

Stimuli-induced Pulsatile or Triggered Release Delivery Systems for Bioactive Compounds

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Abstract: As is frequently found in the living body, many vital functions are regulated by pulsed or triggered release of bioactive substances at a specific site and time. Thus it is important to develop new drug delivery devices to achieve pulsed delivery of a certain amount of drugs in order to mimic the function of the living systems to minimize the undesired side effects. The pulsed or triggered delivery systems are designed to alter their rate of drug delivery in response to stimuli such as changes in a specific molecule, a magnetic or electric field, temperature, light or mechanical forces. Such systems are suitable for the release of therapeutics that benefit from non-constant plasma concentrations. In this article, several types of drug delivery systems which cause the pulsed or triggered release of bioactive compounds due to certain external stimuli, mostly focuses on thermally-, electrically- and magnetically- induced release are described in detail. The recent patents on various delivery systems which release the active compounds only with the external stimuli are described in detail.

Keywords: Pulsatile release, triggered release, bioactive compounds, reservoir devices, thermo-responsive, electro-responsive.

INTRODUCTION

Major efforts, in both academic and industrial laboratories, have been directed towards developing effective formulations for peptide and protein drug candidates for the past several decades. With the development of genetic engineering, a variety of macromolecular, potent therapeutic agents such as, human growth hormones (hGH), interferon beta 1-b (IFNB), interleukin-2 (IL-2), colony stimulating factors (CSF), and others have become available. However, in spite of these major efforts, relatively little progress has been made in reaching the target of safe and effective formulations for peptides and proteins. The main barriers to get success in formulating to get maximum bioavailability for these drugs are normally ascribed to: i) poor intrinsic permeability of peptides and proteins across biological membranes due to their hydrophilic nature and large molecular size; ii) susceptibility to enzymatic attack by gastrointestinal proteases and peptidases; iii) rapid post-operative clearance; and iv) chemical instability, including tendencies to aggregate and/ or nonspecifically absorbed to a variety of physical and biological surfaces [1,2].

The number of products based on new drug delivery systems has significantly increased in the past few years, and this growth is expected to continue in the near future. Recent advances in the field of genomics of biopharmaceuticals, and today a large number of companies are busy developing protein-and peptide-based drugs. Incorporating an existing medicine into a new drug delivery system can significantly improve its performance in terms of efficacy, safety and improved patient compliance. The need for delivering drugs to patients efficiently and with fewer side effects has prompted pharmaceutical companies to engage in the

development of new drug delivery systems. Today, drug delivery companies are engaged in the development of multiple platform technologies for controlled release, delivery of larger molecules, liposomes, taste-masking, oral fast dispensing dosage forms, technology for insoluble drugs and delivery of drugs through intranasal, pulmonary, transdermal, vaginal, colon, intramammary and transmucosal routes.

Over the last two decades, the field of controlled drug delivery has been faced with two major challenges. One has been achieving sustained zero-order release of a therapeutic agent over a prolonged period of time. This goal has been met by a wide range of techniques, including osmotically driven pumps [3], matrices with controllable swelling [4], diffusion [5], or erosion rates [6], non-uniform drug loading profiles [7-9], and multi-layered matrices [10-12]. The second of these challenges is the controlled delivery of therapeutic molecules or protein in a pulsatile or triggered fashion. Two different methodologies have been broadly investigated as possible solutions to these requirements. One is the fabrication of a delivery system that releases its payload at a predetermined time or in pulses of a predetermined sequence. The other is to develop a system that can respond to changes in the local environment. These systems have been shown to alter their rate of drug delivery in response to stimuli including the presence or absence of a specific molecule, magnetic fields, ultrasound, electric fields, temperature, light, and mechanical forces. Such systems are suitable for release of therapeutics that benefit from non-constant plasma concentrations. Treatment of diabetes with insulin is an example where this type of delivery system is expected to be beneficial.

Pulsatile release is commonly found in the body, for example during hormone release, in which a baseline release is combined with pulsed, one-shot type release within a short time range [13,14]. Insulin is one good example of a

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hormone experiences pulsatile release in the body. Basal release of insulin stimulates the synthesis of proteins and glycogen in muscle and adipose tissues. In addition, pulsatile insulin release is observed during and after the intake of foods to regulate blood glucose levels in the body. Pulsatile release of gastrointestinal hormones, stimulated by existence of the food in the gastrointestinal tract, generally causes the release of digestive enzymes from pancreas and stomach. Many other hormones, including follicle stimulating hormone (FSH), leutinizing hormone (LH), leutinizing hormone releasing hormone (LHRH), estrogen and progesterone are regulated in the body in pulsatile manner. Many biological functions in the body are thus regulated by the temporal and pulsatile release of hormones. A continuous dose of hormones generally induces down regulation of hormone receptors on the target cellular membranes and shows undesired side effects in the body. To prevent the down regulation of hormone receptors and to achieve efficient therapeutic effects, the pulsatile release system is recognized as one of the most important technologies necessary for an intelligent drug delivery that is able to regulate drug release in response to the external chemical, physical and biological stimuli. This has application in field such as insulin delivery, contraceptive programme, controlled animal breeding and growth promotion [15].

Pulsatile devices may have many applications in areas of other medicine where a constant rate of drug release does not match the physiological requirements of the body. This is often the case when treatments involve hormone-based drugs. Secretion of many hormones exhibits pulsatile patterns comprising frequent pulses over periods from hours to weeks [16], so it is more effective to mimic this with a synthetic delivery system. Current research in the field of drug delivery devices, by which triggered and/or pulsatile release is achieved, has been intensified. This review article focuses on recent developments on several types of responsive delivery systems due to external stimuli, using various formulations such as microparticles, coarse particulates, large solid implants, hydrogels that showed triggered and/or pulsatile drug delivery characteristics.

STIMULI INDUCED PULSATILE/ TRIGGERED RELEASE SYSTEM

Several polymeric delivery systems undergo phase transitions and demonstrate marked swelling-deswelling changes in response to environmental changes including solvent composition ionic strength, temperature, electric fields, and light [17]. Responsive drug release from those systems results from the stimuli-induced changes in the gels or in the micelles, which may deswell, swell, or erode in response to the respective stimuli. The mechanisms of drug release include ejection of the drug from the gel as the fluid phase synerges out, drug diffusion along a concentration gradient, electrophoresis of charged drugs towards an oppositely charged electrode and liberation of the entrapped drug as the gel or micelle complex erodes.

THERMO-RESPONSIVE PULSATILE/ TRIGGERED RELEASE

Temperature is the most widely utilized triggering signal for a variety of triggered or pulsatile drug delivery systems.

The use of temperature as a signal has been justified by the fact that the body temperature often deviates from the physiological temperature (37°C) in the presence of pathogens or pyrogens. This deviation sometimes can be a useful stimulus that activates the release of therapeutic agents from various temperature-responsive drug delivery systems for diseases accompanying fever. The drug delivery systems that are responsive to temperature utilize various polymer properties, including the thermally reversible coil/globule transition of polymer molecules, swelling change of networks, glass transition and crystalline melting.

Thermoresponsive hydrogels have been investigated as possible drug delivery carriers for stimuli-responsive drug delivery systems. Hydrogels are crosslinked networks of biological, synthetic, or semi-synthetic polymers. Because hydrogel polymer chains are held together by crosslinking, they behave like solids, despite the fact that they contain at least 20% moisture content. A significant property of hydrogels is the equilibrium degree of swelling (Q), which is the amount of water absorbed by the gel expressed as the ratio of swollen gel volume (or mass) to dry gel volume (or mass). Many hydrogels are responsive to external stimuli in that they expel or absorb water in response to changes in pH, and other external stimuli. The resulting change in hydrogel water content results in a corresponding reversible change in volume.

Hydrogels that undergo reversible volume changes in response to changes in temperature are known as thermo-sensitive gels. These gels shrink at a transition temperature that is related to the lower critical solution temperature (LCST) of the linear polymer from which the gel is made. Specifically, typically thermo-sensitive hydrogels have a certain affinity for water, and thus swell at temperatures below the transition temperature, whereas they expel water and thus shrink or “deswell” at temperatures above the transition temperature. However, one of the common characteristics of temperature-sensitive polymers is also the presence of hydrophobic groups, such as methyl, ethyl and propyl groups. Of the many temperature-sensitive polymers, poly(N-isopropylacrylamide) (PNIPAA) is probably the most extensively used. PNIPAA cross-linked gels have shown thermoresponsive, discontinuous swelling/deswelling phases; swelling, for example temperatures below 32°C, while shrinking above this temperature. A sudden temperature increase above the transition temperature of these gels resulted in the formation of a dense, shrunken layer on the gel surface, which hindered water permeation from inside the gel into the environment. Drug release from the PNIPAA hydrogels at temperatures below 32°C was governed by diffusion, while above this temperature drug release was stopped completely, due to the ‘skin layer’ formation on the gel surface (on-off drug release regulation) [18-20]. The hydrogels made of polymer PNIPAA due to its uncertain biocompatibility, it is still questionable to be safely used in drug delivery system.

Kaneko *et al.* [21] introduced a method to accelerate gel swelling/deswelling kinetics based on the molecular design of the gel structure, by grafting the free mobile linear PNIPAA chains within the cross-linked PNIPAA hydrogels. These novel-graft types PNIPAA gels had the same transition

temperature as the conventional cross-linked PIPPAm gels and existed in the swollen state below the transition temperature, while above this temperature, they shrank. A dense skin layer formed on the conventional PIPPAm gels upon temperature change above the transition temperature, which limited the complete shrinkage of the gel. In contrast, the PNIPPA-grafted gels showed rapid deswelling kinetics without the formation of a skin layer on the gel surface. This is probably due to the rapid dehydration of the graft chains formed by hydrophobic aggregation on the three-dimensional cross-linked gel chains. The low molecular weight compounds released immediately from conventional PIPPAm gels after a temperature increase, after which the release was terminated due to the formation of a dense impermeable skin layer on the surface. In comparison, 65% of the drug was released in one burst from free PIPPAm-grafted hydrogels with a graft molecular weight of 9000, following the temperature increase. Graft-type gels with a molecular weight of 4000 showed oscillating drug release profiles. The release of high molecular weight compound (e.g. Dextran, MW 9300) from PIPPAm graft type gels was shown to burst after a temperature increase of 40°C, while release was suppressed from IGG 4000. The difference in drug release profiles for two graft-type gels is probably due to the different strengths of aggregation forces between the formed hydrophobic cores within the graft-type gels. That is the large molecular weight graft chains formed more hydrophobic cores within the gels upon the temperature increase, which induced rapid gel deswelling. In contrast, aggregation forces between graft chains in IGG 4000 were relatively weak, thus leading to the formation of skin layer on the gel surface, which limited the drug diffusion from gel interior.

A similarly rapid deswelling phase was achieved by incorporating poly(ethylene glycol) (PEG) graft chains into PIPPAm cross-linked hydrogels [22]. The introduction of PEG chains did not alter the transition temperature. This is due to the structural independence of the PEG chains from the cross-linked PIPPAm main chains. In this case, however, deswelling mechanism is different from PIPPAm graft-type gels. During the shrinking process, the graft PEG chains formed hydrophilic channels for water molecules, most likely due to a phase separation within the shrinking gels. Therefore, a rapid deswelling was achieved. The majority of the drugs in the gels were release through the PEG formed channels with water molecules. By introduction of graft chains independent from main chains of gel, can accelerate the deswelling of cross-linked hydrogels and could be activated by temperature change to achieve the pulsed release of compounds.

Recently, some studies have conducted on nanocomposite hydrogels for photo-thermally modulated drug delivery. Gold nanoshells can be designed to absorb light strongly at desired wavelengths, in particular, in the near infrared between 800-1200 nm where tissue is relatively transparent. When optically absorbing gold nanoshells are embedded in a matrix material, illuminating them at their resonance wavelength causes the nanoshells to transfer heat to their local environment. This photothermal effect can be used to optically modulate drug release from a non-shell polymer composite drug delivery system [23]. They

observed the pulsatile release of insulin and other proteins in response to near-infrared irradiation, when gold nanoshells were embedded in NIPAAm-co-acrylamide hydrogels.

Clinical applications of thermosensitive hydrogels based on NIPAAm and its derivatives have limitations. The monomers and crosslinkers used in the synthesis of the hydrogels are still not known to be biocompatible and biodegradable. The observation that acrylamide-based polymers activate platelets upon contact with blood, together with the unclear metabolism of poly(NIPAAm), requires extensive toxicity studies before clinical applications can merge [24].

Temperature-sensitive hydrogels can also be placed inside a rigid capsule containing holes or apertures. The on-off release is achieved by the reversible volume change of temperature-sensitive hydrogels [25,26]. Such a device is called a squeezing hydrogel device because the drug release is affected by the hydrogel dimension. In addition to temperature, hydrogels can be made to respond to other stimuli, such as pH. In this type of system, the drug release rate was found to be proportional to the rate of squeezing of the drug-loaded polymer.

The reverse thermo-responsive phenomenon is also known as Reversed Thermal Gelation (RTG). The gel obtained from such types of polymers display low viscosity at ambient temperature, and exhibit a sharp viscosity increase as temperature rises within a very narrow temperature interval, producing a semi-solid gel once they reach the body temperature. US Patent 4188373 [27] describes the use of this system using a type of polyol polymer, such as Pluronic^R. Adjusting the concentration of the polymer gives the desired liquid-gel transition. However, concentrations of the polyol polymer of at least 15-20% by weight are needed to produce a composition which exhibits such a transition at commercially or physiological temperatures. Also, solutions of these concentrations are typically very viscous even under the lower viscosity state of responsiveness, so that these solutions cannot function under conditions where viscosity low, free-flowing is required prior to transition. The high concentrations of these polymers may cause unfavorable interactions during use under physiological conditions. While US Patent 5252318 [28] reports reversible gelling compositions which are made of physical blends of a pH-sensitive gelling polymer (such as a cross-linked polyacrylic acid) and a temperature-sensitive gelling polymer (such as methyl cellulose or block copolymers of polyoxoethylene and polyoxopropylene). This patent also describes a gel system from the mixtures of polyoxyethylene and polyoxypropylene condensed with ethylenediamine. This system is liquid at room temperature but forms a semi-solid when warmed to about body temperature. These both types of systems which exhibit reversible gelation are limited in that they require large solids content and/ or in that the increase in viscosity are less than 10-fold.

To overcome these problems, US Patent 5939485 [29] describes responsive polymer networks exhibiting the property of reversible gelation or viscosification, triggered by a change in diverse environmental stimuli, such as temperature, pH and ionic strength and which have improved stability over simple blends of the constituent polymers. The

gelling polymer network is comprised of less than 4% of total polymer solids of which less than about 2 wt% is the responsive component and less than 2 wt% is the structural component. The responsive component is a triblock polyol having the formula (ethylene oxide, EO) (Polyethylene oxide, PO) (EO) while the structural component is sodium acrylate. The viscosity of this system increases at least 5-fold with the increase in temperature of about 5°C.

US Patents 6733788 [30] and 20020015712A1 [31] describe a medical device containing thermo-sensitive cellulose gel structure, which can deliver the bioactive solute compounds to a target location in the body. The gel structure deswells at certain temperature and expels the biologically active solute with an increase in gel temperature. The cellulose gels release the solute upon shrinking in a sustained, convective release pulse such that substantially all of the loaded solute is released in a relatively short period of time with the influence of increased temperature of the body.

The polymer network is characterized by the positive molecular interactions existing between the different components of the system. These interactions may be physical in nature, such as chain entanglements, or chemical such as ionic interactions, hydrogen bonding, Van der Waals attractions and covalent bonding. In addition to these types of interactions, physical interactions, such as entanglement and templating, contribute to the interacting nature of these polymers which may provide a unique synergistic properties. US Patent 5503893 [32] discloses a polymer network in which the interpolymer attractions are strong enough to permit a three-dimensional polymer network without the use of covalent cross-linking between the constituent polymers. The polymer gel exhibits a volume change in response to an external trigger. US Patent 20030078339A1 [33] provides a class of semi-interpenetrating polymeric networks that include a linear polymer molecule functionalized with a bioactive moiety. The linear polymer is physically entangled with a bioactive moiety. The polymer network which can be used as matrices in tissue engineering, flowable at room temperature, becoming solid or semi-solid at elevated temperatures, such as at mammalian body temperature.

The increased temperature may enhance the micro-circulation and drug solubility. A prolonged period of heat application may slightly decrease the barrier property of the skin, which may result in increased irritation as well as uncontrolled levels of drug in the skin and systemic circulation. Certain patch-like heating devices have been disclosed in which heat is chemically generated by oxidation that is modulated by varying the exposure of the patch surface to oxygen. Such a device, when placed on top of a passive transdermal patch, is reported to increase the temperature of skin and subsequently the absorption of drug being administered by the patch. US Patents 5226902 [34] and 6488959 [35] have proposed to use short and rapid bursts of thermal energy to create pores in the surface of the skin, which may be done by including an external device that provides a heat source to metallic filaments embedded in the patch. While US Patent 0135911A1 [36] invented a trans-body-surface drug delivery device for the administration of bioactive molecules to an individual at a therapeutically effective rate. The device includes a reservoir with bioactive

compounds and a thermoeffector having a first surface that is controllable of either heating or cooling to affect passage rate of the bioactive molecules through the body surface. An effective way to control the amount of bioactive molecules is to control the amount of bioactive compounds' compositions that is available to the body surface. The system comprises thermo-responsive gel which has capability of reversible swelling and de-swelling to control the release of embedded bioactive molecules.

ELECTRO-RESPONSIVE PULSATILE/ TRIGGERED RELEASE

An electric field as an external stimulus has advantages such as the availability of equipment, which allows precise control with regards to the magnitude of current, duration of electric pulses, interval between pulses etc. Electrically responsive delivery systems are prepared from polyelectrolytes (polymers which contain relatively high concentration of ionisable groups along the backbone chain) and are thus, pH-responsive as well as electro-responsive. Under the influence of electric field, electro-responsive hydrogels generally deswell or bend, depending on the shape of the gel lies parallel to the electrodes whereas deswelling occurs when the hydrogel lies perpendicular to the electrodes. Synthetic as well as naturally occurring polymers, separately or in combination, have been used. Examples of naturally occurring polymers include hyaluronic acid, chondroitin sulphate, agarose, carbomer, xanthan gum and calcium alginate. The synthetic polymers are generally acrylate and methacrylate derivatives such as partially hydrolyzed polyacrylamide, polydimethylaminopropyl acrylamide. Many of these gels are prepared by either cross-linking the water-soluble polymers using radiation or chemical agents such as Ca^{2+} , ethylene diglycidylether, N,N'-methylenebis acrylamide, ethylene glycol dimethacrylate or by free-radical polymerization of monomers. Complex multi-component gels or interpenetrating networks have been prepared in order to enhance the gels or interpenetrating networks have also been prepared in order to enhance the gel's electro-responsiveness [37]. They prepared calcium alginate/poly(acrylic acid) composites, where the polyacrylic acid (PAA) chains were expected to be entangled through the calcium alginate matrix. PAA, which contains a large number of free carboxylic groups, was included to increase the gel's sensitivity to pH and electrical stimuli. The increased proportion of PAA in the composites led to a greater pH- and electro-response. Such enhanced electro-response upon increasing the proportion of the ionisable groups in the gels has also been demonstrated in interpenetrating networks of polyvinyl alcohol and polyacrylic acid [38]. Kwon *et al.* [39] synthesized a different type of electro-responsive hydrogel. The gels were formed when two aqueous polymer solutions were mixed and a complex was formed due to hydrogen bonding or ionic bonding between the polymers over a certain pH range. When the polycationic polyamine solution was mixed with the polyanionic heparin solution, a complex was formed via ionic bonding between the positively charged NH_3^+ groups in polyallylamine and the COO^- and SO_3^- groups in heparin, over the broad pH range 3-10. They also achieved 'on-off' drug release utilizing a polyethyloxazoline (PEO) and polymethacrylic acid (PMAA) from solid complexes by hydrogen bonding

below pH 5, but the complexes dissolve above pH 5.4. When an electric current was applied through the disk-shaped matrix of the complex in a saline solution, the matrix dissolved at the surface facing the cathode because local pH increase near the cathode and resultant hydrogen bonding was disrupted. Insulin released from the matrix with dissolution in response to application of the electric current.

Kiser *et al.* [40] has designed lipid-coated microgels for the triggered release of drugs. Ionic microgels are synthesized from the monomers of methylenebisacrylamide (MBAM), methylacrylic acid (MAA) and 4-nitrophenyl methacrylate (NPMA) and coated with a lipid bilayer. The release of drug is triggered from the gels using either lipid-solubilizing surfactants or electroporation. The authors described the events for the swelling and release of drugs in three stages: i) the permeability of the membrane might be sufficiently compromised (e.g. by electroporation or membrane dissolution or other permeabilizing species), but only to an extent that allows proton efflux from the microgel and a sodium ion influx into the gel particle; ii) microgel begins to swell due to occurrence of exchange process, allowing additional ions to be transported across the membrane and so that disruption of membranes causes uncoating of microgel; and iii) drug is exchanged from the hydrogel by Na^+ ions and diffuse down its concentration gradient out of the expanded polymer network into the surrounding medium over a period of time, resulting in a triggered release.

Electronic microelectromechanical devices are manufactured using standard microfabrication techniques that are used to create silicon chips for computers, and they often have moving parts or components that enable some physical or analytical function to be performed by the device. Microfabrication techniques, the same processing techniques used to make microprocessors for computers and other microelectronic devices, have been used increasingly to produce microscale devices whose primary functions are mechanical, chemical and optical in nature; such devices are commonly referred to as "microelectromechanical systems" (MEMS). MEMS are found in ink-jet printers, automotive applications, and microtube engines used in the aerospace industry. MEMS for biological applications are classified as either microfluidic devices or nonmicrofluidic devices. The ultimate goal of MEMS is to develop a microfabricated device with the ability to store and release multiple chemical substances on demand by a mechanism devoid of moving its parts [41,42]. A wide variety of microreservoirs, micropumps, cantilevers, rotors, channels, valves, sensors and other structures have been fabricated, typically from the materials that have been demonstrated to be biocompatible and can be sterilely fabricated and hermetically sealed.

The usage of MEMS is triggered, particularly pulsatile delivery of drugs represents a new area of study that is to be explored. The digital capabilities of MEMS may allow greater temporal control over drug release compared to traditional polymer-based systems, while the batch-processing techniques used in the microelectronics industry can lead to greater device uniformity and reproducibility than is currently available to the pharmaceutical industry. The use of MEMS for drug delivery necessitates the

existence of drug depot or supply within or on the device. One straightforward approach to achieve this drug reservoir is the fabrication of silicon microparticles that contain an internal reservoir loaded with drug [43]. These devices could be used for oral drug delivery, with release of the drug triggered by binding of a surface-functionalized molecule to cells in the digestive tract.

The completely implantable minipump made by Minimed^R, has also a pulsatile, radio-controlled injection rate through a catheter into the intraperitoneal region. One study found that patients with the implantable pump did not differ from control subjects on any measure of psychosocial function but that pump users monitored their blood glucose levels more frequently and had lower average blood glucose levels [44]. Even though this type of device may improve patient's mobility and reduce infections by eliminating transcutaneous catheters, they may still be hampered by their size, cost, ability to deliver only drugs in solution, and the limited stability of some drugs in solution at 37°C. Ikemoto and Sharpe [45] have developed a stepmotor micropump for the injection of nanolitre volumes of D-amphetamine solution into discrete brain regions of freely moving rats was well tolerated. This micropump delivered a reliable volume of 50 nl per infusion over an hour at a rate of one infusion per minute.

Another development in MEMS technology is the microchip. The microchip consists on an array of reservoirs that extend through an electrolyte-impermeable substrate. The prototype microchip is made of silicon and contains a number of drug reservoirs, each reservoir is sealed at one end by a thin gold membrane of material that serves as an anode in an electrochemical reaction and dissolves when an electric potential is applied to it in an electrolyte solution; the reservoirs are filled with any combination of drug or drug mixtures in any form (i.e. solid, liquid or gel) through the opening opposite the anode membrane by ink jet printing or microinjection, and are then sealed with a waterproof material. A cathode is also required for the electrochemical reaction to take place; the cathode is usually made of the same conductive material as the anode to simplify the fabrication procedure. The device is submerged in an electrolyte solution containing ions, and upon electric stimulation forms a soluble complex with the anode in its ionic form. When release is desired, an electric potential is applied between an anode membrane and a cathode, the gold membrane anode dissolved within 10-20 seconds and allows the drug in the reservoir to be released. This electric potential causes oxidation of the anode material to form a soluble complex with the electrolytes which then dissolves allowing release of the drug [42]. Complex release patterns (such as simultaneous constant and pulsatile release) can be achieved from the microchips. Microchip has the ability to control both release time and release rate. The rate of release from a reservoir is a function of the dissolution rate of the materials in the reservoir, the diffusion rate of these materials out of the reservoir, or both. Therefore, the release rate from an individual reservoir can be tailored to a particular application by the proper selection of the materials placed inside the reservoir (e.g. pure drug (s), drugs with polymers etc.). The pulsatile release can be achieved by using materials that quickly dissolve when the reservoir is opened.

Microchip delivery devices, described in US Patents 579898 [46], US2006123861 [47] and 0121486 [48] provide a means to control both the rate and time of release of variety of bioactive molecules, in either a continuous or pulsatile manner. Hundreds or thousands of reservoirs can be fabricated on a single microchip. The molecules to be delivered are inserted into the reservoirs by injection or spin coating methods in their pure form or in a release system. The release systems include polymers and polymeric matrices, non-polymeric matrices, and other common excipient or diluents. The physical properties of the release system control the rate of the release of molecules. The reservoirs can contain multiple drugs or other molecules in variable dosages. The filled reservoirs are capped with materials that either degrade or allow the molecules to diffuse passively out of the reservoir over time or materials that oxidize and dissolve with the use of electric potentials. Release from an active device is controlled by a preprogrammed microprocessor, remote control, or by biosensors. These devices have also been found a means for storing the bioactive compounds in their most stable form. These patents describe, for example, implanting the microchip devices by themselves into a patient for delivery of bioactive molecules. Still it needs to adapt the precise control of molecule release from these microchips into a variety of other applications. Recently, US Patents 20060057737A1 [49] and 20060178655A1 [50] describe about a device and method for the time and/ or rate-controlled release of one or more drugs. The device includes implan-table microchips which have reservoirs containing the bioactive compounds for the triggered or controlled release. The microchip devices include i) a substrate, ii) at least two reservoirs in the substrate containing the molecules for release, and iii) a reservoir cap positioned on, or within a portion of, the reservoir and over the molecules, so that the molecules are controllably released from the device by diffusion through or upon disintegration or rupture of the reservoir caps. Each of the reservoirs of a single microchip can contain different molecules and/or different amounts and concentrations, which can be released independently. The filled reservoirs can be capped with materials that passively or actively disintegrate. Passive release reservoir caps can be fabricated using materials that allow the molecules to diffuse passively out of the reservoir over certain time. Active release reservoir caps can be fabricated using materials that disintegrate upon application of electrical, mechanical, or thermal energy. Release from an active device is also controlled by a preprogrammed microprocessor, remote control, or by biosensors. Similar types of devices have been described in US Patents 20060121486A1 [51] and 20060100608A1 [52]. The device includes a reservoir cap formed of an electrically conductive material, which prevents the reservoir contents from passing out from the device and prevents exposure of the reservoir contents to molecules outside of the device; electrical input and output leads connected to the reservoir cap, such that upon application of an electrical current through the reservoir cap, via the input and output lead, the reservoir cap ruptures to release or expose the reservoir contents.

It would be advantageous to have micro-reservoir devices that have a high area density in order to pack more reservoir

contents into as small a total device volume as possible, particularly for applications where the device is to be implanted for controlled drug delivery or biosensing. It is thus, desirable to develop improved devices and new methods of making them in which the reservoir volume in these devices can be increased without adversely affecting the area density of reservoirs on/ in a substrate. US Patent 20060105275A1 [53] describes a modified fabrication methods and structures for micro-reservoir devices. The multi-reservoir device comprising i) patterning one or more photoresist layers on a substrate; ii) depositing onto the substrate at least one metal layer by a sputtering process to form a plurality of reservoir caps and conductive traces; iii) removing the photoresist layers using a liftoff process; iv) forming a plurality of reservoirs in the substrate; v) loading each reservoir with bioactive molecules; and vi) sealing of each reservoir. The reservoir cap comprises a first conductive material coated with one or more protective metal films, such as of gold, platinum, silicon carbide, silicon dioxide and platinum silicide. In alternative approach, the reservoirs may comprise interior sidewalls of silicon doped with boron or another impurity to enhance the resistance of the silicon to etching under *in vivo* conditions under the application of electric impulses.

MAGNETICALLY INDUCED PULSATILE/ TRIGGERED RELEASE

The use of an oscillating magnetic field to modulate the rates of drug release from polymer matrix was one of the old methodologies. Magnetic carriers receive their magnetic response to a magnetic field from incorporated materials such as magnetite, iron, nickel, cobalt etc. For biomedical applications, magnetic carriers must be water-based, biocompatible, non-toxic and non-immunogenic.

Saslowski *et al.* [54] developed different formulations for *in vitro* magnetically triggered delivery of insulin based on alginate spheres. In an experiment, ferrite microparticles (1 μm) and insulin powder were dispersed in sodium alginate aqueous solution. The ferrite-insulin-alginate suspension was later dropped in aqueous calcium chloride solution which causes the formation of crosslinked alginate spheres, which were further crosslinked with aqueous solution of poly(L-lysine) or poly-(ethylene imine). They described that the magnetic field characteristics due to ferrite microparticles and the mechanical properties of the polymer matrices could play roles in controlling the release rates of insulin from this system. They investigated the effect of magnetic field frequency and repeated-field application on insulin release from alginate matrices. They found the inverse effects with repeated applications as high frequency 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 polymer matrix also affect the extent of magnetic enhancement. Higher release rate enhancement was found with less rigid crosslinked alginate matrices.

Another mechanistic approach based on magnetic attraction is the slowing down of oral drugs in the gastrointestinal system. This is possible by filling an additional magnetic component into capsules or tablets. The speed of travel through the stomach and intestines can then

be slowed down at specific positions by an external magnet, thus changing the timing and/ or extent of drug absorption into stomach or intestines. Slowing down the passage of magnetic liposomes with a magnet actually increased the blood levels of drug [55]. Babincova *et al.* [56] had developed magnetoliposomes for triggered release of drug. In their delivery systems, they entrapped dextran-magnetite and model drug, 6-carboxyfluorescein in the liposomes and used laser as triggering the release of model agent. The magnetite absorbs the laser light energy to heat the lipid bilayer above the gel-liquid crystal phase transition temperature T_c , which is 41°C for dipalmitoylphosphatidylcholine. Liposomes made from this lipid release their content as soon as temperature is reached to this level. They have also suggested that the absorption of laser energy by magnetite particles provide a means for much localized heating and controlled release of liposome with a single laser pulse. This may have potential applications for selective drug delivery especially to the eye and skin. Even though the magnetic modulated therapeutic approach is one of the promising, it still needs very careful attention for a number of physical and magnetism-related properties. The magnetic force, which is defined by its field and field gradient, needs to be large and carefully shaped to activate the delivery system within the target area. The magnetic materials should be tissue stable and compatible.

US Patent 20016251365 [57] describes about the magento-somes comprising magnetic monocrystals having a maximum diameter of 45 nm surrounded by a phospholipids membrane and their use in triggered release in the body. The membrane consists of phosphatidylethanolamine, phosphatidyl glycerol and phosphatidyl choline containing mainly the fatty acids such as palmitic acid, palmitoleic and oleic acid. These magnetosomes having cationic charge increase the probability that the antibodies and therapeutic agents can be correctly bound to them. The US Patent 20036514481B1 [58] describes about the nanosized particles termed as “nanoclinics” or “nanoparticles” or “nanobubbles”. These nanoparticles are prepared from iron oxide particles and are synthesized using a reverse micelle colloidal reaction. After the synthesis of ferric oxide particles, a multi-step synthetic process is used to fabricate the nanoparticles. A tracking agent such as a two photon is attached to the surface of the particles to track the nanoparticles using two-photon laser scanning microscopy. Silica (sodium salt) is added to perform the silica shell. A carbon spacer is then attached to the silica surface. The spacer reduces the steric hindrance for the binding of the targeting agent to its target molecule. A target molecule is then attached to the spacer. These nanoparticles can be used for lysis of cells, such as for the treatment of cancer. For the lysis of tumor cells, the targeting agent is selected based on the molecules on the surface of the tumor cells. Following binding and/ or internalization of the nanoparticles by the tumor cells, the particles are exposed to DC magnetic field. DC magnetic field can be obtained by standard Magnetic Resonance Imaging (MRI) equipment which typically has a magnetic field in the range of 0.1 to 5 Tesla.

Hyperthermia for treatment of disease using magnetic fluids exposed to radio-frequency (RF) fields has been recognized for several decades. However, a major problem

with magnetic fluid hyperthermia has been the inability to selectively deliver a lethal dose of particles to the cells or pathogens. US Patent 2006997863B2 [59] provides a treatment method that involves the administration of a magnetic material composition, which contains single-domain magnetic particles attached to a target-specific ligand, to a patient and the application of an alternating magnetic field to inductively heat the magnetic material composition, which cause the triggered release of therapeutic agents at the target tumor or cancerous cells.

CURRENT & FUTURE DEVELOPMENTS

The number of products based on new drug delivery systems has significantly increased in the past few years, and this growth is expected to continue in the near future. Incorporating an existing medicine into a new drug delivery system can significantly improve its performance in terms of efficacy, safety and improved patient compliance. Delivery systems with a pulsatile or triggered release pattern are receiving increasing interest for the development of various drugs, where conventional systems with a continuous release are not ideal. Biomicroelectronic and microfabricated systems are actively targeted by many researchers and even by companies. A commercially available microchip, ChipRx, which integrates silicon and electroactive polymer technologies for controlled delivery and micromachined particles for a variety of drug delivery applications. Products that are currently under development for commercialization are external and implantable microchips for the delivery of proteins, hormones, pain medications, and other pharmaceutical compounds. Microchips can be developed as a “medicine on a chip” because different drugs can be placed in different reservoirs of the same microchip, and the release could be achieved by applying the electrical potential to a specific reservoir. Some of the current programmable drug delivery systems that employ polymer-based include Covera-HS, Verelan PM, Cardizem LA, Innopran XL, Uniphyl, and naproxen sodium from Andrx Pharmaceuticals [60]. The major drawbacks in these polymer-based triggered release systems arise from biological variations among individuals. The medical and pharmaceutical scientists should now focus concisely over the importance of triggered release of drugs. The key considerations in the design of these systems are their biocompatibility and the toxicity of the polymer-based devices, response to external stimuli, the ability to maintain the desired levels of drugs in serum, shelf life and reproducibility.

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