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Review

"Programmed Polymeric Devices" for Pulsed Drug Delivery

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Pharmaceutical research strives to design drug delivery systems that respond to therapeutic needs. Considering the facts that physiologic parameters (e.g., heart rate, blood pressure, and plasma concentration of hormones, plasma proteins, and enzymes) display constancy over time, drug delivery systems with a constant release profile have been designed. However, because of circadian rhythms in physiologic parameters and pathologic conditions (e.g., asthma, angina pectoris), the conventional paradigm concerning drug concentrations "the flatter the better" may not be what the organism may need. Instead, to correlate with our biological needs, "precisely timed drug delivery," which could be accomplished with "programmable dosage forms," is required. Precisely timed drug delivery may maximize therapeutic efficacy, may minimize dose frequency, and may reduce toxicity by avoiding side effects and drug tolerance. This paper outlines the concepts that have been proposed to release drugs in a pulsed manner from pharmaceutical devices.

KEY WORDS: drug delivery; pulsatile programmed drug delivery; pulsed drug release; vaccine delivery.

INTRODUCTION

A common feature of many current controlled release devices is that they provide a continuous release over a prolonged period of time. However, there are many applications in medicine where a nonuniform release profile would be more beneficial (1). For bioactive agents such as hormones, many have suggested that pulsed release may offer advantages over continuous release (2–4) as hormones are generally secreted by the body in a pulsed manner. Also, a pulsatile drug release pattern could be advantageous for drugs with an extensive first-pass metabolism, for drugs that develop biological tolerance when they are constantly present at their target site, and for drugs that require dosing at night. Also, devices that could give pulses of drug release at well-defined times after injection could be used to provide "single-shot" vaccines where the initial and booster doses are contained in one delivery system. Such devices could improve vaccination coverage by reducing the number of vaccination sessions required to generate immunity.

"Pulsed drug release" is defined as the rapid and transient release of a drug after a predetermined off-release period. One way to classify "pulsed drug delivery systems" is based on the physicochemical and biological principles that trigger the release. These devices are classified into "programmed" and "triggered" drug delivery systems. In programmed delivery systems, the release is completely governed by the inner mechanism of the device (i.e., the lag time prior to the drug release is controlled primarily by the delivery system). In triggered delivery systems, the release is governed by changes in the physiologic environment of the device (biologically triggered systems) or by external stimuli (externally triggered systems).

Some examples of biologically triggered pulsed delivery systems include the delivery of insulin in response to glucose levels (5–7) and the delivery of anti-inflammatory drugs in response to increased concentrations in hydroxyl radicals and hyaluronidase as may occur at inflammatory sites (8–10).

In externally triggered systems, external stimuli such as magnetism (11), ultrasound (12,13), temperature changes (14), electrical effects and irradiation (15–17) activate the drug release. Because Kost and Langer have recently reported on pulsed delivery by biological and external triggers (18), this article aims to review pulsed drug delivery from programmed devices. We have focused especially on programmed drug delivery devices that are able to generate more than one pulse ("multiple pulse") and are of interest in treating diseases requiring repeated drug administration (see Scheme 1).

PULSED DELIVERY BY DEGRADATION OF THE DEVICE

This section outlines the delivery systems designed for pulsed release based on the spontaneous hydrolysis or enzymatic degradation of the polymer comprising the device. The major idea to obtain pulsed release from such degradable polymer devices is that drugs (especially those with a higher molecular weight) can be physically entrapped in the nondegraded polymer matrix, and upon polymer degradation the matrix releases the drug. A combination of polymer matrices, one degrading faster than the others, in a single device may

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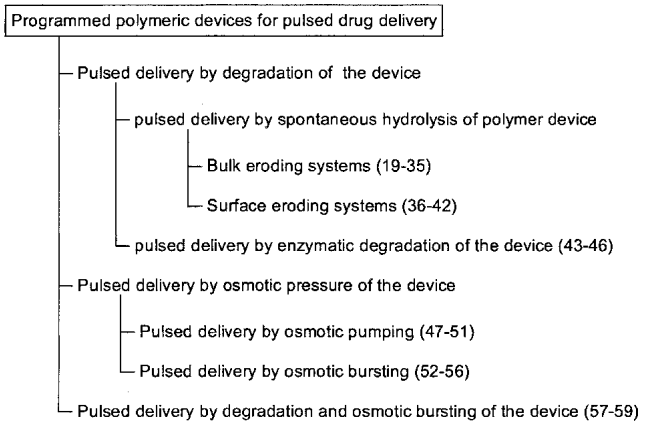

Scheme 1. Overview of the programmed polymeric devices for pulsed drug delivery.

create opportunities to design multiple pulsed drug release systems.

Pulsed Delivery by Spontaneous Hydrolysis of Polymer Devices

Bulk-Eroding Systems

D,L-Polylactic acid (PLA) is the most established biocompatible polymer that undergoes bulk erosion in aqueous conditions by ester linkage hydrolysis. To alter the degradation rate of PLA, the polymer is co-polymerized with glycolic acid (GA). Cleland and co-workers (19–22) prepared microspheres with different PLGA compositions to achieve a "single-shot" HIV-1 vaccine. *In vitro* release studies showed a substantial initial release of the antigen. After a lag of several weeks, a continuous (not pulsed) release over a period of 4 weeks occurred (19). PLGA microspheres were also investigated to achieve pulsed release of tetanus toxoid (M_w of 150 000 g/mol) and malaria antigens (M_w of 16 000 g/mol) (23–27). Figure 1A shows the typical *in vitro* release profile of tetanus toxoid antigens from PLGA microspheres (27). It is characterized by an initial release, due to diffusion of the antigen near the surface of the microspheres, followed by a booster release after a certain lag phase that depends on the degradation rate of the matrix. Typically, the booster release occurs over a period of several weeks. Pulsed release is not obtained from PLGA microspheres. Moreover, PLGA shows some well-known disadvantages. First, the exposure of the antigen to the acidic microenvironment inside the degrading PLGA-microspheres may degrade the antigen, [although basic additives like $Mg(OH)_2$ and $Ca(OH)_2$ may stabilize the antigens (28,29)]. Second, the encapsulated drugs, especially proteins, may react with erosion products (like glycolic and lactic acid monomers and oligomers) (30).

Sanchez *et al.* developed "oil-filled PLGA microcapsules" (31) to overcome the PLGA limitations (as protein denaturation) described above. The microcapsules consist of an oil core, which contains the antigen, surrounded by an outer PLGA shell. As shown in Fig. 1B, the time of tetanus toxoid release from the oil-filled microcapsules could be engineered by selection of an appropriate PLGA composition. The initial tetanus toxoid release could be substantially decreased by lowering the amount of GA. Also, by lowering the amount of GA, the booster release occurred after 7 weeks instead of after 3 weeks. However, the booster release was once again not pulsed but continuous over several weeks.

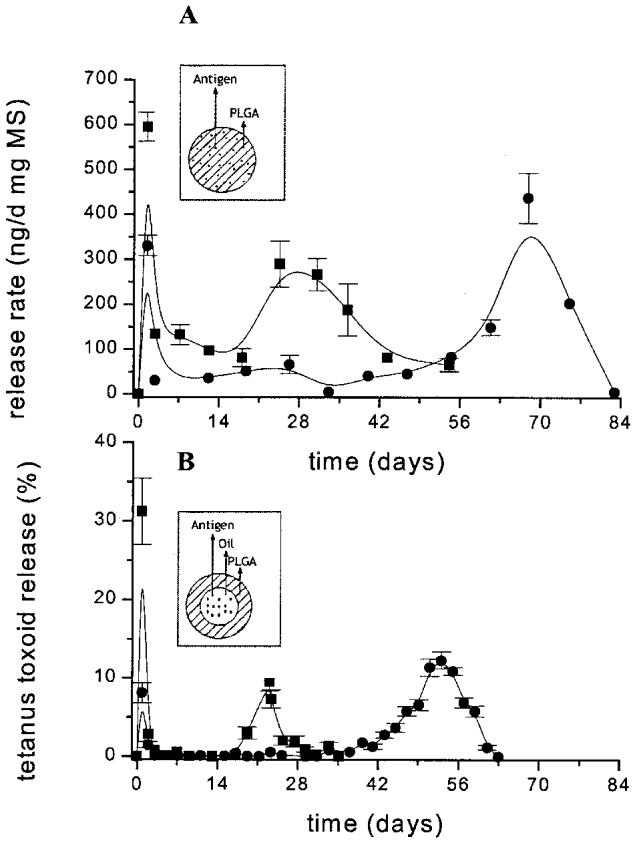

Fig. 1. (A) *In vitro* release rates (in mg antigen per day and per mg microspheres) of tetanus toxoid antigen from spray-dried PLGA [50:50 (■)] and co-acervated PLGA [75:25 (●)] microspheres (26). (B) *In vitro* release of tetanus toxoid antigens from "oil-filled PLGA microcapsules." The lactic acid/glycolic acid ratio was 50:50 (■) and 75:25 (●), respectively (31).

Khoo and Thiel proposed PLGA-based implants to obtain pulsed release of antigens (32). The implant consists of a core of antigen in dibasic calcium phosphate coated with Eudragit S 100, which dissolves above a pH of 7.0. In turn, the Eudragit S 100 layer is coated with a blend of PLGA and ethyl cellulose. After hydratation of the outer layer, PLGA degrades and forms pores. Consequently, the Eudragit layer dissolves causing hydratation of the core and release of the antigen. The use of the Eudragit layer greatly delays the initial drug release. As an example, vitamin B12 was released after a lag time of 75 days. Co-administration of an uncoated and a coated implant resulted in pulsed release of antigens after 1 day and 75 days, respectively, and allowed complete vaccination of an animal in a single handling (32).

Pharmaceutical formulation of proteins under aqueous conditions is highly desirable to avoid protein degradation, which may occur when using organic solvents as in the preparation of PLGA devices. The group of Hennink introduced degradable dextran-based microspheres, formed in aqueous environments, for pulsed delivery of proteins (33). The dextran-hydroxyethylmethacrylate (dex-HEMA) microspheres degrade under physiologic conditions due to hydrolysis of carbonate esters in the cross-links of the microgels. To obtain

degradation controlled release and to avoid having the entrapped proteins passively diffuse from the microspheres, the initial mesh size of the dextran network is kept smaller than the hydrodynamic diameter of the encapsulated proteins. Figure 2 shows the *in vitro* release of IgG from dex-HEMA microspheres, which differ in cross-link density. The initial release was lower than 10% of the load. Increasing the cross-link density of the microspheres delayed the onset of release from 5 to 15 days, whereas the booster release occurred over a week, which is considerably shorter than observed for PLGA microspheres. To lower further the initial release and to enhance the loading of lipophilic drugs into the aqueous microspheres, drug-loaded liposomes were entrapped in the dex-HEMA microspheres. In this way, intact drug-carrying liposomes were released in a pulsed manner over a period of months (34).

A possible disadvantage of the dextran-based microgels described above is the use of chemicals to cross-link the dex-HEMA. The group of Okano focused on calcium alginate beads that were prepared through physical cross-linking of an aqueous alginate solution (35) and which degrade (dissolve) due to exchange of chelated calcium ions with sodium ions from the medium. They showed that sterical entrapment in the gels, which is necessary to avoid initial release, could only be obtained for high molecular weight compounds (dextran $\geq$ 145,000 g/mol). Also, the lag time was short; it increased from 0.5 to 8 h by increasing the alginate concentration and size of the beads. By combining calcium alginate beads of three different diameters, three pulses of dextran release could be established. However, the bead sizes were $\geq$1 mm. Much smaller sizes would be necessary, thus reducing the already short delay times.

Surface-Eroding Systems

Polyanhydride (36,37) and poly(ortho)ester (38) based matrices degrade by surface erosion because the hydrolysis of the polymer occurs faster than the water penetration into the matrices. Consequently, mass is lost more rapidly from the surface than from the bulk. This property may be attractive for pulsed delivery systems employing multilaminated devices that consist of drug-containing layers altered with (drug-free) isolating layers. The length of both the lag times and the active delivery phases can be tailored by changing the type and thickness of the isolating and drug-containing layers.

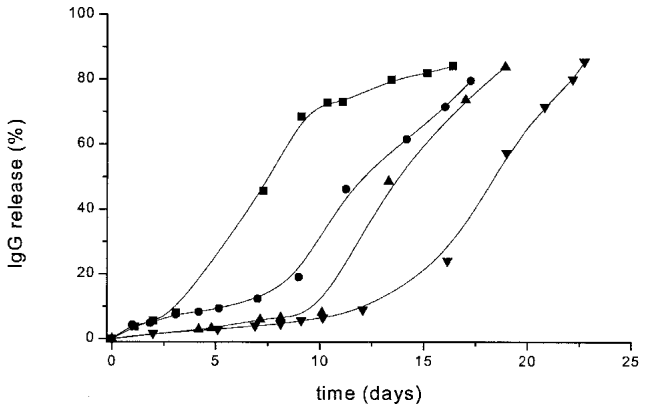

Fig. 2. *In vitro* release of IgG from degrading dex-HEMA microspheres (33). The dex-HEMA concentration of the microspheres was 50% (w/w), whereas the degree of substitution (i.e., the amount of HEMA groups per 100 glucopyranose units) equalled 3 (■), 6 (●), 8 (▲), and 11 (▼), respectively.

Göpferich and co-workers investigated the use of polyanhydrides in surface erodable implants (37,39,40). The first reported implants consisted of a core and a mantle (Fig. 3A), respectively 4 and 6 mm in diameter, both made of poly[1,3 bis(carboxy phenoxypropane)-*co*-sebacic acid], or p(CPP-SA). As shown in Fig. 3A, brilliant blue (BB), which was entrapped in the mantle, was released immediately, whereas carboxyfluorescein (CF), present in the core, was released after 2 days, being too short for many applications. To overcome this, they suggested a combination of surface and bulk eroding polymer layers (Fig. 3B); a drug-loaded p(CPP-SA) core, surrounded by a drug-free mantle of p(CPP-SA), which was then coated with PLA to prevent early erosion and drug release from the core. Finally, a mantle of p(CPP-SA) was applied, containing the drug to be released initially. Two pulses occurred (Fig. 3B). BB was released immediately, whereas CF release, delayed by the erosion of the PLA-layer, started after 2 weeks. The rapid release of BB from the mantle was explained by its high water solubility. When the less water-soluble CF was in the outer layer, a pulse that lasted for about 1 week was observed. It indicates that the release from the outer layer strongly depends on the hydrophilicity and probably also on the molecular weight of the drug. The implants described above were intended to locally treat brain cancer. Again, a problem of these implants is their size, certainly when several implants need to be inserted. Moreover, the onset of drug release has to be adjusted from days to months. Therefore, the drug-loaded p(CPP-SA) core was directly coated with PL(G)A to trigger the onset of drug release (39). Only "tempered" PLGA and PLA matrices (i.e., matrices that were thermally treated in silicon oil to close pores and cracks) showed a pulsed release of pyranine *in vitro* with an onset time of release on day 4 and day 70, respectively (Fig. 3C). Experiments on mice in which the matrices were subcutaneously implanted (39) suggested that the *in vivo* release is in reasonable agreement with the release results observed *in vitro*.

Jiang *et al.* have recently proposed another laminated device for pulsed protein delivery (41). As the insert in Fig. 4 shows, the cylindrical device consists of protein-loaded layers and isolating polyanhydride layers that govern the lag time between the pulses. The cylindrical device is surrounded by a polycarbonate coat and shows one open end. It was observed that the inner alternate layers gradually degrade from the open end. An interesting feature is that in the drug layer, the protein is complexed to a polymer [i.e., poly(methacrylic acid)/polyethoxazoline]. This complexation, which is pH-sensitive, promotes protein stability in the acidic microclimate created during polyanhydride degradation. As shown in Fig. 4, at low pH the complexation retains the proteins in the drug layer until the upper drug-free polyanhydride layer degrades totally. For myoglobine and FITC-BSA (Fig. 4), sharp release pulses were obtained. Both the lag times and the duration of the pulses could be tailored by varying thickness and composition of the polyanhydride layers. Because the device is only useful for drugs that can be complexed to the polymer, Qiu *et al.* suggested using pH-sensitive degradable layers consisting of polyphosphazene (42). The release profiles depend on the type of drug: the more hydrophilic the drug, the more easily

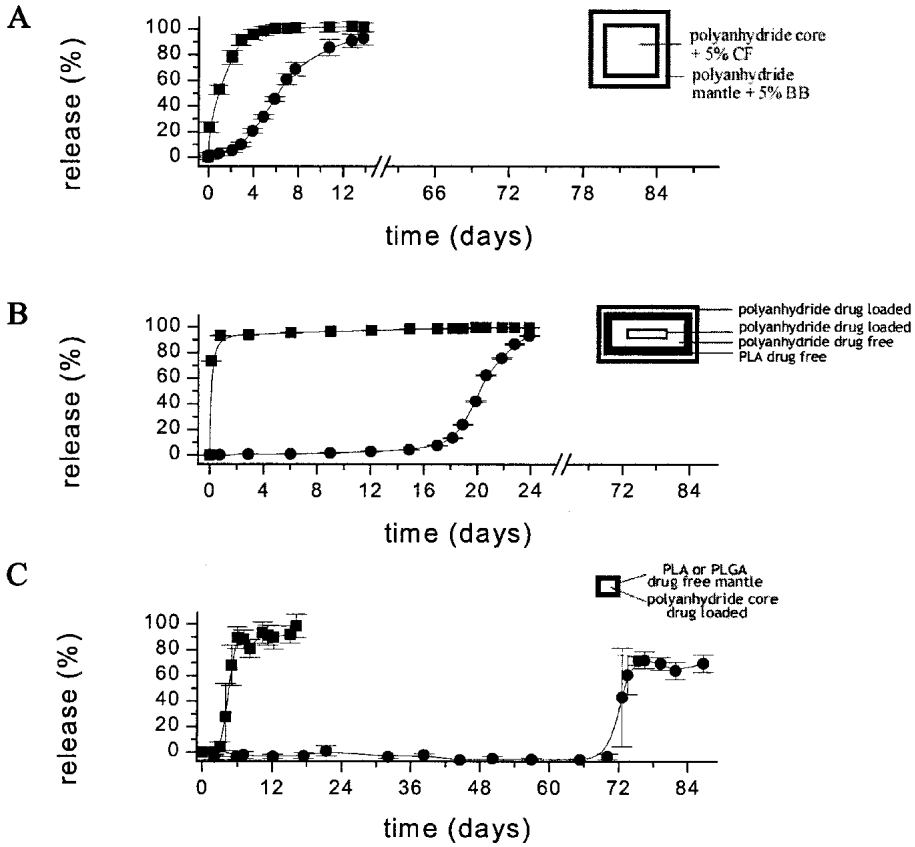

Fig. 3. (A) Release of brilliant blue (BB; ■) and carboxyfluoresceïne (CF; ●) from a cylindrical polyanhydride device, which is schematically represented in the insert (37). The core contains CF, whereas the mantle is loaded with BB. (B) Release of BB (■) and CF (●) from the implant as shown in the insert (37). The core contains CF, whereas the mantle contains BB. (C) *In vitro* release of pyranine from the device shown in the insert. The PLGA [(■), M_w of 10,500g/mol] and PLA [(●), M_w of 30,000 g/mol] matrices are tempered (37).

it diffuses out, seriously influencing the intervals between the pulses. Lag times could be tailored from 18 to 165 h, and the duration of the pulse varied between 19 and 40 h. As a contrasting test, a device was examined that was composed of polyanhydride isolating layers and drug-loaded PEG (not pH sensitive) layers. Similar to most other eroding devices mentioned above, an initial burst of the drug was followed by a sustained release phase instead of a second pulse. Therefore, the combination of polyanhydride layers with a pH-sensitive layer seems to be providing passively degrading devices for multiple pulsed drug release. The major disadvantage of these systems for single-shot vaccination is their large size (2–3 mm diameter and 11–14 mm height) and their complexity to manufacture (multilayered).

Pulsed Delivery by Enzymatic Degradation of the Device

Pharmaceutical matrices can also be degraded by incorporation of enzymes in the matrix during manufacturing. Franssen *et al.* studied enzymatic degrading dextran hydrogels (43). The model protein IgG along with dextranase was incorporated during polymerization of methacrylated dextran (dex-MA). The release of IgG was fully dependent on the degradation rate of the gel, which was strongly affected by both the concentration of dextranase and the cross-link density of the gel. At low dextranase concentration, a delay in the release was indeed observed, whereas at higher concentrations of dextranase, the release of IgG started immediately. To obtain multiple release pulses, the authors suggested simultaneously injecting micrometer-sized dex-MA hydrogel particles with different amounts of dextranase and/or different compositions. However, miniaturization of the gels seemed to be difficult because the release from dextranase-containing microspheres followed zero-order kinetics without lag time (44).

Kibat *et al.* designed another enzymatic degrading device. (45). Phospholipase A_2–coated liposomes were encapsulated in alginate microgels further coated with polylysine (see insert in Fig. 5). Following hydratation, the phospholipase degraded the phospholipids, thus allowing release of entrapped drugs by diffusion through the microcapsule. As Fig. 5 shows, a delay in the release of bovine serum albumin was observed and depended on the amount of phospholipase used. Pulsed release *in vivo* was demonstrated after subcutaneous implantation in mice (45): the hydrogel matrix protected the liposomes from degradation and dispersion in the body, the liposomes acted as a drug depot, while the polylysine coat prevented dissolution of the alginate gel in the physiologic environment.

Similar to the device shown in Fig. 4 (41), Moriyama *et al.* described a nondegradable silicone tube containing alternat-

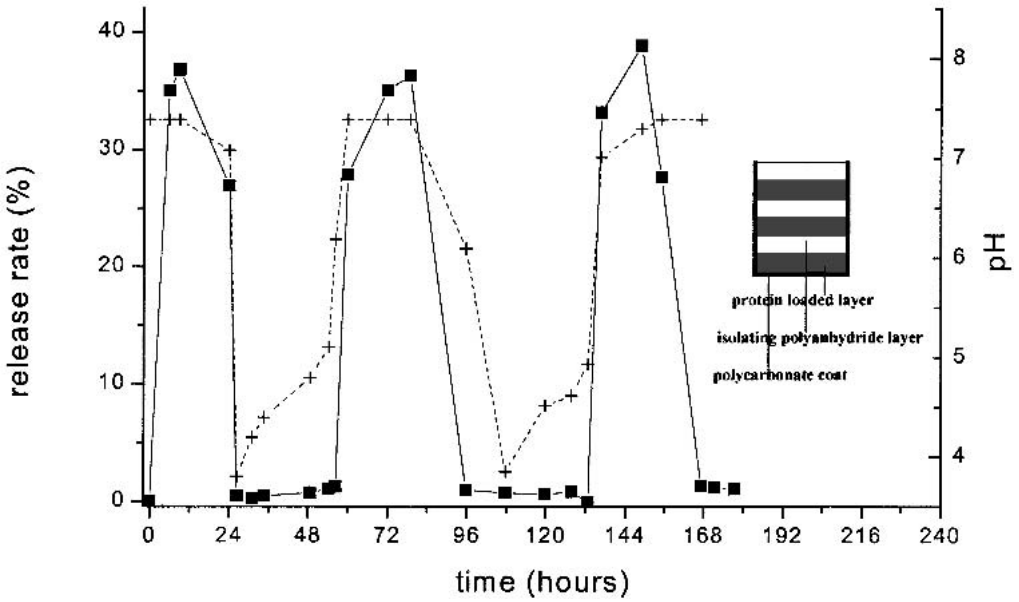

Fig. 4. *In vitro* BSA release (■) from the laminated device (see insert) reported by Zhu *et al.* (41). In the protein layer, the proteins are complexed to PMAA/PEO. The pH of the dissolution medium is also shown (+).

ing dextran layers and PEG-grafted dextran layers loaded with insulin (46). The PEG domains prevented diffusion of insulin into the dextran layers. *In vitro* pulsed insulin release occurred after 10 and 50 h, respectively, due to surface degradation by the (nonphysiologic) dextranase that cleaves dextran from both open ends of the silicone tube. A similar device that could be degraded by hyaluronidase, which is present in higher concentrations at inflammatory sites, was also proposed (8).

PULSED DELIVERY BASED ON THE OSMOTIC PRESSURE OF THE DEVICE

Establishing a pressure (osmotic and/or swelling pressure) in a pharmaceutical device requires a membrane surrounding the device that is permeable by water but impermeable by the drug and the pharmaceutical ingredients. Delivery from such devices is not only controlled by the osmotic or swelling agent but also by the water permeability of the mem-

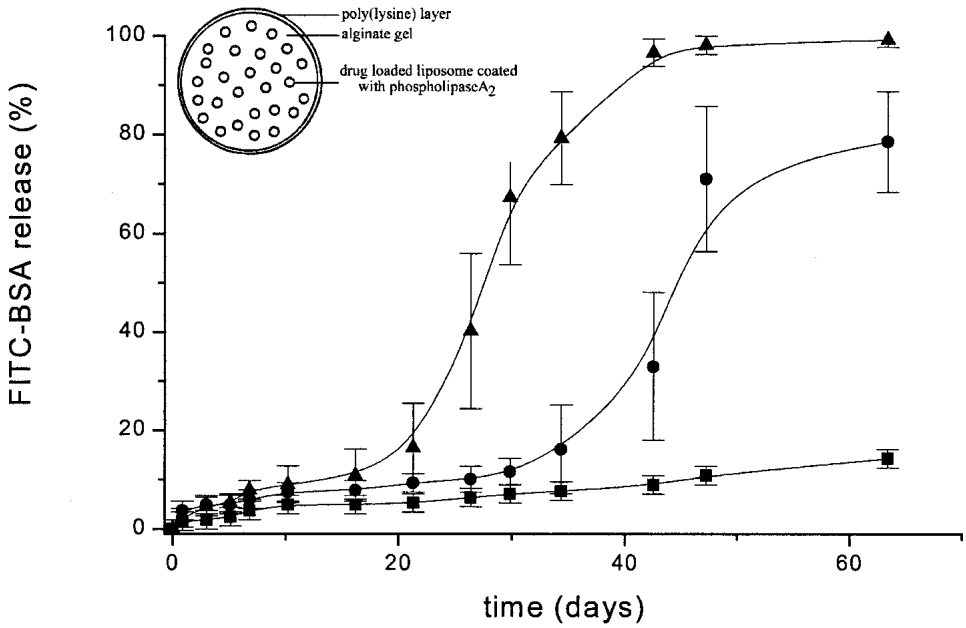

Fig. 5. *In vitro* release of FITC-BSA from alginate-poly(lysine) microgels loaded with liposomes without phospholipase A_2 (■) and with phospholipase A_2 [(●) 1 unit; (▲) 10 units] (45).

brane, which in turn, is governed by the composition and thickness of the membrane.

Pulsed Delivery by Osmotic Pumping of the Device

Osmotic delivery systems have achieved wide acceptance, as they can deliver drugs at a constant rate and are largely independent from the environment (47). However, researchers from Alza Corporation modified the osmotic pump to achieve pulsed delivery for circadian therapeutic requirements.

A veterinary pulsed delivery system (for implantation or oral intake) was derived from the Higuchi-Leeper pump (48). Water diffuses through the semipermeable membrane into the chamber containing a solution with excess solid salt. Due to the dissolution of the salt, the osmotic pressure rises, which stretches the elastic cap. Once a crucial pressure is produced, the orifice opens, releasing the drug as a pulse. The pressure then falls, the orifice closes, and the cycle repeats.

The elementary osmotic pump Volmax is used to treat nocturnal asthma by delivering a pulse of salbutamol several hours after being swallowed (49). Volmax contains sodium chloride as the osmotic agent in the core. Sodium chloride also lowers the solubility of salbutamol. When the sodium chloride is expulsed after swallowing, the salbutamol quickly dissolves, which results in an abrupt increase in the release rate of salbutamol. Only a single pulse of the drug can be delivered by Volmax. Moreover, the concept is only useful for delivery of drugs with specific solubility properties.

Concerta, used to treat attention deficit hyperactivity disorder (ADHD) for school-aged children, is a modified push-pull osmotic pump that releases methylphenidate hydrochloride in a pulsed manner (50,51). As shown in the insert of Fig. 6, the Concerta capsule comprises a trilayer core surrounded by an immediate-release drug coat. The trilayer core is composed of two drug layers and a push layer containing osmotic active components. In the gastrointestinal tract, the drug coat dissolves within 1 h, providing an initial dose of methylphenidate. Water can cross the semipermeable membrane, hydrating the push layer and the interior drug layers. The push layer causes the release of methylphenidate through the precision laser-drilled orifice on the drug-layer end of the capsule. As Fig. 6 shows, an initial plasma concentration is reached in 1–2 h. Five to 6 h after being swallowed, methylphenidate hydrochloride is suddenly released (51).

Pulsed Delivery by Osmotic Bursting of the Device

As early as 1975, Baker described the delivery of drugs by osmotic bursting of the device (52). Figure 7A shows the device consisted of a water-permeable membrane that enclosed the core containing the drug and an osmotic attractant, such as NaCl or other salts. In an aqueous environment, water is osmotically drawn into the core, which swells until the membrane ruptures and releases the already dissolved drug in a "single" pulse (Fig. 7). This process, which is basically governed by the osmotic pressure of the core and the strength of the membrane, has been mathematically described by Kuethe *et al.* (53). The concept is comparable with the osmotic pump design; however, the device does not have an orifice in the outer membrane. This fact makes it less expensive because laser technology, which drills the orifice in the outer membrane, is not necessary.

Ueda *et al.* presented the "time-controlled exploding system" (TES) (54). TES, which has a four-layer spherical structure (see insert in Fig. 7B), consists of a polystyrene core (3.2 mm in diameter) on which the drug is loaded. The penetration of water through the water-insoluble membrane (e.g., ethylcellulose) hydrates the swelling agent (e.g., hydroxypropylcellulose). The expansion of the swelling agent destroys the membrane, and subsequent rapid drug release occurs. The authors showed that the lag time could precisely be programmed by the thickness of the outer membrane. Oral administration of TES particles with different lag times shows potential for short-term (hours) multiple pulsed drug delivery (see Fig. 7B). Because the pressure of the swelling agent destroys the outer membrane, the lag time is independent of the physicochemical properties of the encapsulated drug.

An osmotic bursting implant was reported by Thiel *et al.* (55). An antigen was included in a compressed core of Ex-

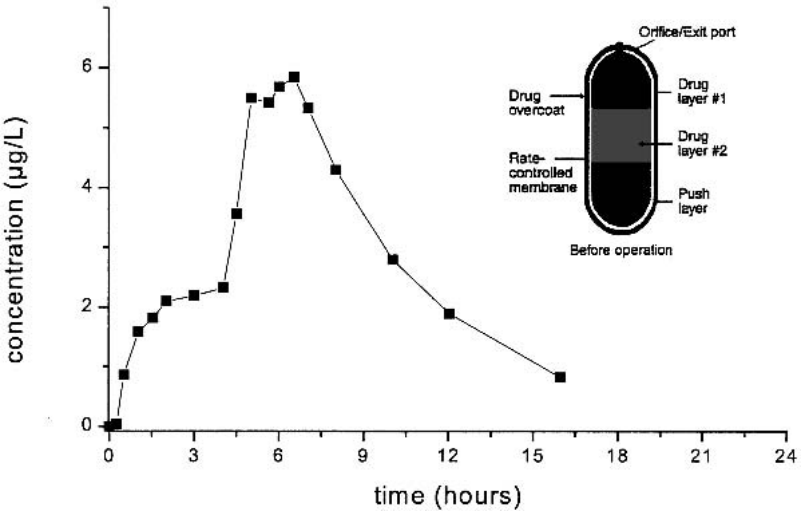

Fig. 6. Blood concentration of methylphenidate hydrochloride after oral administration of a Concerta (18 mg) capsule from which pulsed delivery is obtained by osmotic pumping (51).

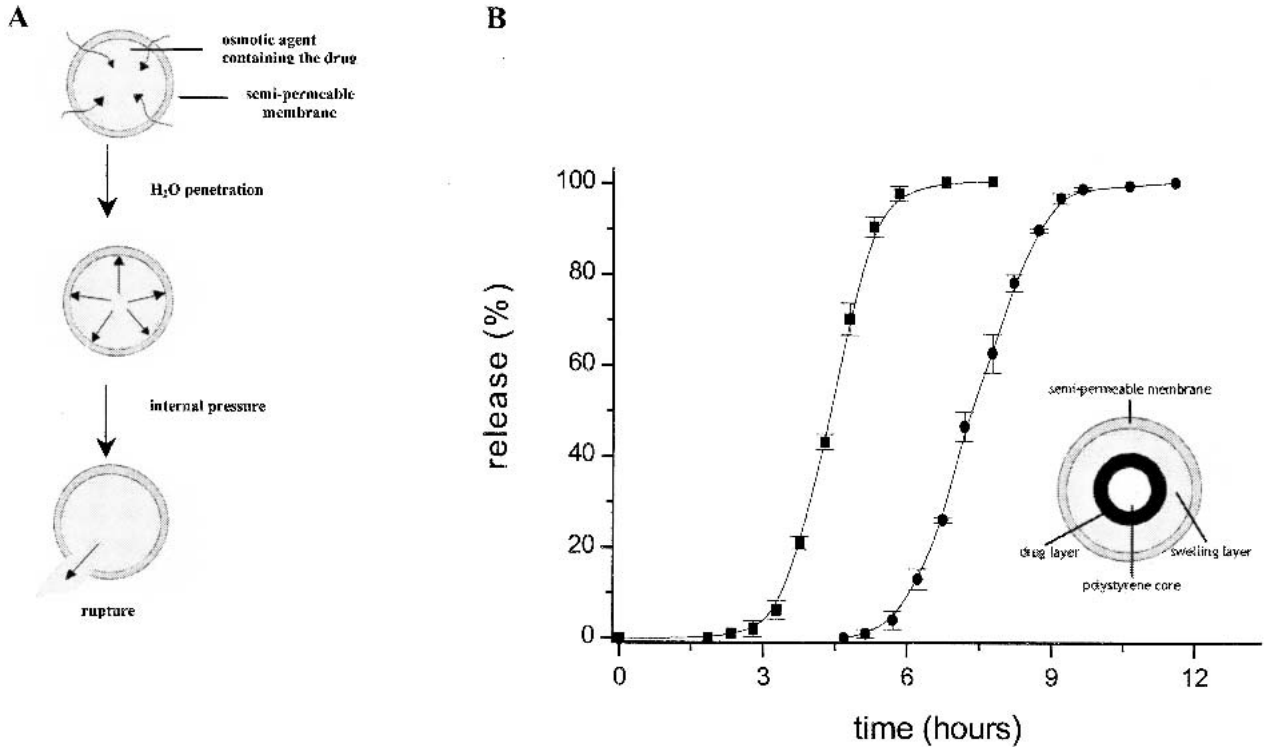

Figure 7. (A) Schematic representation of an osmotic bursting device when placed in a biological fluid. Water penetrates through the membrane. Due to the high solubility of the incorporated active agent, a high osmotic pressure is created, which ruptures the wall and leads to a sudden release of the drug. (B) *In vitro* release profile of diclofenac sodium from TES (see insert) with a lag time of 3 h (■) and 6 h (●), respectively (60).

plotab (sodium starch glycolate). The core was coated with a pH-sensitive Eudragit S 100 film, which was again coated with an insoluble Eudragit NE30D film containing hydroxypropylmethylcellulose (HPMC) as a pore former. In an aqueous environment, the HPMC in the outer coat dissolved, creating pores that allowed water to access the Eudragit S 100 coating (which dissolves at tissue pH). Consequently, the water enters the core, thereby swelling and rupturing the outer membrane, which results in a pulsed release of the antigen. *In vitro*, the release of antigens could be delayed for 14 to 26 days. Also, *in vivo* pulsed antigen delivery has been achieved by co-administering coated and uncoated implants.

To achieve pulsed release of antigens, Cardamone *et al.* packed alternate active and spacer tablets into a water impermeable tube (5 cm in length by 8 mm in outer diameter) (56). One end of the tube was plugged and the other end contained a swellable agent ("driver tablet") surrounded by a porous polymer cap. Water entered through the porous cap to swell the driver tablet, pushing the plug out of the tube. Hence, the surface of the first tablet was exposed to the environment.

PULSED DELIVERY BY DEGRADATION AND OSMOTIC BURSTING OF THE DEVICE

In the devices described above, the increase in osmotic pressure, which governs the drug release, is mainly controlled by the rate at which water flows through the membrane. Rather recently, devices have been reported where the degradation of the matrix determines the kinetics of osmotic pressure increase.

The group of Okano investigated the release from millimeter-sized calcium alginate beads coated with a polyacrylamide layer (see insert in Fig. 8) (57). Drug release occurs by sodium ions diffusing from the medium into the gel and exchanging with calcium ions. Consequently, alginate gels turn into alginate solutions, increasing the osmotic pressure. This cracks the polymer coating, resulting in a pulsed release of the contents (Fig. 8). Only for high molecular weight dextran (≥145,000 g/mol) could the initial release be suppressed to levels below 10% of the load. Applying thicker coats on the beads resulted in lag times of up to 60 h. A fast booster

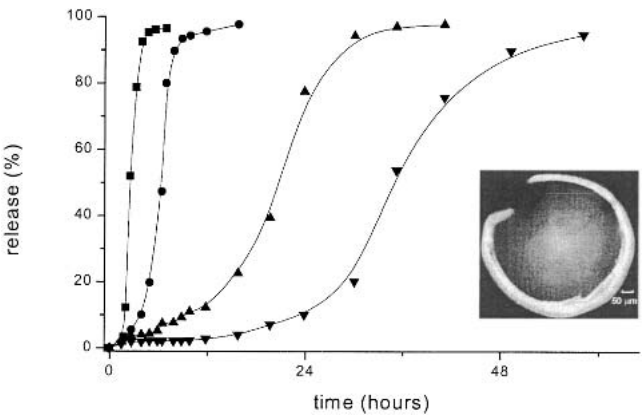

Fig. 8. *In vitro* dextran (MW of 145,000 g/mol) release from calcium alginate beads without coating (■) and with a polyacrylamide coating of 25 μm (●), 50 μm (▲), and 75 μm (▼) (57). The insert shows the crack in a coat surrounding the alginate bead (loaded with FITC-dextran) after 24 h exposure to buffer.

release was observed. Multiple pulsed deliveries of macromolecular drugs may be realized by mixing alginate beads with various coat thicknesses. However, the design of injectable micrometer-sized alginate beads of this type could be a problem.

Our group recently proposed a "degradation controlled exploding microcapsule" for pulsed delivery (58,59). As in the concept of Okano, the capsule would consist of a water-permeable membrane (allowing transport of water and preventing large molecular weight drugs from leaving the capsule) and an entrapped gel. However, the entrapped gel would be biodegradable. In contrast to the alginate beads, where the sodium ion flux determines the rate at which the alginate turns into a solution, the degradation rate of the gel (through spontaneous or enzymatic hydrolysis) would govern the osmotic pressure increase and thus the time of explosion of the microcapsules. Though the onset of release is rather short for the polymer-coated alginate beads, much longer lag times would be obtained in this way. The major challenge to realizing this concept will be the coating of the degrading gel core. The membrane surrounding the gel has to be i) very homogeneous, ii) permeable by water, iii) impermeable by the entrapped drug and the degradation products of the gel, and iv) rupture at the time the polymer gel turns into a polymer solution.

CONCLUSIONS

This review shows that, especially within the past decade, different concepts and devices have been proposed for precisely timed drug delivery. The list of potential uses of programmed devices for multiple pulsed drug delivery becomes longer as our knowledge of chronotherapy rapidly grows. Examples include the pulsatile administration of gonadotropin releasing hormone (for the induction of fertility), vaccines, and corticosteroids (in the treatment of adrenal insufficiency) to name but a few. However, research on most of the programmed drug delivery devices is still in the concept phase. Most systems are only for academic use, their performance *in vivo* has often not been tested, and clinical results are clearly lacking. Obviously, the concepts and devices will have to be closely examined before they may be rendered applicable for practical use. Crucial considerations are the biocompatibility of the pharmaceutical ingredients used, shelf life, and ease and cost of large-scale manufacturing, which appears to be complicated, requiring special equipment and many manufacturing steps.

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