

Time-Controlled Pulsatile Delivery Systems for Bioactive Compounds

Anil K. Anal*

Riddet Centre, Massey University, Private Bag 11222, Palmerston North, New Zealand

Received: September 29, 2006; Accepted: December 6, 2006; Revised: December 7, 2006

Abstract: In the body under physiological conditions, many vital functions are regulated by pulsed or transient release of bioactive substances at a specific time and site. Thus, to mimic the function of living systems, it is important to develop new drug delivery devices to achieve pulsed delivery of a certain amount of a bioactive compound at predetermined time intervals. The ability to deliver bioactive compounds and/or therapeutic agents to a patient in a pulsatile or staggered release profile has been a major goal in drug delivery research over the last two decades. The plasma peak is obtained at an optimal time by timing the drug administration. The number of doses per day can be reduced. Based on the relevance of potential therapeutic applications, a variety of design strategies have been formulated in the pursuit of pulsatile release. Overall, these systems can be categorized into reservoir, capsular and osmotic devices. In this review article, several types of dosage forms, including microparticles, coarse particulates, large solid implants, hydrogels, osmotic pumps and liposomes, for time-controlled pulsatile release are discussed. This review describes the recent patents related to pre-programmed delivery systems, such as systems with eroding, soluble or rupturable barrier coatings, and systems with capsular structures.

Keywords: Pulsatile release, time-controlled release, bioactive compounds, reservoir devices, capsular devices, osmotic pumps.

INTRODUCTION

Advances over the last decade in site-specific and temporally controlled drug delivery systems are contributing to new and/or improved drug therapies. Numerous bioactive peptides and proteins for use as novel therapeutic agents have been identified as a result of progress in biotechnology and genetic engineering. Formulation to achieve effective delivery of these bioactive compounds has been recognized as a fundamental requirement for their clinical application because these bioactive compounds are often poorly absorbed and rapidly metabolized. Furthermore, the administration of large amounts of bioactive compounds can cause undesired side effects, which could be minimized by the use of regulated release systems.

Over the last few decades, the field of controlled drug delivery has been challenged to develop sustained zero-order release systems. This challenge has been met by a wide range of techniques, including osmotically driven pumps [1], matrices with controllable swelling [2-4], diffusion [5] or erosion rates [6], non-uniform drug loading profiles [7-9] and multi-layered matrices [10-12]. A second major challenge has been the controlled delivery of bioactive compounds in a pulsatile or staggered fashion. For this mode of delivery, it is assumed that constant plasma drug levels are not preferred and that an optimal therapeutic effect comes from a periodically fluctuating drug concentration. Two different methodologies have been broadly investigated as possible solutions to this challenge. One is the fabrication of a delivery system that releases its payload after a predetermined time delay or in pulses of predetermined sequences. The other is to develop a system that can respond

to changes in the local environment. These responsive or triggered 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, ultrasound, temperature, light or mechanical forces. Such systems are suitable for the 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.

This review focuses on recent developments in the time-controlled release of bioactive compounds using various formulations such as microparticles, coarse particulates, large solid implants, hydrogels, osmotic pumps and liposomes. Externally and internally controlled systems are discussed, spanning a range of technologies that include pre-programmed systems for the time-controlled pulsatile release of bioactive compounds.

POTENTIAL APPLICATIONS OF PULSATILE RELEASE SYSTEMS

Many endogenous bioactive compounds are released under physiological responses. For instance, insulin is an example of a hormone that experiences triggered release in the body. Basal release of insulin stimulates the synthesis of proteins and glycogen in muscle and adipose tissues. In addition, triggered insulin release occurs during and after the intake of foods to regulate blood glucose levels [13]. Pulsatile release of gastrointestinal hormones, stimulated by food in the gastrointestinal tract, generally causes the release of digestive enzymes from the pancreas and the stomach. Many other hormones, including follicle stimulating hormone (FSH), leutinizing hormone (LH), leutinizing hormone releasing hormone (LHRH), estrogen and progesterone, are released upon certain responses and are regulated in the body in a pulsatile manner. A continuous dose of hormones gene-

*Address correspondence to this author at the Riddet Centre, Massey University, Private Bag 11222, Palmerston North, New Zealand; Tel: +64-6-3505356; Fax: +64-6-3505655; E-mail: A.Anal@massey.ac.nz

rally induces down-regulation of hormone receptors on the target cellular membranes and leads to undesired side effects in the body. Consequently, to prevent down-regulation of hormone receptors and to achieve efficient therapeutic effects, triggered-release technologies are highly desirable. These systems will have application in fields such as insulin delivery, contraception, controlled animal breeding and growth promotion [14].

TIME-CONTROLLED PULSATILE RELEASE

Time-dependent dosage forms are formulated to release their drug load after a predetermined lag time. To achieve a drug release that is independent of the environment (e.g. pH, enzymatic activity, intestinal motility) and/or other stimuli, the lag time prior to the release of the drug has to be controlled primarily by the delivery system [15]. The release mechanisms employed include bulk erosion of polymers in which drug release by diffusion is restricted, surface erosion of layered devices composed of alternating drug-containing and drug-free layers, and osmotically controlled rupture [16].

SYSTEMS WITH ERODING, SOLUBLE OR RUP-TURABLE BARRIER COATINGS

These types of system generally comprise reservoir devices coated with a barrier layer. The barrier dissolves or erodes after a specified lag period, after which the drug is released rapidly from the reservoir core. In general, the lag time prior to drug release from a reservoir-type device can be controlled by the thickness of the coating layer, e.g. the Chronotropic^R system, which consists of a drug-containing core layered with hydroxypropyl methyl cellulose (HPMC), optionally coated with an outer enteric coating. The lag time prior to drug release is controlled by the thickness and the viscosity grade of the HPMC layer [17]. The Chronotropic^R system is an oral dosage form that is designed to achieve time-controlled delivery. This system has been developed keeping in view interaction between gastro-intestinal fluids and the coating polymer, which causes time- or site-controlled release. This reaction causes the liberation of drugs by the mechanism of swelling of the polymer, increased permeability and dissolution/erosion phenomena. A release pattern with two pulses was obtained from a three-layer tablet consisting of two drug-containing layers, separated by a drug-free gellable polymeric barrier layer, as described in US Patent 4865849 [18]. The three-layer tablet was coated on three sides with an impermeable coating (ethyl cellulose) and the top side of the tablet remained uncoated. Upon contact with dissolution fluids, the initial dose incorporated into the top layer was released rapidly from the uncoated surface of the tablet. The second pulse was obtained from the bottom layer after the gelled barrier layer (HPMC) had been eroded and dissolved.

Other types of systems of pulsatile release after a certain lag period, based on multiparticulates for oral administration, are described in US Patents 5260068 [19] and 5508040 [20]. The delivery system can be a capsule or tablet composed of a large number of pellets consisting of two or more particle populations. Each pellet has a core that contains the therapeutic drug and a water-soluble osmotic agent (e.g. NaCl). A water-permeable, water-insoluble polymer film encloses each core. A hydrophobic water-insoluble agent

that alters permeability (e.g. wax, fatty acid or salts of fatty acids) is incorporated into the polymer film. The rate at which water passes from the film coating through to the core differs for each pellet population in the dosage form. The osmotic agent dissolves in water, which causes the pellets to swell and thereby regulates the rate of diffusion of the drug from the dosage form. The effect of each pellet releasing its drug into the environment sequentially provides a series of pulsatile administrations of the drug from a single dosage form. The coating thickness may also vary among pellet populations. A combination of osmotic and swelling effects also occurs when using the permeability controlled system (PCS), comprising a core and a coating, developed by Amidon and Leesman [21]. The core contains the drug, a low bulk density solid and/or a lipid material (e.g. mineral oil) and possibly disintegrants, and is coated by cellulose acetate. When the system is immersed into medium, water penetrates into the core and displaces the lipid material. The core is expected to maintain a constant weight until all the lipid material is depleted, after which the internal pressure increases to rupture the coating. Upon water ingress, the swellable layer expands, resulting in film rupture and subsequent triggered release of core material. In this system, the release is described as being independent of the environmental pH and the solubility of the drug.

US Patent 5110597 [22] described a multi-unit delivery system, particularly suited for the delivery of pharmacologically active peptides and protein anabolic hormones such as growth promoting hormones. The device is designed to deliver a plurality of discrete longitudinally aligned individual drug units by the linear expansion of a fluid-activated driving member. The dispenser comprises a dispensing component and a driving component. The dispensing component should be either semi-permeable or substantially impermeable to the passage of external fluid.

Pozzi *et al.* [23] proposed the TIME CLOCK^R system for oral dosage, which should enable fast and complete release of a drug after a predetermined lag time. A tablet containing the drug molecule and bulking agents (lactose, polyvinylpyrrolidone (PVP), corn starch and magnesium stearate) was made. This core was coated with a hydrophobic dispersion of carnauba wax, bees' wax, poly(oxyethylene) sorbitan monooleate and HPMC in water. The lag time could be proportionally modulated by altering the thickness of the coating. *In vitro* results indicated rapid release after a certain lag time for the TIME CLOCK^R system with the hydrophobic coating. This approach may also be used to control the release onset time. Because the drug core is formulated with soluble ingredients, shell dissolution/disintegration becomes the key factor in controlling the lag time. Furthermore, drug release is independent of normal physiological conditions, such as pH, digestive state and anatomical position at the time of release. This approach could be applicable for implant systems as well as for oral systems. Fan *et al.* [24] have investigated pulsatile release tablets that can suppress release of the drug in the stomach and can release the drug rapidly after a predetermined time of about 3 h in the intestine. The system consists of a core, a swelling agent of cross-linked PVP and a coating film of ethyl cellulose/Eudragit L. Eudragit L dissolves in an environment of pH above 6 and creates pores in the coating film.

Penetration of water molecules from the surroundings through the pores into the core causes expansion of the swelling agent, bursting the film and releasing the drug with a single pulse. Manipulation of the thickness of the coating film can control the lag time. US Patent 5593697 [25] describes a pharmaceutical implant containing a biologically active material, an excipient comprising at least one water-soluble material and a polymer film coating adapted to rupture at a predetermined period of time after implantation. In one form, a bilayer film coating forms an impermeable barrier to the drug. An insoluble outer film controls the degree of access of physiological fluid to the inner film. A film coating comprising a mixture of ethyl cellulose and a copolymer of glycolic and lactic acids is used. As ethyl cellulose is an insoluble polymer, when the poly(lactide-glycolic acid) (PLGA) polymer in the film hydrolyzes, the film becomes porous and allows release of the drug. The rate of hydrolysis of the PLGA depends on the ratio of lactic acid to glycolic acid in the polymer. US Patents 5260069 [26] and 5472708 [27] describe a dosage form for delivering drugs, and particularly drugs that cannot be released by diffusion through a porous coating, such as water-insoluble drugs. Pellets in a unit dosage form, such as a capsule or tablet, are provided. The pellets are composed of a core containing the drug and a swelling agent, which expands in volume when exposed to physiological fluid. The core is enclosed within a thin membrane that is permeable to moisture. The membrane is composed of a water-insoluble but permeable film-forming polymer, a water-soluble film-forming polymer and a permeability-reducing agent. Water diffuses through the coating and into the core. As water is taken up by the swelling agent, the core expands, exerting force on the coating until it bursts, thus releasing the drug. The permeability-reducing agent reduces the rate at which water reaches the swelling agent, thereby delaying the release time. The release timing is reported to be effectively controlled by varying the proportions of the three coating ingredients and/or the coating thickness. US Patent 4897270 [28] also describes a similar sort of pharmaceutical tablet comprising a tablet core and a film coat to mask the taste of the core. The film coat allows permeation of moisture to the core and ruptures very rapidly upon contact with gastrointestinal fluid. Thus the core immediately disintegrates, allowing burst release of the drug.

Another class of reservoir-type time-controlled pulsatile release systems is based on rupturable coatings. The drug is released from a core after the rupture of a surrounding polymer layer, caused by a pressure build-up within the system. The pressure necessary to rupture the coating can be achieved with gas-producing effervescent excipients, inner osmotic pressure or swelling agents. An effervescent mixture of citric acid and sodium bicarbonate was incorporated in the core of a tablet, which was coated with ethyl cellulose. The development of carbon dioxide after water penetration into the core resulted in release of the core materials after rupture of the coat, which was generally dependent on the mechanical properties of the coating layer; the weak and non-flexible ethyl cellulose film ruptured sufficiently when compared with more flexible films. The lag time before release increased with increasing coating level and increasing hardness of the core tablet [29].

US Patent 6555136B2 [30] describes a dosage form to provide for time-controlled pulsatile release of methylphenidate. Methylphenidate hydrochloride, the hydrochloride salt of α -phenyl-2-piperidine-acetic acid methyl ester, is a central nervous system stimulant that is used in the treatment of attention deficit disorder (ADD). This drug is additionally used in symptomatic treatment of narcolepsy, depression and the cognitive decline associated with acquired immunodeficiency syndrome (AIDS). A controlled-release dosage form is needed as this drug has a very short half-life. This invention may provide a dosage form for the pulsatile release of this drug, thereby maximizing its efficacy and reducing the potential for abuse or non-compliance. The dosage form is prepared by (i) formulating three individual compressed tablets, each having a different release profile (i.e. immediate release or delayed release), and (ii) encapsulating all three different types of tablets into a gelatin capsule and then closing and sealing the capsule. The immediate-release tablet comprises the disintegrants, such as microcrystalline cellulose and sodium starch glycolate, whereas the delayed-release tablets have delayed-release coating material, such as Eudragit. This dosage form is designed to have at least three pulses of release, such as release within 1-2 h, 3-5 h and then 7-9 h following administration. US Patent 6500457B1 [31] describes a similar dosage form but with different agents (antiarrhythmic agents).

US Patent 6632451B2 [32] describes a two-pulse gastrointestinal dosage form, comprising a swellable core material, surrounded by an inner coat of water-insoluble polymer. The inner coat serves to control the rate of liquid entry into the core. The inner coat may be composed of a combination of hydrophobic polymers or polymers sparingly soluble in water and hydrophilic, non-water-soluble particulates that are embedded within the material. This enables the inner coat to determine the rate of water uptake, whereas the swelling of the core, which depends on the rate of water uptake and on the swelling properties of the core itself, determines the time of breach of the coat. The hydrophobic polymers used to make the inner coat can be derivatives of cellulose, such as ethyl cellulose, or Eudragit. The water-insoluble but hydrophilic particulates in the inner coat can be calcium alginate, calcium pectinate, calcium xanthate or metal salts of such polysaccharides. This inner coat is further covered by an outer coat that contains an additional amount of active agent. The outer coat may comprise a combination of lactose, povidone, starch, pectin etc. When the dosage form enters the gastrointestinal tract, the outer coat releases the desired agent contained therein and disintegrates, exposing the inner coat. The outer coat can be designed to resist release of the desired agent until and unless a certain physiological stimulus, e.g. pH and enzyme, is present. The particulate matter in the inner coat takes up the liquid, thus forming channels interconnecting the drug-containing core with the outside of the delivery device. Liquid enters the core through these channels; the core then swells to the point at which the inner coat is broken, which causes the immediate release of core materials into the surrounding environment. By controlling and manipulating the parameters, such as the active core material, the carrier materials in the coating and the particulate matter, the loca-

tion of release of both pulses of the drug can be controlled. This dosage form seems to be useful for the treatment of disease by the release of drugs in the gastrointestinal tract at a particular location and in a time-dependent manner.

SYSTEMS WITH CAPSULAR STRUCTURE

Several single unit pulsatile dosage forms with a capsular design have been developed. Most consist of an insoluble capsular body, which contains the drug, and a plug, which is removed after a predetermined lag time because of swelling, erosion or dissolution.

Linkwitz *et al.* [33] described the delivery of agents from osmotic systems based on an expandable orifice technology. The system is in the form of a capsule from which the drug is delivered by the capsule's osmotic infusion of moisture from the body. The delivery orifice opens intermittently to achieve a pulsatile delivery effect. The orifice forms in the capsule wall, which is constructed of an elastic material, preferably elastomer (e.g. styrene-butadiene copolymer), which stretches under a pressure differential caused by the pressure rise inside the capsule as the osmotic infusion progresses. The orifice is small enough that, when the elastic wall is relaxed, the flow rate of drug through the orifice is substantially zero; however, when the elastic wall is stretched, because of the pressure differential across the wall exceeding a threshold, the orifice expands sufficiently to allow the release of the drug at a physiologically required rate. This osmotically driven delivery device can be used as an implant in the anal-rectal passageway, in the cervical canal, as an artificial gland, in the vagina, as a ruminal bolus and so on.

Niwa *et al.* [34] prepared a novel capsule made from ethyl cellulose for the time-controlled release of drugs in the colon. Initially, the capsule was prepared using a gelatin capsule with ethyl cellulose, followed by dissolution of the gelatin in water. The thickness of the ethyl cellulose capsule body was varied and the effect of the wall thickness on the release of the drugs in the capsules was investigated. The ethyl cellulose capsules contained a large number of mechanically made micropores (400 μm) at the bottom. A swellable layer, consisting of low-substituted hydroxypropyl cellulose (L-HPC), was also located in the bottom of the capsule body. Above the swellable layer was the drug reservoir, which contained a mixture of the model drug, fluorescein and a bulking agent, such as lactose or starch. The capsule was then capped and sealed with a concentrated ethyl cellulose solution. After administration of the drug-containing capsule, water molecules penetrated the capsule through the micropores in the bottom of the capsule body. Hydration and swelling of the L-HPC induced an increase in the internal osmotic pressure, which resulted in the "explosion" of the capsule and a burst-like drug release was observed. The lag time of the drug release could be altered by altering the thickness of the capsule. The effectiveness of so-called superdisintegrants, highly swellable agents, was demonstrated for a capsule-based system consisting of a drug-containing core capsule, a swelling layer and a rupturable polymeric layer. Croscarmellose, sodium starch glycolate and L-HPC were used as swelling substances, which resulted in complete film rupture followed by rapid drug release. The lag time was controlled by the composition

of the outer polymer layer; water-soluble polymers such as HPMC increased the permeability and therefore reduced the lag time. The swelling energy of several excipients decreased in the following order: croscarmellose sodium > L-HPC > crospovidone > HPMC. Both solid and liquid drug formulations could be delivered with this system [35-37].

A similar approach for the burst release of a drug, in which a hydrostatic pressure was generated inside the capsules, was reported by Jimoh *et al.* [38]. The hollow biodegradable capsules with a thinner membrane at one end were prepared using PLGA with effervescent agents, i.e. citric acid/sodium bicarbonate. As water penetrated into the capsule through the thin PLGA membrane side, it generated an effervescent reaction caused by the citric acid/sodium bicarbonate mixture. The carbon dioxide gas generated accumulated in the capsule and finally ruptured the thin membrane and released the core materials. The lag time of drug release could be modulated by the dimensions of the capsule (thickness of the membrane, hollow size and the amount of effervescent agents). The capsule burst time could be modulated from 2 h to up to 7 days *in vitro* by altering the ratio of citric acid/sodium bicarbonate to PLGA. These capsules were then utilized for the controlled release of FSH in female rabbits.

The Pulsincap^R system consists of a water-insoluble capsule body, which is filled with the drug formulation. The capsule is closed at the open end with a swellable hydrogel plug. The dimensions and the position of the plug can control the lag time prior to drug release. In order to ensure rapid release of the drug, effervescent agents or disintegrants can be included in the drug formulation, in particular with water-insoluble drugs. This system is coated with an enteric layer, which dissolves upon reaching the higher pH region of the small intestine. This system comprises insoluble capsules and plugs. The plugs consist either of swellable materials, which are coated with insoluble but permeable polymers (e.g. polymethacrylates), or of erodible substances, which are compressed (e.g. HPMC, polyvinyl alcohol, polyethylene oxide) or prepared by congealing melted polymers (saturated polyglycolated glycerides or glyceryl monooleate). The erosion of the plug can also be controlled enzymatically; a pectin plug can be degraded by incorporating pectinolytic enzymes directly into the plug [39-41]. Another group of researchers [42,43] developed a "Chronopharmaceutical capsule" using an ethyl-cellulose-coated gelatin capsule as the insoluble shell and a high swelling L-HPC excipient, which was found to be a more reliable expulsion system than effervescent agents.

Recently Qui and Zhu [44] designed a core-shelled cylindrical dosage form, comprising a hydrophobic polycarbonate coating and a cylindrical core of alternating polyanhydride isolating layers and drug-loaded poly[(ethyl glycinate) (benzyl amino acethydroxamate) phosphazene] (PEBP) layers, for a programmable drug delivery system for single dose vaccine and other related applications. The pulsatile release of model compounds (fluorescein isothiocyanate-dextran and myoglobin) with certain lag times (18-118 h) was achieved on the basis of the pH-sensitive degradation of PEBP and its cooperative interaction with polyanhydrides. In another experiment, Jiang and Zhu [45,

46] designed a laminated device comprising polyanhydrides as isolating layers and pH-sensitive complexes of poly (sebacic anhydride)-b-polyethylene glycol (PSA-b-PEG) and poly(trimellitylimidoglycine-co-sebacic anhydride)-b-polyethylene glycol (P(TMA-gly-co-SA)-b-PEG) as protein-loaded layers. Model proteins (bovine serum albumin and myoglobin) showed a typical pulsatile release. The lag time prior to the release correlated with the hydrolytic duration of the polyanhydrides, which varied from 30 to 165 h depending on the polymer types and the thickness of the isolating layers.

Pulsatile systems based on multiparticulates for oral administration are described by Percel [47]. The delivery system can be a capsule or tablet composed of a large number of pellets consisting of two or more particle populations. Each pellet has a core that contains the therapeutic drug and a water-soluble osmotic agent (e.g. NaCl). A water-permeable, water-insoluble polymer film encloses each core. A hydrophobic water-insoluble agent that alters permeability (e.g. wax, fatty acid or salts of fatty acids) is incorporated into the polymer film. The rate at which water passes from the film coating through to the core differs for each pellet population in the dosage form. The osmotic agent dissolves in water, which causes the pellets to swell and thereby regulates the rate of diffusion of the drug from the dosage form. The effect of each pellet releasing its drug into the environment sequentially provides a series of pulsatile administrations of the drug from a single dosage form. The coating thickness may also vary among pellet populations. US Patent 20010046964 [48] describes a capsule capable of delivering therapeutic agents into the body in a time-controlled or position-controlled pulsatile release fashion; it is composed of a multitude of multicoated particulates (beads, pellets, granules etc.). Each of these beads, except an immediate-release bead, has at least two coated membrane barriers. One is composed of a mixture of a water-insoluble polymer and an enteric polymer. The composition and the thickness of the polymeric membrane barriers determine the lag time and the duration of the drug release from each of the bead populations.

US Patent 6627223B2 [49] describes a capsule having the capability of delivering therapeutic agents into the body in a time-controlled or position-controlled pulsatile release fashion. The dosage form comprises a multitude of multicoated particulates. The time-controlled series of pulses occurs several hours after oral administration, with or without immediate release. One of the coating membranes is composed of an enteric polymer and the second membrane barrier is composed of a mixture of a water-insoluble polymer and an enteric polymer. The composition and the thickness of the polymeric membranes determine the lag time and the duration of drug release from each of the bead populations. In other preparations, an organic acid, such as fumaric acid, citric acid, succinic acid, tartaric acid or malic acid, is included and a maleic-acid-containing membrane may be provided between the first and second membrane layers to provide for the time-separated pulses. The acids in between the membranes may delay the dissolution of the enteric polymer in the inner layer, thereby increasing the lag time as well as decreasing the rate of release of the active ingredient from the coated microparticulates. The enteric

coating membrane is generally incorporated in the innermost layer to have the drugs released in the lower intestine. One of the membrane layers is made of plasticized enteric polymer whereas the other may be a mixture of a water-insoluble polymer and a plasticized water-soluble/dispersible enteric polymer. The esters of cellulose and their derivatives (such as cellulose acetate phthalate (CAP), hydroxypropyl methyl cellulose phthalate (HPMCP), hydroxypropyl methyl cellulose succinate (HPMCS)) and polyvinyl acetate phthalate (PAP) or shellac were used as water-soluble enteric polymers. Ethyl cellulose, polyvinyl acetate, ethyl acrylate and methmethacrylate were used as water-insoluble enteric polymers. The therapeutic agents suitable for incorporation into these time-controlled pulsatile release systems could be acidic, basic, zwitterionic or neutral organic/inorganic bioactive molecules or their salts.

US Patent 7048945B2 [50] provides a method for manufacturing a multiparticulate dosage form having a time-controlled series of pulses occurring several hours after oral administration, with or without an immediate-release pulse upon oral administration. The dosage form consists of an active core, a first membrane of an enteric polymer and a second membrane of a mixture of water-insoluble and enteric polymers.

US Patent 6531152B1 [51] describes a delivery system for targeted delivery with burst release within the gastrointestinal tract. The delivery system contains a core and a coating. The core contains a drug in combination with a carrier material. The carrier material has the property of swelling upon contact with an aqueous medium. The core has the ability to absorb larger quantities of fluid and disintegrates faster in that fluid. The carrier material comprises a water-insoluble polymer (e.g. calcium pectinate, calcium alginate etc.), which swells considerably but does not form a strong gel, a disintegrant (e.g. croscopovidone) and a hardness enhancer (e.g. microcrystalline cellulose). This type of delivery system allows the controlled introduction of water from the surrounding medium into the device. When an aqueous medium comes in contact with particulate matter, the particulate matter swells. The particles eventually form channels from the outer part of the device to the core containing the drug. The core imbibes fluid and then swells, breaks the coating and disintegrates, and all or most of the drug is released with a burst effect. A time-controlled explosion system is described in US Patent 4871549 [52]. In this system, a drug is coated on to the seed along with the swelling agent, and the finished pellets are then coated with water-insoluble materials. Drug release is time controlled by the breakage of the external water-insoluble membrane, which is caused by the explosive swelling effect of the swelling agent. The coating thickness of the particles is increased to delay release of the drug. However, this system has the drawback of failing to release the drug if the swelling agent fails to rupture the water-insoluble coating. Further, it lacks the flexibility of enabling various delivery patterns because the thickness of the coating determines the release of the drug. To improve this system, a pulsatile drug delivery system has been described in US Patent 5472708 [53]; it uses a minor portion of water-soluble polymer and a permeability-reducing agent added to the water-insoluble coating to ensure release of the drug. This system provides a

pulsatile input of drug into the intestine, with the timing of the release regulated by the thickness of the coating and the amount of water-soluble polymer. The duration of each pulse is the same among four groups of particles, creating four different periods of fluctuation of plasma drug concentration, which is indistinct from four separate administrations. The disadvantage of a water-soluble polymer to regulate time release is that, once micro-sized patches of water polymers are dissolved, the active agent may start leaching out before the coating is broken, leading to premature drug release and inconsistency in drug efficacy. The system also has a similar disadvantage to other time-controlled release systems, by lacking flexibility in the release patterns.

US Patent 5840329 [54] describes a drug delivery system that comprises a plurality of particles enclosed in a tablet or capsule. The plurality of particles are divided into several delivery units, with each group having its own unique inner structured active core and specific external coating. These particles contain a polymer-blend hydrogel for the controlled-release matrix layer delivering controlled prolonged pulsed doses, and a swelling agent for the rapid-release layer delivering recurring short pulsed doses. These particles contain an outer coating of a major portion of water-insoluble, water-permeable polymer, and water-permeation adjusting agents for dispensing single or multiple precisely timed pulsed releases. The controlled-release layer and the swelling rapid-release layer can each contain one or more active agents, which can be alike or different in nature. US Patent 5017381 [55] describes a dispenser comprising a rigid block, a plurality of movable active agent units filling a portion of the block, a fluid-activated driving member for dispensing the active agent units filling the remainder of the block, and an active agent unit outlet means. Each active agent unit is composed of an active agent dosage or filling contained within a fluid-impermeable cup-shaped member, the cup-shaped members being oriented within the block with the base of the cup-shaped members facing the outlet means. This invention can provide a variety of drug or core bioactive substances for the pulsed delivery of a single compound or mixed formulations separately or simultaneously, and the pulsed delivery of a sequence of different compounds. US Patent 5387421 [56] describes a multi-stage drug delivery system for the time-controlled pulsed release of bioactive compounds. The delivery system includes a first capsule having an inner chamber containing a bioactive compound. A plug in a passageway of the capsule plugs the opening. The plug can be released from the passageway opening on the application of pressure from within the inner chamber. A pump mechanism causes an increase in pressure within the inner chamber and forces the plug out of the passageway to release the drug from the inner chamber and out of the passageway, thereby providing a second pulse of release at a predetermined time after initial ingestion of the capsule.

CURRENT & FUTURE DEVELOPMENTS

Controlled-release formulations have many advantages over immediate-release formulations. With these formulations, less frequent drug administration is possible, lower plasma peak concentrations can be obtained to avoid adverse effects, and patient compliance can correspondingly be

improved. The category of controlled-release formulations can be divided into the subgroups rate-controlled-release, delayed-release and pulsed-release formulations. In the field of drug delivery, increased attention has recently been focused on the potential of systems that are able to release drugs after a programmable lag phase commencing at administration time, i.e. in a pulsatile mode. During the last two decades, technologies to ensure time-controlled pulsatile release of bioactive compounds have been developed. Significant progress has been made towards achieving pulsatile drug delivery systems that can effectively treat diseases with non-constant dosing therapies, such as diabetes. However, there is much work that needs to be carefully demonstrated and considered before devices based on these technologies become clinically available. Also, for the pulsatile delivery of bioactive compounds, especially hormones, information on the natural pulse frequency, the amplitude and the number of pulses required to achieve physiological changes is needed.

REFERENCES

- [1] Sefton MV. Implantable pumps. *CRC Crit Rev Biomed Eng* 1987; 14: 201-40.
- [2] Conte U, Maggi L. A flexible technology for the linear, pulsatile and delayed release of drugs allowing for easy accommodation of difficult *in vitro* targets. *J Control Release* 2000; 64: 263-68.
- [3] Bhopatkar D, Anal AK, Stevens WF. Iontropic alginate beads for controlled intestinal protein delivery: effect of chitosan and barium counterions on entrapment and release. *J Microencap* 2005; 22: 91-100.
- [4] Anal AK, Stevens WF, Remuñán-López C. Iontropic cross-linked chitosan microspheres for controlled release of ampicillin. *Int J Pharm* 2006; 312: 166-73.
- [5] Lee ES, Kim SW, Kim SH, Cardinal JR, Jacobs H. Drug release from hydrogel devices with rate-controlling barriers. *J Membr Sci* 1980; 7: 293-303.
- [6] Yang L, Fassihi R. Modulation of diclofenac release from a totally soluble controlled release drug delivery system. *J Control Release* 1997; 44: 135-40.
- [7] Hildgen P, McMullen JN. A new gradient matrix: formulation and characterization. *J Control Release* 1995; 34: 263-71.
- [8] Lu S, Anseth K. Polymerization of multilaminated poly(HEMA) hydrogels for controlled release. *J Control Release* 1999; 57: 291-300.
- [9] Lu S, Ramirez F, Anseth K. Photopolymerized, multilaminated matrix devices with optimized non-uniform initial concentration profiles to control drug release. *J Pharm Sci* 2000; 89: 45-51.
- [10] Qui Y, Chidambaram N, Flood K. Design and evaluation of layered diffusional matrices for zero-order sustained release. *J Control Release* 1998; 51: 123-30.
- [11] Anal AK, Bhopatkar D, Tokura S, Tamura H, Stevens WF. Chitosan-alginate multilayer beads for gastric passage and controlled intestinal release of protein. *Drug Dev Ind Pharm* 2003; 29: 713-24.
- [12] Anal AK, Stevens WF. Chitosan-alginate multilayer beads for controlled release of ampicillin. *Int J Pharm* 2005; 290: 45-54.
- [13] Tolic IM, Mooskeilde E, Sturis J. Modeling the insulin-glucose feedback system: the significance of pulsatile insulin secretion. *J Theor Biol* 2000; 207: 361-75.
- [14] Cohen S, Bernstein H (Eds). *Microparticulate systems for the delivery of proteins and vaccines*. New York, Marcel Dekker, Inc. 1995.
- [15] Bussemer T, Otto I, Bodmeier R. Pulsatile drug-delivery systems. *Crit Rev Ther Drug Carrier Syst* 2001; 18: 433-58.
- [16] Medlicott NJ, Tucker IG. Pulsatile release from subcutaneous implants. *Adv Drug Dev Rev* 1999; 38: 139-49.
- [17] Maroni A, Zema L, Cerea M, Sangalli ME. Oral Pulsatile drug delivery systems. *Expert Opin Drug Delivery* 2005; 2: 855-71.
- [18] Conte, U., Arsizio, B., Manna, A.L., Comolobo, P.: *US4865849 (1989)*.
- [19] Chen, C.M.: *US5260068 (1993)*.

- [20] Chen, C.M.: US5508040 (1996).
- [21] Amidon, G.L., Leesman, G.D.: US5229131 (1993).
- [22] Wong, P.S.L., Theeuwes, F., Eckenhoff, J.B., Larsen, S.D., Huynh, H.T.: US5110597 (1992).
- [23] Pozzi F, Furlani P, Gazzaniga A, Davis SS, Wilding IR. The TIME CLOCK system: a new oral dosage form for fast and complete release of drug after a predetermined lag time. *J Control Release* 1994; 31: 99-108.
- [24] Fan TY, Wei SL, Yan WW, Chen DB, Li J. An investigation of pulsatile release tablets with ethylcellulose and Eudragit L as film coating materials and cross-linked polyvinylpyrrolidone in the core tablets. *J Control Release* 2001; 77: 245-51.
- [25] Barr, I.G., Thiel, W.J.: US5593697 (1997).
- [26] Chen, C.M.: US5260069 (1993).
- *[27] Chen, C.M.: US5472708 (1995).
- [28] Deutsch, D.S., Anwar, J.: US4897270 (1990).
- [29] Krogel I, Bodmeier R. Floating or pulsatile drug delivery systems based on coated effervescent cones. *Int J Pharm* 1999; 187: 175-84.
- *[30] Midha, K.K.: US200365550136B2 (2003).
- *[31] Midha, K.K., Hiroshi, M., Lo, W.Y.: US20026500457B1 (2002).
- *[32] Penhasi, A., Yam, B., Flashner, M., Tikva, P., Lerner, E.I., Tikva, P.: US20036632451B2 (2003).
- [33] Linkwitz, A., Magruder, J.A., Merrill, S.: US5318558 (1994).
- [34] Niwa K, Takaya T, Morimoto T, Takada K. Preparation and evaluation of a time-controlled release capsule made of ethylcellulose for colon delivery of drugs. *J Drug Target* 1995; 3: 83-89.
- [35] Bussemer T, Peppas NA, Bodmeier R. Evaluation of the swelling, hydration and rupturing properties of the swelling layer of a rupturable pulsatile drug delivery system. *Eur J Pharma Biopharma* 2003; 56: 261-70.
- [36] Bussemer T, Peppas NA, Bodmeier R. Time-dependent mechanical properties of polymeric coatings used in rupturable pulsatile release dosage forms. *Drug Dev Ind Pharm* 2003; 29: 623-30.
- [37] Sungthongjeen S, Puttipatkhachorn S, Paeratakul O, Dashevsky A, Bodmeier R. Development of pulsatile release tablets with swelling and rupturable layers. *J Control Release* 2004; 95: 147-59.
- [38] Jimoh AG, Wise DL, Gresser JD, Trantolo DJ. Pulsed FSH release from an implantable capsule system. *J Control Release* 1995; 34: 87-95.
- [39] Krogel I, Bodmeier R. Pulsatile drug release from an insoluble capsule body controlled by an erodible plug. *Pharm Res* 1997; 15: 474-81.
- [40] Krogel I, Bodmeier R. Evaluation of an enzyme-containing capsular shaped pulsatile drug delivery system. *Pharm Res* 1999; 16: 1424-1429.
- [41] Gohel MC, Sumitra M. Modulation of active pharmaceutical material release from a novel "tablet in capsule system" containing an effervescent blend. *J Control Release* 2002; 79: 157-64.
- [42] Ross AC, MacRae RJ, Walther M, Stevens HNE. Chrono-pharmaceutical drug delivery from a pulsatile capsule device based on programmable erosion. *J Pharm Pharmacol* 2000; 52: 903-909.
- [43] Sutch JCD, Ross AC, Kockenberger W, *et al.* Investigating the coating-dependent release mechanism of a pulsatile capsule using NMR microscopy. *J. Control Release* 2003; 92: 341-47.
- [44] Qui LY, Zhu KJ. Design of core-shelled polymer cylinder for potential programmable drug delivery. *Int J Pharm* 2001; 219: 151-160.
- [45] Jiang HL, Zhu KJ. Preparation, characterization and degradation characteristics of polyanhydrides containing polyethylene glycol. *Polymer Int* 1999; 48: 47-52.
- [46] Jiang HL, Zhu KJ. Pulsatile protein release from a laminated device comprising of polyanhydride and pH-sensitive complexes. *Int J Pharm* 2000; 194: 51-60.
- *[47] Percel, P., Vishnupad, K.S., Venkatesh, G.M.: US20010046964 (2001).
- [48] Percel, P., Vishnupad, K.S., Venkatesh, G.M.: US20010046964 (2001).
- *[49] Percel, P., Vishnupad, K.S., Venkatesh, G.M.: US20036627223B2 (2003).
- *[50] Percel, P., Vishnupad, K.S., Venkatesh, G.M., Lee, D.Y.: US20067048945B2 (2006).
- *[51] Lerner, E.I., Tikva, P., Flashner, M., Penhasi, A., Yam, B.: US20036531152B1 (2003).
- [52] Ueda, Y., Hata, T., Yamaguchi, H., Ueda, S., Kotani, M.: US4871549 (1989).
- [53] Chen, C.M.: US5472708 (1995).
- *[54] Bai, J.P.: US5840329 (1998).
- [55] Maruyama, F., Cortse, R.: US5017381 (1991).
- *[56] Amidon, G.L., Leesman, G.D., Sherman, L.B.: US5387421 (1995).