Expert Opinion

Pulsed drug delivery

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Modern drug delivery aims to develop drug delivery systems that are able to meet specific therapeutic requirements. Whereas sustained drug release aims to maintain a constant drug level within the body, pulsed drug delivery intends to release the drug rapidly within a short period of time, as a result of a biological or external trigger, after a specific lag time. This editorial highlights some of the recent advances in new concepts for pulsed drug delivery and proposes some future strategies.

Keywords: drug delivery, pulsed drug release, single-shot vaccination, triggered release

Expert Opin. Drug Deliv. (2006) 3(4):459-462

1. Introduction

During the past few decades much effort has been made on the development of dosage forms for sustained drug release, to provide a constant release rate and concentration in the bloodstream. Pulsed drug release can be defined as the rapid and transient release of a drug after a lag phase with no or little drug being released [1]. It could be of interest (e.g., to prevent drug tolerance, as in the case of nitrate therapy where a sustained therapy leads to the rapid development of tolerance), to satisfy circadian requirements (that can modulate the pharmacokinetic and pharmacodynamic responses, as in the case of attaining night-time theophylline levels in antiasthmatic therapy) and to achieve on-demand responses (as in insulin therapy).

Drug delivery scientists have worked on several concepts that hold promise to establish pulsed drug release profiles. One way to classify the pulsed drug delivery systems that are under development is based on the physicochemical and biological principles that trigger their release. In programmed delivery systems the release is completely governed by an inner mechanism of the device (i.e., the lag time prior to drug release is controlled primarily by the delivery system). In triggered delivery systems, the release is governed by changes in the physiological environment of the device (biologically triggered systems) or by external stimuli (such as the application of an electromagnetic field, ultrasound or laser light for example).

In the editorial of the latest workshop on pulsatile drug delivery in Königswinter, Germany in 1992, [2] NA Peppas concluded that 'one is convinced that this relatively young field of controlled release will continue being the subject of innovative research and dramatic developments'. In this editorial, De Smedt *et al.* will briefly overview some of the most recent advances towards new materials that hold promise for pulsed drug delivery after implantation or injection. Section 4 describes some of the considerations that may have to be taken into account in future pharmaceutical research on pulsed delivery of vaccines and therapeutics.

2. Implantable microchips for pulsed drug release

Langer *et al.* reported on the fabrication of implantable microchips for the controlled release of therapeutics [3]. The microchips consist of several microreservoirs, containing the therapeutics, embedded in a matrix. The drug release from any desired microreservoir can be triggered by applying an electric current to the seal of the corresponding microreservoir, inducing the dissolution of the seal, leading to

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the release of drug molecules. In another approach, biodegradable polymers, such as poly(lactic acid) and poly(lactic-co-glycolic acid), were used to fabricate the seals of the microreservoirs [4]. By tailoring the degradation rate of the seal material, it was possible to tailor the exact moment at which the drug molecules were released from a specific microreservoir, creating a steep release profile.

3. Injectable exploding microcapsules for pulsed drug release

Microcapsules, releasing their content in response to an internal or external trigger, are of great interest in the field of pulsed drug delivery. Due to their micrometer dimensions, they can be administered by injection, offering considerable advantages towards patient compliance as they are less invasive than implants. Recently, several research groups reported on 'exploding' microcapsules. A first type of exploding microcapsules was reported by the research groups of Sukhorukov [5] and Caruso [6]. Polyelectrolyte microcapsules containing gold nanoparticles were fabricated using the layer-by-layer technique. Therefore, a sacrificial colloidal template was coated with several polyelectrolyte layers of opposite charge and also one layer of gold nanoparticles, followed by the dissolution of the template resulting in the formation of hollow capsules. Afterwards, the capsules could be filled with macromolecules by reversibly changing the permeability of the layer-by-layer membrane. Irradiation of the microcapsules with infrared light induced local heating of the gold nanoparticles, causing a disruption of the layer-by-layer membrane and thus the release of the encapsulated molecules. As infrared light is able to penetrate the skin over several millimetres, such microcapsules, once injected subcutaneously, could be interesting for pulsed drug delivery. De Smedt and colleagues recently reported a second type of exploding microcapsules, which consist of a biodegradable microgel core surrounded by a semipermeable membrane [7,8]. When the microgel core degrades, an internal (swelling) pressure is created, finally leading to rupturing of the membrane and release of the encapsulated material. The evolution of the swelling pressure, and thus the time of explosion of the microcapsules, is determined by the degradation rate of the microgel core, which can be tailored from days to weeks by varying the crosslink density of the microgels. Such microcapsules hold promise as a pulsed drug delivery system (e.g., for single-shot vaccination where several populations of microcapsules, each population with a different degradation rate, could generate multiple vaccine pulses after a single injection). Importantly, on both types of the exploding microcapsules, only *in vitro* data are now available. A major challenge of current research is to make the microcapsules explode in animals.

It could be interesting to make use of physicochemical differences between the extra- and intracellular medium to deliver therapeutic molecules, such as peptides and nucleic acids, to an intracellular target. It is well known that the pH in the endo/lysosomes is up to two units lower than the extracellular pH (i.e., pH 7.4). Recently Lynn *et al.* reported on a novel family of pH-sensitive degradable polycations (so called poly-β-aminoesters) [9]. These polymers exhibit some unique features as they seem to be only soluble at a pH < 6.5. Poly-β-aminoester-based micro- or nanoparticles rapidly dissolve when they are transferred from pH 7.4 to a slightly acidic pH [10]. These characteristics are highly interesting as it would allow such microparticles to release their drug content following cellular internalisation. DNA and antitumour agents have been encapsulated in such microparticles and have been successfully used for cellular delivery *in vitro*.

4. Expert opinion

'Precisely timed drug delivery may maximise therapeutic efficacy, may minimise dose frequency and may reduce toxicity by avoiding side effects and drug tolerance' is a slogan that is often cited. The question remains whether this will remain hype or whether this may become reality.

It is claimed by the WHO and research funding foundations (e.g., the Bill and Melinda Gates Foundation) that single-shot vaccines, where the initial and booster doses are contained in one delivery system, could improve vaccination coverage by reducing the number of vaccination sessions that are required to generate immunity. Single-shot vaccination would be a major step forward not only in delivering established vaccines but also for future vaccines. As an example, it is expected that women will need three to four antigen doses, spread over a number of months, to become well protected against human pappiloma virus-induced cervical cancer. Thus, both the developing countries as well as the Western World could benefit from single-shot vaccines. To develop these vaccines, many preclinical studies that have been undertaken in recent years have proven that biodegradable microspheres (often based on poly[lactic acid]/poly[glycolic acid]) that release the antigen in a sustained (i.e., not pulsed) method are promising in generating immunity [11]. Clinical testing would be the next step; however, the financial resources that are available today seem to be a major bottleneck for clinical research on single-shot vaccination. The major question on whether pulsing single-shot vaccines should be preferred over slowly releasing single-shot vaccines also remains unanswered. Considering the impact that single-shot vaccines could have on human health, the authors of this editorial strongly encourage pharmaceutical and clinical researchers to focus on pulsed delivery of antigens. Both the implantable microchips, as well as the exploding microcapsules that have been described above, should be evaluated for this purpose.

In the last decade, material scientists were able to fabricate new materials with unique properties to respond to biological triggers, at least *in vitro* and *in vivo*. Biocompatible glucose sensors can open opportunities as triggered devices to guide insulin release from implanted subcutaneous supplies [12]. It is

important to notice that the major part of the pulsed drug delivery devices reported are prototypes performing well *in vitro*; however, no data are available on their performance *in vivo*. Therefore, it remains a huge challenge to cope with the influences of a biological environment on the integrity of the drug delivery devices and on their drug release profile. Another question is whether fluctuations in temperature, pH and so on that are under physiological or pathophysiological conditions are sufficiently large enough to meaningfully influence the drug release.

It is the authors' opinion that the rather limited progress in *in vivo* pulsed delivery of therapeutic agents is also partially due to limited knowledge of which drugs and indications would benefit from pulsatile or temporally modulated release. Quite a lot of challenges remain in this regard. Many diseases display symptoms and onset characteristics that are randomly distributed within 24 h: for example, coronary infarction and angina pectoris (activity related), asthmatic attacks (early morning) and peptic ulcer pain (night). Data, primarily concerned with the chronopharmacokinetics of propranolol, organic nitrates, nifedipine, antiasthmatics and histamine H_2-blockers, can be taken as examples [13,14]. Pulsed drug delivery should make glucocorticoid replacement therapy as physiological as possible; the normal pattern of secretion including a diurnal rhythm and a pulsatile ultradiurnal rhythm. It may enable dividing the daily delivered dose and temper the long-term side effects, such as adrenal suppression and lowered bone mineral density [15].

Even with relatively small and well-known molecules, indirect approaches can be hypothesised to pathological conditions. It has been clearly demonstrated that benzodiazepine administration affects the activity of the hypothalamus–pituitary–adrenal axis (HPA) with a variety of effects at both the central and peripheral level. An inhibitory effect of diazepam on the adrenocorticotropic hormones has been reported. Alprazolam possesses the most remarkable inhibitory effect on the HPA axis, being 40-times more potent than diazepam. This finding could enable programmed release in the case of panic that is provoked by central HPA axis hyperactivation [16].

As far as benzodiazepines are concerned, pulsed drug delivery of diazepam may be beneficial in case of addiction by releasing appropriate doses diminishing in time.

It seems that the consequences of circumstantial change of sleep and wakefulness by shift work are largely underestimated. Disrupted nocturnal production of melatonin and reproductive hormones are of relevance for breast cancer aetiology. Studies that have been completed to date have found an increased risk of breast cancer associated with indicators of exposure to light-at-night and night shift work [17]. More insight into the neurophysiology of sleep and wakefulness may enable the installation of a programmed sleep pattern by releasing agents relevant to different sleep phases [18].

We should be encouraged to further challenge the pharmacokinetic paradigm that 'flatter is better': what drugs and/or therapeutic indications will benefit indeed from temperature, pH, ionic strength and so on induced release? Further pharmaceutical research in pulsed drug delivery should also be supported by biologists who should try to obtain better insights into circadian rhythms.

On the other hand, assuming that we would know what the optimal delivery equation looks like for a certain drug, as material scientists the authors wonder whether it will ever be possible to design delivery systems based on biocompatible building blocks, as this is a primary requirement needed to reach clinical phase testing, which truly meet the (very likely complicated) delivery characteristics. We continue to share the opinion as formulated by NA Mazar 15 years ago [2] that 'programmable electronic pumps with multiple microsensor inputs' (which we now call microchips) [3,4] will ultimately be the better (and possibly even the only) way to achieve highly sophisticated (quantitatively precise and flexible) temporally modulated drug release. Considering these criticisms, De Smedt *et al.* believe that in the coming years pulsed drug delivery scientists should define (in a trans-disciplinary approach) which type of drugs/diseases will be the focus for pulsed drug delivery research, with the hope that within the next decade (at least) one injectable pulsed drug delivery system will become available to a large group of patients. To define this focus, a workshop on pulsatile drug delivery, 15 years after Königswinter, would be welcome.

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