropyl acrylamide in which the lectin, Con A is immobilized. When the saccharide dextran sulphate is added to the gel, it swells to a volume up to 5 times greater. While replacing dextran sulphate with non-ionic saccharide α-methyl-D-mannopyronoside brings about collapse of gel back to almost its native volume.

Taylor *et al.*[105] proposed a self-regulating insulin delivery device, responsive to glucose. The device comprises a reservoir of insulin and a gel membrane that determines the delivery rate of insulin. The gel consists of a synthetic polysucrose, lectin and Con A. Obaind and Park[106,107], Lee and Park[108] also presented a similar approach of preparing glucose-sensitive membrane based on the interaction between polymer bound glucose and Con A. Kitano[109] proposed a glucose-sensitive insulin release system based on a sol-gel transition. Insulin was incorporated into a polymeric complex, which on addition of glucose transforms from gel to sol state, resulting in release of insulin from the polymeric complex. Hisamitsu *et al.*[110] modified the approach suggesting glucose-responsive gel based on the complexation between polymers having PBA groups and PVA. The introduction of an amino group into PBA polymers caused increase in the complexation ability and the glucose responsivity at physiological pH.

Urea-responsive delivery:

Heller and Trescony[111] were the first to attempt use of immobilized enzymes to alter the local pH and thus cause change in polymer erosion rates. This system is based on the conversion of urea to NH_4CO_3 and NH_4OH by the action of urease. In this case a polymer is required which is subjected to erosion at high pH. Polymers like esterified methyl vinyl ether and maleic anhydride which show pH dependent erosion have also been suggested[112]. The pH-sensitive polymer containing dispersed hydrocortisone is surrounded with urease immobilized in a hydrogel prepared by crosslinking a mixture of urease and bovine serum albumin with gluteraldehyde. When urea diffuses in to the hydrogel, its interaction with the enzyme leads to a pH increase, therefore enhancing erosion of the pH sensitive polymer with concomitant changes in the release of hydrocortisone.

Ishihara *et al.*[113,114] suggested a nonerodible system comprised of a pH-sensitive membrane prepared 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.

Glucose-responsive insulin delivery:

These systems are based on pH-sensitive polymers consisting immobilized glucose oxidase in a pH-responsive hydrogel, enclosing a saturated solution of insulin[115-119]. As glucose diffuses in to the hydrogel, glucose oxidase catalyzes its conversion to gluconic acid, thereby lowering the pH in the microenvironment of the hydrogel and causing swelling. As insulin permeates the swelled hydrogel more rapidly, faster delivery of insulin in the presence of glucose is anticipated. With the decrease in glucose concentration in response to the released insulin, the hydrogel should contract and decrease the rate of insulin delivery.

Kost *et al.*[120], Horbett and coworkers[121,122] immobilized glucose oxidase in a crosslinked hydrogel made from N,N dimethylaminoethyl methacrylate (DMA), hydroxyethyl methacrylate (HEMA) and tetraethylene glycol dimethacrylate (TEGDMA). To obtain sufficient insulin permeability through the gels, porous HEMA/DMA gels were prepared by polymerization under conditions that 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 area where the solvent/monomer phase existed, become fixed in

place as pores in the polymer matrix. The rate of insulin permeation through the membranes was measured in the absence of glucose in a standard transport cell. Thereafter glucose was added to one side of the cell to a concentration of 400 mg/dl 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/dl, glucose was 2.4 to 5.5 times higher than before glucose was added. A mathematical model describing these glucose responsive hydrogel demonstrates two important parameters, (a) progressive response to glucose concentration over a range of glucose concentration can be achieved only with a sufficiently low glucose oxidase loading; otherwise depletion of oxygen causes the system to become insensitive to glucose; and (b) 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 bufferring of the amines.

Ishihara *et al.*[123-126] reported insulin delivery by preparing polymers from 2-hydroxyethyl acrylate (HEA)-DMA and 4-trimehylsilystyrene (TMS) by radical polymerization of the corresponding monomers in dimethylformamide. Poudal *et al.*[127] reported similar approach of insulin delivery based on hydrogels of poly (diethyl aminoethyl methacrylate-g-ethylene glycol) containing glucose oxidse and catalase. Iwata and Matsuda[128], Iwata[129] employed pretreated porous poly(vinyledene fluoride) membranes containing glucose oxidase by air plasma and subsequently acrylamide was graft-polymerized on the treated surface. Ito *et al.*[130] used porous cellulose membrane with surface grafted poly(acrylic acid) as a pH sensitive membrane. This membrane became responsive to glucose concentration when immobilized by glucose oxidase. Siegel[131], Siegel and Firestone[132] proposed an implantable "mechanochemical" pump that functions by converting changes in blood glucose activity into a mechanical force, generated by the swelling polymer that pumps insulin out of device. Siegel[133] reported self-regulating oscillatory drug delivery based on a polymeric membrane whose permeability to the substrate of an enzyme catalyzed reaction is inhibited by the product of that reaction. This negative feedback system can, under certain conditions, lead to oscillations in membrane permeability and in the levels of substrate and product in the device.

Heller *et al.*[134,135] suggested a system in which insulin is immobilized in a pH-sensitive bioerodible polymer prepared from 3,9-bis (ethylidene 2,4,8,10-tetraoxaspirol-(5,5)-undecane and N-methyldiethanolamine which is surrounded by a hydrogel containing immobilized glucose oxidase. The diffusion of glucose causes the formation of gluconic acid. This resultant lowering of pH triggers enhanced polymer degradation and release of insulin from the polymer in proportion to the concentration of glucose. Glucose-dependent insulin release was proposed by Brown and coworkers[136,137] based on the fact that insulin solubility is pH-dependent. Insulin was incorporated into poly(ethylene vinyl acetate) copolymer (EVAc) matrices in solid form. Thus, the release was governed by its dissolution and diffusion rates.

Morphine-triggered naltraxone delivery system:

Heller and coworkers[138-143] have developed a naltraxone drug delivery system that would be passive until drug release is initiated by the appearance of morphine external to the device. Activation is based on the reversible inactivation of enzymes achieved by the covalent attachment of hapten close to the active site of the enzyme-hapten conjugate with the hapten antibody.

Systems utilizing antibody interactions:

The utilization of hapten-antibody interaction to suppress enzymatic degradation and permeability of polymeric reservoirs or matrix drug delivery system was first proposed by Pitt[144]. The delivery device consists of naltrexone contained in a polymer reservoir or dispersed in a polymer 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. 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.

Pitt[144,145] also proposed hypothetical reversible antibody system for controlled release of ethinyl estradiol (EE). EE stimulates 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 EE release rate.

Systems utilizing chelation:

In this system delivery of drugs is self-regulated by chelation[146]. These include certain antibiotics and drugs for the treatment of arthritis as well as chelators used for the treatment of metal poisoning. The concept 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. Hydrophilic desferrioxamine (DFO) and the lipophilic salicylaldehyde isonicotinoyl hydrazone (SIH) are iron chelators which inhibit *in vitro* proliferation of *Plasmodium falciparum* with similar potency. The *in vivo* assessment of these drugs was performed[147] on Swiss mice infected with *Plasmodium vinckei petteri* with novel modes of drug administration and release. This study indicates that polymeric devices for slow drug release might be highly advantageous for both hydrophilic and lipophilic drugs whose antimalarial efficacy might depend on the maintenance of sustained blood levels.

CONCLUSION

Research in the field of MDDS or Intelligent Drug Delivery systems as they are sometimes referred to, has taken a quantum leap over the last few decades. Need for development of safe drug delivery systems particularly for treating conditions such as cancer, diabetes, angina pectoris and arthritis, which require prolonged drug interaction coupled with enabling technological advancements particularly in polymer technology have lead to intensive research towards development of MDDS. Presently, such systems are largely in developmental stage and there is long way to go before they can be put to practical applications. From this viewpoint, portability shall be the single most important factor in case of pulsatile drug delivery systems. In case of responsive systems, stability of the formulation and elimination of accidental release shall also be important from practical applicability viewpoint. There is no doubt that this field will continue to attract attention of researchers all over the world due to sheer potential it holds for the mankind.

REFERENCES

1. Kost, J., Leong, K. and Langer, R., **Proc. Natl. Acad. Sci. U.S.A.,** 1989, 86, 7663.
2. Miyazaki, S., Yokouchi, C. and Takada, M., **J. Pharm. Pharmacol.,** 1988, 40, 716.
3. Kost, J. In; Berner, B. and Dinh, S., Eds., Electronically Controlled Drug Delivery, CRS Press, Boca Raton, Fla, 1998, 215.
4. Kost, J. and Sanger, R., In; Shah, V. and Maibach, H., Eds, Cutaneous Bioavailability, Bioequivalence and Penetration, Plenum Press, Boca Raton, Fla, 1994, 91.
5. Leavy, D., Kost, J., Meshulam, Y. and Langer, R., **J. Clin. Invest.,** 1989, 83, 2074.
6. Miyazaki, S., Mizuoka, O. and Takada, M., **J. Pharm. Pharmacol.,** 1990, 43, 115.
7. Bommannan, D., **Pharm. Res.,** 1992, 9, 1043.
8. Tachibana, K., **Pharm. Res.,** 1992, 9, 52.
9. Tachibana, K. and Tachibana, S., **Anesthesiology,** 1993, 78, 1091.
10. Tachibana, K. and Tachibana, S., **J. Pharm. Pharmacol.,** 1991, 43, 270.
11. Mitragotri, S., Blankschtein, D. and Langer, R., **Pharm. Res.,** 1996, 13, 411.
12. Mitragotri, S., Blankschtein, D. and Langer, R., **Science,** 1995, 269, 850.
13. Mitragotri, S., Edwards, D., Blankschtein, D. and Langer, R., **J. Pharm. Sci.,** 1995, 84, 697.
14. Lavon, I. and Kost, J., **J. Control. Release,** 1998, 54, 1.
15. Marin, A., Muniruzzaman, M. and Rapoport, N., **J. Control. Release,** 2001, 71, 239.
16. Grimshaw, P.E., Grodzinsky, A.J., Yarmush, M.L. and Yamush, D.M., **Chem. Eng. Sci.,** 1989, 104, 827.
17. Prausnitz, M., Bose, R., Langer, R, and Weaver, J., **Proc. Natl. Acad. Sci. U.S.A.,** 1993, 90,10504.
18. Rolf, D., **Pharm. Technol.,** 1988, 12, 130.
19. Kwon, I.C., Bae, Y., Okano, T. and Kim, S.W., **J. Control. Release,** 1991, 17, 149.
20. Hsu, C. and Block, L., **Pharm. Res.,** 1996, 13, 1865.
21. D Emanuele, A. and Staniforth, J.N., **Pharm. Res.,** 1991, 8, 913.
22. D Emanuele, A. and Staniforth, J.N., **Pharm. Res.,** 1992, 9, 215.
23. Labhasetwar, V., Underwood, T., Schwendemann, S. and Levy, R., **Proc. Natl. Acad. Sci. U.S.A.,** 1995, 92, 2612.
24. Nakhare, S., Jain, N.K. and Verma, H.V., **Pharmazie,** 1994, 49, 672.
25. Langkjaer, L., Brange, J., Grodsky, G.M. and Guy, R.H., **J. Control. Release,** 1998, 51, 47.
26. Oh, S.Y., Jeong, S.Y., Park, T.G. and Lee, J.H., **J. Control. Release,** 1998, 51, 161.
27. Jaskari, T., Vuorio, M., Kontturi, K., Urtti, A., Manzanares, J.A. and Hirvonen, J., **J. Control. Release,** 2000, 67, 179.
28. Sung, K.C., Fang, J.Y., and Hu, O.Y., **J. Control. Release,** 2000, 67, 1.
29. Rowland, C.A. and Chilcott, R.P., **J. Control. Release,** 2000, 68, 157.
30. Ramanathan, S. and Block, L.H., **J. Control. Release,** 2001, 70, 109.
31. Creque, H., Langer, R. and Folkman, J., **Diabetes,** 1980, 29, 37.
32. Brown, L., **Diabetes,** 1986, 35, 692.
33. Kost, J., Wolfrum, J. and Langer, R., **J. Biomed. Mater. Res.,** 1987, 21, 1367.
34. Edelman, E., Kost, J., Bobeck, H. and Langer, R., **J. Biomed. Mater. Res.,** 1985, 19, 67.
35. Saslavski, O., Couvrer, P., and Peppas, N., In; Controlled Release of Bioactive Materials, Controlled Release Society, Basel, 1988, 26.
36. Kost, J., Noecker, R., Kunica, E. and Langer, R., **J. Biomed. Mater. Res.,** 1985, 19, 935.
37. Edelman, E., Brown, L., Taylor, J. and Langer, R., **J. Biomed. Mater. Res.,** 1987, 21, 339.

38. Mamada, A., Tanaka, T., Kugwatchkakun, D. and Irie, M., **Macromolecules,** 1990, 23, 1517.
39. Suzuki, A. and Tanaka, T., **Nature,** 1990, 346, 345.
40. Yui, N., Okano, T., and Sakurai., Y., **J. Control. Release,** 1993, 26, 141.
41. Bisby, R.H., Mead, C. and Morgan, C.G., **Photochem. Photobiol.,** 2000, 72, 57.
42. Bondurant, B., Mueller, A. and O'Brien, D.F., **Biochim. Biophys. Acta,** 2001, 1511, 113.
43. Trubetskoy, V.S., Whiteman, K.R., Torchilin, V.P. and Wolf, G.L., **J. Control. Release,** 1998, 50,13.
44. Hoffman, A.S., **J. Control. Release,** 1987, 6, 297.
45. Ueda, T., Ishihara, K. and Nakabayashi, N., **Macromol. Chem., Rapid Commun.,** 1990, 11, 345.
46. Urry, D.W., **Proc. Natl. Acad. Sci. U.S.A.,** 1988, 85, 3407.
47. Yoshida, M., **Drug Des. Delivery,** 1991, 7, 159.
48. Palasis, M. and Gehrke, H., **J. Control. Release,** 1992, 18, 1.
49. Okano, T., Bae, Y.H., and Kim, S.W., In; Kost, J., Eds., Pulsed and Self Regulated Drug Delivery, CRS Press, Boca Raton, Fla, 1990, 17.
50. Okahata, Y., Noguchi, H. and Seki, T., **Macromolecules,** 1986, 19, 493.
51. Katano, H., **J. Control. Release,** 1991, 16, 215.
52. Vakkalanka, S., Brazel, C. and Pappas, N., **J. Biomater. Sci. Polym.,** 1996, 8, 119.
53. Serres, A., Baudys, M. and Kim, S., **Pharm. Res.,** 1996, 13, 196.
54. Ogata, N., **J. Control. Release,** 1997, 48, 149.
55. Chung, J.F., **J. Control. Release,** 1998, 53, 119.
56. Baundys, M., Serres, A., Ramkissoon, C. and Kim, S.W., **J. Control. Release,** 1997, 48, 304.
57. Ganorkar, C.R., Liu, F., Baudys, M. and Kim, S.W., **J. Control. Release,** 1999, 59, 287.
58. Chung, J.E., Yumato, M., Yokoyama, M., Aoyagi, T., Sakurai, Y. and Okano, T., **Proc. Int. Symp. Control Release Bioact. Mater.,** 1998, 25, 380.
59. Kim, Y.H., Kwon, I.C., Bae, Y.H. and Kim, S.W., **Macromolecules,** 1995, 28, 939.
60. Fukashi, K., Sakai, K., Aoyagi, T., Yokoyama, M., Sakurai, Y. and Okanno, T., **J. Control. Release,** 1998, 55, 87.
61. Kurisawa, M., Yokoyama, M. and Okano, T., **J. Control. Release,** 2000, 69, 127.
62. Jeong, B., Bae, Y.H., and Kim, S.W., **J. Control. Release,** 2000, 63, 155.
63. Ichikawa, H. and Fukumori, Y., **J. Control. Release,** 2000, 63, 107.
64. Hinrichs, W.L.J., Schuurmans-Nieuwenbroek, N.M.E., Van de Wetering, P. and Hennink, W.E., **J. Control. Release,** 1999, 60, 249.
65. Needham, D., Anyarambhatla, G.K. and Dewhirst, M.W., **Cancer Research,** 2000, 60, 1197.
66. Ichikawa, H. and Fukumori, Y., **J. Control. Release,** 2000, 63, 107.
67. Sershen, S.R., Westcott, S.L., Halas, N.J. and West, J.L., **J. Biomed. Mater. Res.,** 2000, 51, 293.
68. Shin, Y., Chang, J.H., Liu, J., Williford, R., Sin, Y. and Exarhos, G.J., **J. Control. Release,** 2001, 73, 1.
69. Tannock, I.F. and Rotin, D., **Cancer Research,** 1989, 49, 4373.
70. Litzinger, D.C. and Huang, L., **Biochim. Biophys. Acta.,** 1992, 113, 201.
71. Bannon-Peppas, L. and Peppas, N.A., **J. Control. Release,** 1989, 8, 267.
72. Annaka, M. and Tanaka, T., **Nature,** 1992, 355, 430.
73. Firestone, B.A. and Siegel, R.A., **Polym. Commun.,** 1988, 29, 204.
74. Dong, L.C. and Hoffman, A.S., **Proc. Int. Symp. Controlled Release Bioact. Mater.,** 1990, 17, 325.
75. Kou, J.H., Fleisher, D. and Amidon, G., **J. Control. Release,** 1990, 12, 241.
76. Prandy, M. and Kopecek, J., **Macromol. Chem.,** 1990, 191, 1887.
77. Siegel, R.A., Falmarzian, M., Firestone, B.A. and Moxley, B.C., **J. Control. Release,** 1988, 8, 179.
78. Kono, A., Tabata, F. and Takagishi, T., **J. Membr. Sci.,** 1993, 76, 233.
79. Hariharan, D. and Peppas, N.A., **J. Control. Release,** 1993, 23, 123.
80. Siegel, R.A. and Firestone, B.A., **Macromolecules,** 1988, 21, 3254.
81. Allcock, H. and Ambrosio, A., **Biomaterials,** 1996, 17, 2295.
82. Bell, C. and Peppas, N., **Biomaterials,** 1996, 17, 1201.
83. Jarvinen, K., **Pharm. Res.,** 1998, 15, 802.
84. Siegel, R.A., Johannes, T., Hunt, A. and Firestone, B.A., **Pharm. Res.,** 1992, 9, 76.
85. Giannos, S., Dinh, S. and Berner, B., **J. Pharm. Sci.,** 1995, 84, 539.
86. Ghandehari, H., Kopeckova, P. and Kopec, J., **Biomaterials,** 1997, 18, 861.
87. Petka, W., **Science,** 1998, 281, 389.
88. Pillay, V. and Fassihi, R., **J. Control. Release,** 1999, 59, 229.
89. Taillefer, J., Jones, M.C., Brasseuer, N., Van lier, J.E. and Lerouse, J.C., **J. Pharm. Sci.,** 2000, 89, 52.
90. De Jaeghere, F. Allemann, E., Kubel, F., Galli, B., Cozens, R., Doelker, E. and Gumy, R., **J. Control. Release,** 2000, 68, 291.
91. Risbud, M.V., Hardikar, A.A., Bhat, S.V. and Bhonde, R.R., **J. Control. Release,** 2000, 68, 23.
92. Leroux, J.C., Roux, E., Garrec, D.L., Hong, K. and Drummond, D.C., **J. Control. Release,** 2001, 72, 71.
93. Yui, N., Okano, T. and Sakurai, Y., **J. Control. Release,** 1992, 22, 105.
94. Brown, K.E., Leong, K., Huang, C.H., Dalal, R., Green, G.D., Haimes, H.P., Jimenez, P.A. and Bathon, J., **Arthritis Rheum.,** 1998, 41, 2185.
95. Brownlee, M. and Cerami, A., **Science,** 1979, 26, 1190.
96. Makino, K., Mack, E.J., Okano, T. and Kim, S.W., **J. Control. Release,** 1990, 12, 235.
97. Sato, S., Jeong, S.Y., McRea, J.C. and Kim, S.W., **J. Control. Release,** 1984, 1, 67.
98. Sato, S., Jeong, S.Y., McRea, J.C. and Kim, S.W., **Pure Appl. Chem.,** 1984, 56, 1323.
99. Seminoff, L., **Proc. Intl. Symp. Control. Release Bioact. Mater.,** 1988, 15, 161.

100. Seminoff, L. and Kim, S.W., In; Kost, J., Ed., Pulsed and Self Regulated Drug Delivery, CRS Press, Boca Raton, Fla., 1990.
101. Kim, S.W., **J. Control. Release,** 1990, 11, 193.
102. Jeong, S.Y., Kim, S.W., Holemberg, D. and McRea, J.C., **J. Control. Release,** 1985, 2, 143.
103. Jeong, S.Y., Kim, S.W., Eenink, M.J.D. and Feijen, J., **J. Control. Release,** 1984, 1, 57.
104. Kokufata, E., Zhang, Y.Q., and Tanaka, T., **Nature,** 1991, 351, 302.
105. Taylor, M., Tanna, S., Taylor, P. and Adams, G., **J. Drug Target.,** 1995, 3, 209.
106. Obaind, A. and Park, K., **Biomaterials,** 1997, 11, 1801.
107. Obaind, A. and Park, K., **Pharm. Res.,** 1996, 13, 998.
108. Lee, S. and Park, K., **J. Mol. Recognition.,** 1996, 9, 549.
109. Kitano, S., **J. Control. Release,** 1992, 19, 161.
110. Hisamitsu, I., Kataoka, K., Okano, T. and Sakurai, Y., **Pharm. Res.,** 1997, 14, 289.
111. Heller, J. and Trescony, P.V., **J. Pharm. Sci.,** 1979, 68, 919.
112. Heller, J., Baker, R., Gale, R. and Rodin, J., **J. Appl. Polym. Sci.,** 1978, 2, 1991.
113. Ishihara, K., Muramoto, N., Fuji, H. and Shinohara, I., **J. Polym. Sci., Polym. Chem. Ed.,** 1985, 23, 2841.
114. Ishihara, K., Muramoto, N., Fuji, H. and Shinohara, I., **J. Polym. Sci., Polym. Lett. Ed.,** 1985, 23, 531.
115. Albin, G., Horbett, T., Ratner, B., In; Kost, J., Eds., Pulsed and self Regulated Drug Delivery, CRS Press, Boca Raton, Fla., 1990, 159.
116. Albin, G., Horbett, T.A., Miller, S.R. and Ricker, N.L., **J. Control. Release,** 1987, 6, 267.
117. Albin, G., Horbett, T.A., and Ratner, B.D., **J. Control. Release,** 1985, 3, 153.
118. Klumb, L.A., and Horbett, T.A., **J. Control. Release,** 1992, 18, 59.
119. Klumb, L.A., and Horbett, T.A., **J. Control. Release,** 1993, 27, 95.
120. Kost, J., Horbett, T.A., Ratner, B.D. and Singh, M., **J. Biomed. Mater. Res.,** 1985, 19, 1117.
121. Horbett, T., Kost, J. and Ratner, B., **Amer. Chem. Soc, Div. Polym. Chem.,** 1983, 24, 34.
122. Horbett, T., Kost, J. and Ratner, B., In; Shalaby, S., Hoffman, A., Horbett, T. and Ratner, B. Eds., Polymers as Biomaterials, Plenum, New York, 1984, 193.
123. Ishihara, K., **Proc. Int. Symp. Control. Release Bioact. Biomater.,** 1988, 15, 168.
124. Ishihara, K. Kobayashi, M. and Shonohara, I., **Macromol. Chem., Rapid Commun.,** 1983, 4, 327.
125. Ishihara, K., Kobayashi, M., Ishimaru, N. and Shinohara, I., **Polym. J.,** 1984, 16, 625.
126. Ishihara, K. and Matsui, K., **J. Polym. Sci. Polym. Lett. Ed.,** 1986, 24, 413.
127. Podual, K., Peppas, N. and Doyle, F., **Proc. Int. Symp. Control. Release Bioact. Mater.,** 1998, 25, 135.
128. Iwata, H. and Matsuda, T., **J. Membr. Sci.,** 1988, 38, 185.
129. Iwata, H., **Proc. Int. Symp. Control. Release Bioact. Mater.,** 1988, 15, 170.
130. Ito, Y., Casolaro, M., Kono, K. and Imanishi, Y., **J. Control. Release,** 1989, 10,195.
131. Siegel, R. In; Kost, J., Eds., Pulsed and Self Regulated Drug Delivery, CRS Press, Boca Raton, Fla., 1990, 129.
132. Siegel, R.A. and Firestone, B.A., **J. Control. Release,** 1990, 11, 181.
133. Siegel, R., In; Park, K., Eds., Controlled Drug Delivery: Chalanges and Strategies, American Chemical Society, Washington, D.C., 1997, 127.
134. Heller, J., Sparer, R.V. and Zenter, G.M. In; Chasin, M. and Hanger, R. Eds. Biodegradable Polymers as Drug Delivery Systems, Marcel Dekker, New York, 1990, 121.
135. Heller, J., **Adv. Drug Del. Rev.,** 1993, 10, 163.
136. Brown, L., Edelman, E., Ghodsian, F. and Langer, R., **Proc. Int. Symp. Control. Release Bioact. Mater.,** 1988, 15, 116.
137. Brown, L., Edelman, E., Fieshel-Ghodsian, F. and Langer, R., **J. Pharm. Sci.,** 1996, 85, 1341.
138. Roskos, K., Tefft, V. and Heller, J., **Clin. Mater.,** 1993, 13, 109.
139. Roskos, K.V., Fritzinger, J.A., Tefft, J.A. and Heller, J.A., **Biomaterials,** 1995, 16, 1235.
140. Roskos, K.V., Tefft, J.A., Fritzinger, B.K. and Heller. J., **J. Control. Release.,** 1992, 19, 145.
141. Tefft, J.A., Roskos, K.V. and Heller, J., **J. Biomed. Mater. Res.,** 1992, 26, 713.
142. Nakayama, G.R., Roskos, K.V. and Fritzinger, B.K. and Heller, J., **J. Biomed. Mater. Res.,** 1995, 29, 1389.
143. Heller, J., Chang, A.C., Rodd, G., and Grodsky, G.M., **J. Control. Release,** 1990, 13, 295.
144. Pitt, C.G., **J. Control. Release,** 1985, 2, 363.
145. Pitt, C.G., **Pharm. Int.,** 1986, 88.
146. Pitt, C.G. In; Kost, J. Eds., Pulsed and Self-Regulated Drug Delivery, CRC Press, Boca Raton,1985, 117.
147. Golenser, J., Domb, A., Teomim, D., Tsafack, A., Nisim, O., Ponka, P., Eling, W. and Cabantchik, Z.I., **J. Pharmacol. Exp. Ther.,** 1997, 281, 1127.