

Recent advances in remotely controlled pulsatile drug delivery systems

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ABSTRACT

Pharmaceutical technology is drastically developing to enhance the efficacy and safety of drug therapy. Pulsatile delivery systems, in turn, gained attraction for their ability to deliver the right drug amount to the right body site, at the right time which is advantageous over conventional dosage forms. Their use is associated with increased patient compliance and allows on-demand drug delivery as well as customizable therapy. Recent technologies have been implemented to further develop pulsatile delivery systems for more precise determination of the dosage timing and duration as well as the location of drug release. Great interests are directed towards externally regulated pulsatile release systems which will be the focus of this review. The recent advances will be highlighted in remotely controlled delivery systems. This includes electro responsive, light-responsive, ultrasound responsive, and magnetically induced pulsatile systems as well as wirelessly controlled implantable systems. The current status of these technologies will be discussed as well as the recent investigations and future applications.

Key words: Light responsive, magnetic, pulsatile delivery, remotely controlled, ultrasound, wireless

INTRODUCTION

Oral drug delivery systems constitute the largest part of delivery systems in being widely distributed in the pharmaceutical market with conventional dosage forms formulated for immediate drug release and complete systemic absorption. Therefore, their administration must be repetitive to attain and maintain the drug level within the required therapeutic range. Limitations to this approach include fluctuating plasma drug levels and poor patient

compliance arising from inconvenience and discomfort.^[1] Different modified delivery systems were later developed to provide a controlled drug release rate over a prolonged time period, and for localization of the drug action by spatial placement. However, in some medical conditions, controlled drug delivery is not the best choice because drug release is not needed during the early periods after dose administration.^[2]

Recently, pulsatile drug delivery systems (PDDS) are gaining a growing interest by researchers. PDDS are defined as drug delivery systems able to provide one or more immediate drug release pulses at a specific time or site, after a programmable lag phase. A single dosage form is designed to provide an initial dose of medication followed by a release-free interval, then release of a second dose

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of medication, which will be again followed by another release-free interval.^[3] PDDS deliver drugs at the precise time, to the target site, in the right amounts, providing maximum efficacy and benefits to the patients.^[4] Drug release from PDDS could be in an immediate or extended form.^[5] As for immediate release, PDDS exhibit rapid and transitory drug release within a short time-period instantly after a predetermined release-free period. However, extended-release forms allow sustained drug release after a lag time. The immediate and sustained drug release patterns of PDDS are represented in Figure 1.

The need for PDDS arises in conditions which are regulated by the circadian rhythm of the body, or when the drug is degraded in the gastric content so the lag time in release becomes important. Additionally, to deliver drugs which are undergoing metabolism through extensive first-pass effect, to target the delivery of drugs to a precise location in the gastrointestinal tract and for cases where the drug action has to be localized to achieve the desired therapeutic outcomes. PDDS show significant benefit to patients suffering from time-dependent diseases where the drug dose becomes essential during a certain time such as bronchial asthma, myocardial infarction, angina pectoris, hypertension, hypercholesterolemia, arthritic disease, gastrointestinal ulcers, and cancer.^[6]

EXTERNALLY REGULATED PULSATILE RELEASE SYSTEMS

Pulsatile drug delivery is a form of drug delivery that is time and site specific, which could either be time-controlled or stimuli mediated allowing either spatial or temporal drug delivery. Spatially controlled drug delivery involves drug release in response to an endogenous chemical or physical stimulus, as a pH change or enzyme trigger, while temporally controlled drug delivery is achieved in response to an exogenous stimulus which is externally regulated. On-demand managed release profiles are possible with remote drug delivery systems.^[7,8]

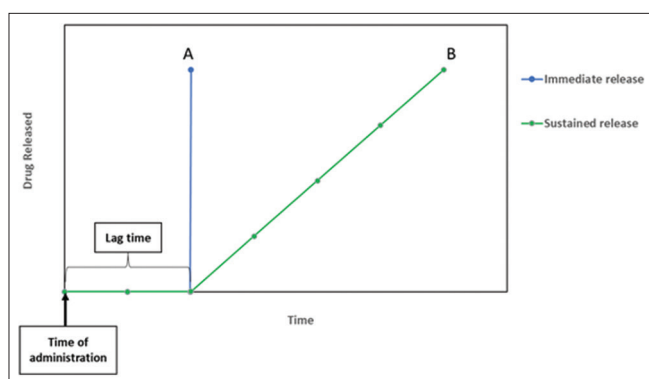


Figure 1: Patterns of drug release from pulsatile drug delivery systems. (A) Immediate release after a lag time (B) Sustained release after a lag time

Advances in remotely controlled delivery systems

Remotely controlled delivery systems are externally regulated, with the release designed to be dependent on an exogenous stimulus that can be remotely controlled, for example, by a smart device. In this article, we will look at some of the recent developments in remotely controlled delivery systems, such as electro responsive, light-responsive, ultrasound responsive, and magnetically induced pulsatile systems, as well as wireless controlled implantable systems.

Magnetic pulsatile drug delivery systems

Magnetic microcarriers were employed for targeted drug delivery due to their superior tumor targeting, therapeutic effectiveness, low toxicity, and ability to be adapted for a variety of purposes. Magnetic pulsatile delivery systems are thought to be an efficient way to distribute drugs to specific disease sites, such as tumors. Chemical agents may be used in high concentrations near the target site without causing damage to the surrounding tissues.^[6]

The design of this system involved the control of drug release from a polymer matrix by using an oscillating magnet. Magnetic microspheres and nanospheres were previously used as magnetic carriers to act as drug reservoirs which were activated by the application of an external magnet. When magnetic carriers are employed in biomedical application, it is of importance to ensure that they are water-based, nontoxic, nonimmunogenic, and biocompatible. Magnetic carriers generate a response to the external effect of a magnetic field from embedded magnetic materials such as magnetite, iron, nickel, and cobalt. This response allows to adjust the time, rate, and degree of drug absorption; to position the drug in a specific location; or to slow down its contact with unfavorable areas.^[9,10]

Magnetic steel beads were embedded in an ethylene and vinyl acetate copolymer matrix. When exposed to a magnetic field, the beads oscillate inside the matrix and thus produce compressive as well as tensile forces alternately. This functions as a pump, expelling a larger number of drug molecules from the matrix.^[11,12] The United States patent describes the targeted release of therapeutic agents to tumor cells, triggered by the application of a magnetic field to previously administered magnetic materials composed of magnetic particles linked to a target-specific ligand.^[13]

Based on alginate spheres, various formulations were developed for magnetically activated insulin delivery. Insulin cross-linked alginate spheres were formulated and the release rate was controlled by the characteristics of the ferrite microparticles, as well as the mechanical properties of the polymer matrices.^[14] More recently, antitumor magnetic dextran microgels with superparamagnetic properties were developed incorporating iron oxide nanoparticles. Doxorubicin was encapsulated and exhibited magnetic

responsive release profiles.^[15] In addition, a magnetic multi-walled carbon nanotube hydrogel was synthesized for the successful magnetic pulsatile delivery of tetracycline hydrochloride.^[16]

Despite some limitations, including the high magnetic field needed, magnetic microcarriers are still useful for selective targeting and regulated drug delivery with a promising future ahead of them. With further testing and long-term toxicity studies, they could be established as novel and effective targeted delivery systems.^[17]

Ultrasound pulsatile drugs delivery systems

Ultrasound has been one of the methods used in recent decades for diagnostic imaging in the medical field. The idea of joining ultrasound with drugs has initiated interest in different clinical fields. It entered the field of cancer therapy, where it was called “sonodynamic therapy,” as well as, for the treatment of diabetes. As for drug delivery, sound waves will be used to stimulate drug release from carriers and enhance vascular permeability. Drug release in a pulsed manner could be achieved by corrosion of the polymeric matrix.^[18,19] When ultrasound is spread in body tissues, the drug release will be stimulated through several resulting effects which are usually pressure variation, acoustic fluid streaming, cavitation, and local hyperthermia [Figure 2].^[20]

Pressure variation is based on the transmission of pressure waves into the body at varying frequencies and amplitudes.^[21] As for cavitation, compressible objects are used such as microscopic bubbles which expand and contract to pass the acoustic waves. These oscillations will therefore enable drug release and increase drug absorption.^[22] The acoustic streaming consists of localized particle displacements and fluid currents resulting from radiation forces subject to reflector and scatters in the ultrasound field.^[23] The acoustic flow helps to push the particles into the target tissues and destabilizes drug carriers.^[24] Hyperthermia involves dissipating the ultrasound energy into thermal energy. Ultrasound waves propagate through the tissues to be heated, where the process can be monitored by

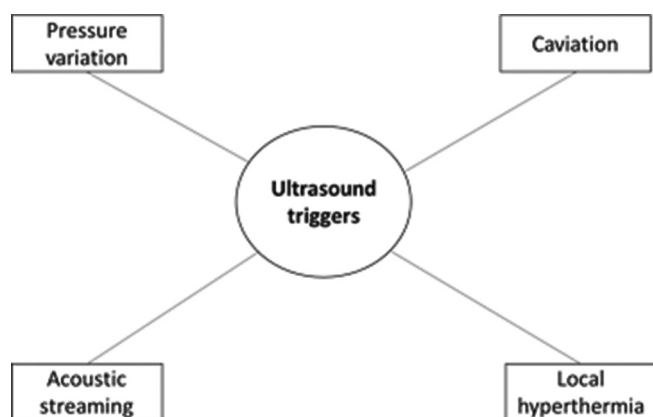


Figure 2: Ultrasound triggers for drug release

specialized thermal imaging techniques. Drugs are released from heat-sensitive vectors designed to destabilize at the ultrasound-generated temperatures.^[20]

Bao *et al.* studied drug release from polylactide matrices and were able to show that the release rate was faster when treated with ultrasound.^[25] In another study conducted on tumorized mice models, microbubbles were produced and were then exploded by ultrasound actuation. This resulted in microcavitations in the tumor cells and allowed the entrance of the anticancer drugs into them. A reduction of 82% in the tumor size was shown with this system in comparison to only 15% reduction in its absence.^[26]

Polymeric nanoparticles were used as a drug carrier and the drug release by an external ultrasound stimulus was investigated.^[27] Kubota *et al.* prepared an effective on-demand release system using hydrogel microbeads with ultrasound-sensitive tungsten particles. They showed the controlled release from the microbeads by ultrasound stimulus.^[28] A further investigation applied ultrasound-targeted microbubble destruction to assist exosome delivery in intrinsically resistant tissues including heart, adipose tissue, and skeletal muscle. It was shown that the exosome infiltration and endocytosis were significantly increased with targeted destruction of the ultrasound microbubbles.^[29]

Due to the interaction of ultrasound with biological tissues, there are safety concerns concerning unwanted tissues interactions. Parameters such as frequency, intensity, duty cycle, and time of application determine safety performance parameters. Additional factors including the type of tissue as well as environmental conditions could also be considered.^[30]

Electrically stimulated pulsatile drug delivery systems

Electrically responsive delivery systems are broadly used to release the drug to a specific place and within a specific time depending on implantable polymers or electronic devices by using external electrical fields.^[31] The voltage could be well controlled by advanced devices, with fine control of drug release. There are many advantages of this system, but at higher voltages, there is unwanted tissue damage and low penetration depth which exhibits a major problem.^[32] Electrically stimulated systems can be prepared using biocompatible polyelectrolytes such as carbomer, xanthan gum, agarose, calcium alginate, and acrylate-methacrylate derivatives.^[33]

The release of insulin from methacrylate hydrogels under the electrical field has been studied by Kwon *et al.* Local pH increased under a small electric field due to the release of hydroxyl ions at the cathode. This caused disturbance of the hydrogen bonds in the solid-state of polymers and liquefied the polymers which lead to the release of the drug.^[34]

Investigations on the release of the ionic drugs cefazolin and theophylline from a hydrogel under an electrical field were done by Kim and Lee.^[35]

Neumann *et al.* formulated an electro-responsive drug delivery system which is composed of a bioresorbable nanocomposite film. The electrochemical stimulation-induced local pH changes at the electrode surface, which in turn resulted in dissolution of the carrier that is composed of a pH-sensitive polymer.^[36] In another study, an electro-responsive drug carrier was formulated using sodium alginate and graphene oxide, crosslinked with Ca²⁺. The electrical conductivity of graphene oxide allowed the successful electrical stimulated release of methotrexate.^[37] More recently, electro-responsive chitosan/magnetic nanoparticles Composite Microbeads were developed and loaded with vancomycin drug.^[38] Furthermore, poly (2-ethylaniline) dextran-based hydrogel was formulated as a transdermal drug delivery system for electrically controlled diclofenac drug release. The application of an electrical stimulus results in drug release by Fickian diffusion combined with matrix swelling.^[39]

Light-responsive pulsatile drug delivery system

Light-responsive delivery systems are advantageous because of their noninvasive nature, chronological control, convenience, and simplicity of use. The major advances in the light-responsive drug release include photo-chemically triggered release, photo-isomerization, and photo-thermal release.^[31] Thermosensitive liposomes and iron oxide nanoparticles are examples of light-responsive delivery systems in the clinical trials stage.^[40,41]

Photo-chemically triggered release is based on light irradiation causing covalent bond cleavage with subsequent drug release. Photoresponsive moieties employed in photochemically triggered drug delivery systems include o-nitrobenzyl, coumarin-, and pyrene-derivatives.^[42-44] Photo-isomerization activation mechanism involves a reversible conformational change resulting from light irradiation with ultraviolet (UV) and visible light. Most commonly, azobenzenes are employed for this reaction.^[7,45] Photo-thermal activation mechanism utilizes a chromophore which upon photo-stimulation, will convert the light energy into thermal energy. The released heat will then stimulate a thermally sensitive carrier and thus result in the release of the drug.^[31] Commonly used materials include gold nanoparticles^[46] and NiPAAm hydrogels.^[47]

Pearson *et al.* formulated Light-responsive glycopolymer micelles using azobenzene and β -galactose units for the purpose of targeting to melanoma cells. The azobenzene units were capable of photoisomerization to the cis isomers by UV irradiation.^[48] Light responsive coumarin-based dendrimers were also synthesized by Wang *et al.* When exposed to irradiation at 365 nm, the coumarin substitutes cross-linked with each other, while upon exposure to

irradiation at 254 nm, the cross-linked assemblies degraded. Therefore, light-responsive drug release took place successfully with the enhancement of anticancer activity.^[49] Furthermore, Near Infrared (NIR) light-responsive alginate hydrogels were prepared for on-demand degradation and drug release. Doxorubicin drug was incorporated in the hydrogels and its release was shown to be suppressed in the normal physiological conditions. However, NIR light irradiation resulted in a rapid drug release.^[50] Doxorubicin was also incorporated in thermosensitive gold nanorods in another study for light-responsive anticancer therapy. Controlled light-triggered drug release and efficient intracellular release was shown upon irradiation with NIR light. Therefore, light-responsive anticancer activity was achieved.^[51]

Wirelessly controlled pulsatile drug delivery systems

Wirelessly controlled drug delivery systems are designed for on-demand and pulsatile drug delivery. With the widespread of smart devices, the control of drug delivery devices became easier, multi-optional and more user-friendly. The use of a safety processor system had been previously suggested which provides enhanced accuracy and safety of programming as well as control of medical devices with a remote-control device, such as a mobile phone. A safety processor works as a link device between the mobile phone and the medical device to recall the transmissions from the mobile phone before being transferred to the medical device. It ensures safe and reliable communication between the mobile phone and medical device, and could also examine whether the operating command entered into the mobile phone is within suitable parameters [Figure 3].^[52]

A wirelessly controlled implantable system for safe and convenient on-demand and pulsatile insulin administration has been designed by Lee *et al.* It is a mixed structure of a magnetically driven pump, external control device, and mobile application. An exact quantity of the drug could be released and adjusted wirelessly by the mobile application. The mobile application provides safety restrictions, as it is programmed to preset the dosing schedule and dose limit to avoid any risk of dosing error. Additionally, the mobile application could be controlled through Bluetooth allowing on request administrations. It could also block all the commands from being processed if the patient is expected to develop hypoglycemia at any point. All the administration history will also be saved on the mobile device.^[53]

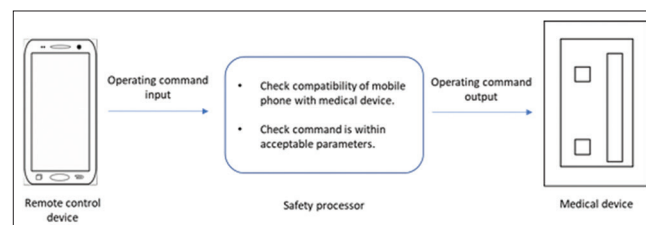


Figure 3: Wireless control of drug delivery

In a human clinical trial, a microchip, controlled wirelessly by a computer-based program, was implanted subcutaneously to deliver a once-daily dose of an antiosteoporosis drug to postmenopausal women having osteoporosis. The resulting drug release showed a similar drug pharmacokinetic profile to that of multiple injection administration with no reduction in the expected drug efficiency.^[54] A wireless polymer conduction controller drug delivery system was developed, which is composed of an electrochemical cell, a wireless remote controller device, and a wireless module that can communicate with the controller device. The communication is managed with a graphical user interface control program and the system was successfully capable of controlling the drug delivery.^[55]

CONCLUSION

The oral route is the most preferred and major route of drug administration, with different modified release dosage forms developed to achieve controlled drug release and improve patient compliance. In many cases, chrono-pharmacotherapy is required, which can be easily accomplished using PDDS in a very organized manner. Pharmaceutical technology has drastically improved in the past decades, and with the implementation of pulsatile drug delivery which delivers the right drug to the right patient at the right place, one could be certain that the target of secure and efficient therapy would be met. Further advances in the field of drug delivery led to the discovery of remotely drug delivery systems which provide significant therapeutic benefits. Remotely triggered drug delivery systems allow on-demand controlled release profiles, which may improve therapeutic efficacy while lowering systemic toxicity. Furthermore, when desired, these methods may provide highly localized drug release. A number of new technologies that are sensitive to light, ultrasound, magnetic fields, electrical stimulation, as well as wirelessly powered implantable systems have recently been developed. This responsiveness can be activated remotely, allowing for versatile dose magnitude and timing control. We reviewed different triggerable systems that could be triggered by a variety of stimuli, which were successfully implemented in recent studies.

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Conflicts of interest

There are no conflicts of interest.

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