

**Recent Trends in Chronopharmaceutics, Pulsatile Drug Delivery System**

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Pulsatile Drug Delivery Systems (PDDS) are getting considerable interest in delivering a drug at the correct position, at the correct time, and in the correct quantity, thus offering temporal, spatial, and intelligent delivery with improving patient compliance. These systems are

intended to meet body's biological rhythm. Here, the delivery of drugs is assisted by the rhythm of disease. The main reason for the using pulsatile drug release is when the continuous drug release is not required. A PDDS must be designed in such a way that after the lag time a complete and fast release of drugs is achieved. The article deals with various systems such as osmotic system, capsular system, single and multi-unit system based on the utilization of erodible or soluble polymer coating and using of rupturable membrane. These systems are favorable to drugs with chronopharmacological behaviors such as drugs used to treat rheumatoid arthritis, ankylosing spondylitis, and osteoarthritis. The current review paper focus on the causes for pulsatile drug delivery system design, types of illness requiring pulsatile release, classification, benefits, and restriction of this drug delivery system.

**Key words:** Pulsatile drug release, Chronotherapy, Circadian rhythm, Lag time.

**التوجهات الحديثة في الادوية الزمنية ونظام توصيل الادوية النابض: نشرة**

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**الخلاصة:**

تحظى أنظمة التوصيل الدوائي النابضة باهتمام كبير في توصيل الدواء في المكان المناسب وفي الوقت المناسب وبالكمية المناسبة، مما يوفر الولادة المكانية والزمانية والذكية لتحرير الدواء وتحسين الامتثال للمريض. تم تصميم هذه الأنظمة لتتزامن مع الإيقاع البيولوجي للجسم. حيث يتم تحرير الدواء عن طريق إيقاع المرض. السبب الرئيسي لاستخدام إطلاق الدواء النابض هو عندما يكون الإفراج المستمر للدواء غير مناسب. يجب أن يتم تصميم النبضة بحيث يحقق إطلاق تام وسريع للأدوية بعد فترة من الزمن. تتناول هذه المقالة الأنظمة المختلفة مثل الأنظمة الناضجة والأنظمة الكيسولية والأنظمة الفردية والمتعددة الوحدات القائمة على استخدام طلاء البوليمر القابل للتناكل أو القابل للذوبان واستخدام الأغشية القابلة للتمزق. هذه الأنظمة مناسبة للأدوية المستخدمة لعلاج التهاب المفاصل الروماتويدي والتهاب الفقار اللاصق والتهاب المفاصل. أوضحت الدراسات الحالية أسباب تصميم نظام توصيل الدواء النابض وأنواع الأمراض التي تتطلب إطلاق النبض وتصنيفها وفوائدها وتقييدات المتعلقة بهذا نظام.

**الكلمات المفتاحية:** إطلاق الدواء النابض، العلاج الزمني، إيقاع الساعة البيولوجية، فترة فاصلة.

**Introduction**

PDDS(s) are timely delivery systems for drugs. These systems are designed according to body's circadian rhythm to accomplish time-

specific and site-specific delivery of drugs [1]. Pulsatile systems are useful for chronopharmacological behavioral drugs. The principle basis for the utilization of pulsatile release system is for the drugs in which a

continuous drug release is not required [2]. The drug release as a pulse after a lag time (a time interval without release of the drug) should be programmed in which that a fast and complete release of the drug follows the lag time as shown in Figure 1.

In timed drug treatment (chrono-pharmacotherapy), the administration of drug was synchronizing with biological rhythms to

achieve optimum therapeutic effect and lowest harmful the patient [3]. In addition, pulsatile release is suitable for targeting of the drug that cause irritation to the stomach or the drug that degradable within it. Furthermore, the drug that developing biological tolerance or for drugs that have extensive first pass metabolism [4].

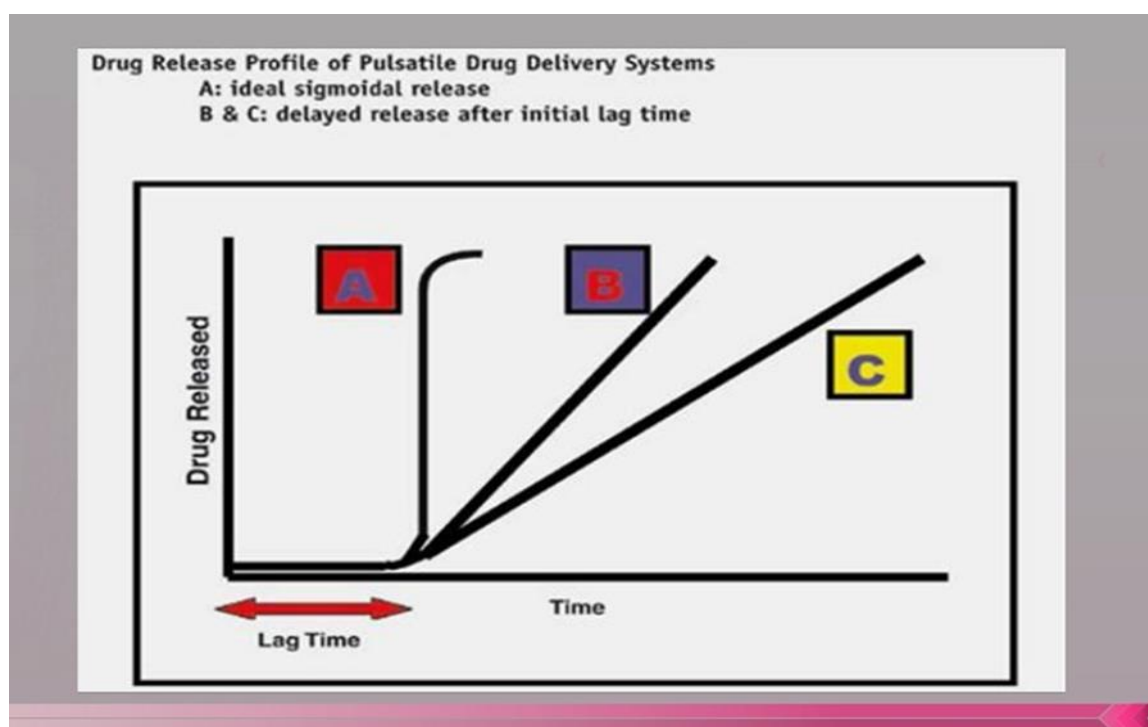


Figure (1): Drug release profile of pulsatile drug delivery systems [5]

**Table 1: Some of diseases that follow chronological behavior [3].**

Disease	Chronological behavior	Drugs used
Peptic ulcer	Acid secretion is high in the afternoon and at night	H <sub>2</sub> blockers
Asthma	Precipitation of attacks during night or at early morning hour	β <sup>2</sup> agonist, Antihistaminics
Cardiovascular diseases	BP is at its lowest during the sleep cycle and rises steeply during the early morning awakening period	Nitroglycerin, Calcium channel blocker, ACE inhibitors, β Blockers etc.
Arthritis	Pain in the morning and more pain at night	NSAIDs, Glucocorticoids
Diabetes mellitus	Increase in the blood sugar level after meal	Sulfonylurea, Insulin, Biguanide
Attention deficit syndrome	Increase in DOPA level in afternoon	Methylphenidate
Hypercholesterolemia	Cholesterol synthesis is generally higher during night than during day time	HMG CoA reductase inhibitors

### Requirements for the pulsatile drug delivery system

There are many disease and conditions in which sustained release formulations do

not show excellent effectiveness. Therefore, the pulsatile DDS useful in such situations.

#### - First pass metabolism

Certain drugs, like salicylamide and beta blocker drugs, suffer extensive first-pass metabolism and need rapid input of drugs to saturate the metabolizing enzymes in order to reduce the pre-systemic metabolism. Consequently, a constant - sustained oral drug delivery technique would lead in decreased oral bioavailability [6].

#### -Special chronopharmacological requirements

Circadian rhythms are well established in definite physiological functions. It was noted that some symptoms and onset of diseases happen at a specific 24-hour day time periods, like angina pectoris and asthma attacks are most common in the morning hours. The recent reported work to develop and evaluate double pulse time programmed press coated tablet containing fixed dose combination of montelukast (10 mg) and levocetirizine (5 mg) intended for chronotherapy of asthma disease, where the first pulse involve rapid release of levocetirizine followed by 2nd pulse after 6 hrs lag time involving rapid release of montelukast. This may provide maximum plasma concentration of both drugs at time of its maximum need, by improving stability and their bioavailability [7].

#### - Biological tolerance

Plasma drug profiles are frequently associated with a decreasing in the drug's pharmacotherapeutic effect, like, salbutamol sulphate, and transdermal nitroglycerin biological tolerance [8].

#### - Local therapeutic requirement

In order to treat local disorders like inflammatory bowel disease, it is extremely desired to obtain the therapeutic effect and reduce the adverse effects due to absorption in the small intestine [9]. The drug is released after a well-defined time period, or site-specific systems in which the drug is released at the desired site within the intestinal tract (e.g., the colon). Environmental factors like pH or enzymes present in the intestinal tract control the release of a site-controlled system, whereas

the drug release from time-controlled systems is controlled primarily by the delivery system and not by the environment [10].

-Gastric instability or irritation of drug in the gastric fluid

Stomach protection is essential for drugs suffering from degradation in the gastric acid medium (like; peptide medicines), stomach mucosa irritation (like; NSAIDS), or cause nausea and vomiting [11].

#### **Benefits of the Pulsatile drug delivery systems:**

-They decrease the dose size, dose frequency, reducing side effects, and cost, thus improving compliance with patients [5].

- It is possible to use these systems for prolonged daytime or night time activities [12].

- It is possible to achieve targeting of drug to a particular site, such as the colon (in the case of ulcerative colitis) [12].

-This system helps to avoid the continued existence of certain drugs that produce biological tolerance (like salbutamol sulphate) and thus enhance their therapeutic effect [5].

-Hormones like aldosterone, renin, and cortisol etc. may change their blood levels with circadian rhythms, so drug delivery via this system suits circadian body function or disease rhythms [5].

-Provide constant levels of drugs at the site of action and avoid fluctuations in peak valleys [5].

-These systems are useful for chronopharmacological drugs behavior which required night-time dosage and for elevated first-pass effect drugs [13].

-Protection from the stomach environment is necessary for drugs that cause stomach irritation (e.g. NSAIDS) or degradation in the stomach medium (e.g. peptide drugs) so that enteric coated of pulsatile drug delivery system can be the best choice [13].

### Restrictions

- Low ability for drug loading and uncompleted drug release <sup>[14]</sup>.
- The in vivo variable of single unit of pulsatile drug delivery system <sup>[14]</sup>.
- Multiple industrial steps in case of Multi-particulate drug delivery system.
- It is not feasible to withdraw the drug immediately <sup>[15]</sup>.
- Manipulation of the drug dose is not feasible in the situation of children and elderly patients <sup>[15]</sup>.

### Classification

Pulsatile drug delivery systems (PDDS) can be divided into 4 general classes;

- (I)- Time controlled pulsatile release.
- (II)- Stimuli induced.

(III)- Chemical stimuli induced pulsatile systems.

(IV)- External stimuli pulsatile release <sup>[16]</sup>.

### (I)-Time controlled pulsatile release systems

The time-controlled system can be divided in to single units (like: tablets or capsules) or as multiple units.

#### A- Single Units System Capsular System 1- Capsule based systems

Different capsular PDDS units were produced. Such systems are generally designed by using insoluble capsule body that stores the drugs and a plug. The plug was removed due to erosion, swelling, or dissolution after a predetermined time lag <sup>[16]</sup> as illustrated in Figure 2.

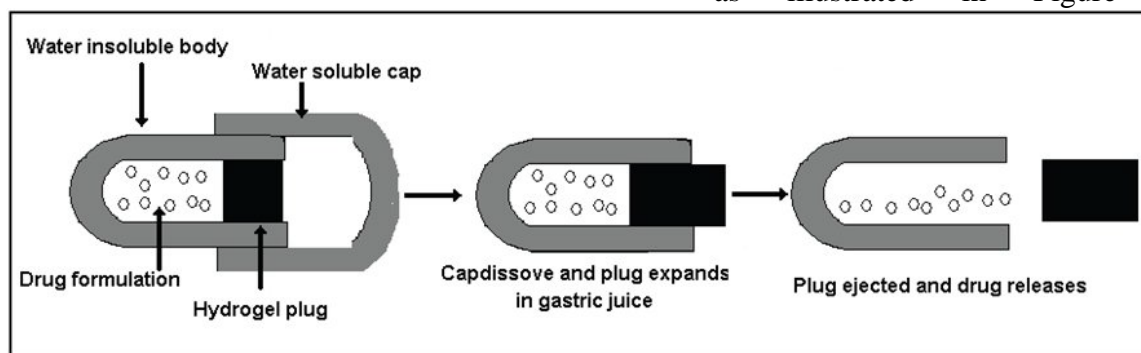


Figure (2): Schematic diagram capsule-based system <sup>[6]</sup>.

The Pulsincap system is a simple example of this system which consists of a body of water-insoluble capsules filled with drug formulations. At the open end, the body is closed by a swellable hydrogel plug. The plug swells after contact with medium or gastrointestinal dissolution liquids, and pushing itself out of the capsule after a lag period of time. Then a spontaneous release of the drug from the capsule follows that. By controlling the dimension and/or position of the plug, the time lag can be regulated <sup>[17]</sup>. The plug materials are consist of insoluble but swellable and permeable polymers like: (poly-methacrylates), congealed melted polymers like: (glyceryl-monoole, saturated poly-glycolated glycerides) erodible compressed polymers like: (poly-vinyl alcohol, poly-ethylene oxide, hydroxyl-propyl-methyl

cellulose), and enzymatic controlled erodible polymers like: (pectin). On the other hand, there was a possible problem involving the variability of the gastric residence time, that can be overcome via the formation of enteric coated of the systems in order to permit its dissolution in the region of high pH of small intestine only <sup>[18]</sup>.

### Pulsatile Systems Based on Osmosis

#### a- Port Systems:

This system comprised of a gelatin capsule covered by a semipermeable membrane (like: cellulose acetate) containing of insoluble plug (like; lipid) and an osmotic active agent together via a drug formulation as shown in Figure 3. Once the capsule became in-contact with the aqueous dissolution medium, the water

diffuses through the semipermeable membrane leading to enhanced internal pressure which eject the plug after a lag time period. The lag time period is regulated by semi-permeable membrane thickness <sup>[19]</sup>.

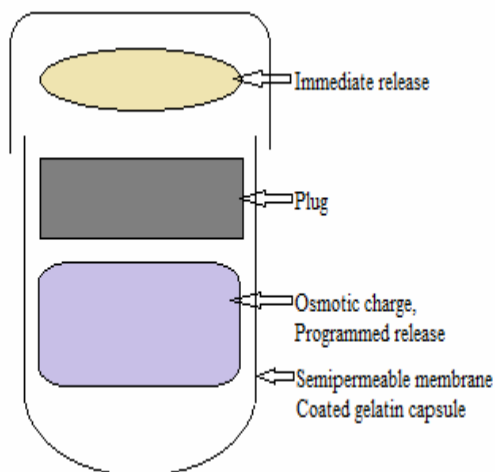


Figure (3): Port Systems <sup>[18]</sup>.

#### b- Delivery by a Series of Stops:

Those systems are described to be used for implantable capsule. The osmotically powered delivery capsule includes a medicinally active agent and a water-absorbing osmotic engine which isolated via a slider partition in order to delivering the drug through the orifice in a pulsatile manner. The lag time required for pulsatile delivery was accomplished via a series of stops positioned along the capsule's inner wall that obstructs its movement. When the hydrostatic pressure increases over the limit point, the partition was compelled to deliver the following drug batch. The intensity of pulse is regulated by the numbers of stops along the longitudinal axis and their position <sup>[20]</sup>.

#### c- Single Unit System Delivery by Solubility Modulation:

This system has a modulator of solubility in order to pulsed delivery a number of drugs. This system was created for salbutamol sulphate delivery. The composition involves the active ingredient (salbutamol sulphate) plus sodium chloride as a modulating agent. The quantity of sodium chloride should be less than the quantity required to achieve saturation in a fluid entering the osmotic device. Pulsed delivery depends on the drug's solubility. The modulating agent could be an inorganic salts, solid organic acids, or organic salts <sup>[21]</sup>.

#### d- The Systems Based on Expandable Orifice:

In order to deliver the medication as a liquid form, an osmotic capsular system was created, in which a liquid drug absorbed into extremely porous particles that deliver a drug via a semi permeable capsule orifice assisted with an expandable osmotic layer after dissolution of the barrier layer <sup>[22]</sup>.

#### Delivery of drug by Reservoir Systems with Soluble or Erodible Barrier

##### Coatings:

In this system, the releasing of drugs was regulated via the erosion or dissolution the outer layer that coat the core which comprising the active ingredients as shown in Figure 4. It is possible to obtain time dependent drugs release by adjusting the outer layer thickness. For example, a chronotropic system which composed of a drug-containing core and a hydrophilic polymer coat of HPMC, the lag time before releasing of drug will depend on the viscosity grade and thickness of the HPMC layer <sup>[23]</sup>.

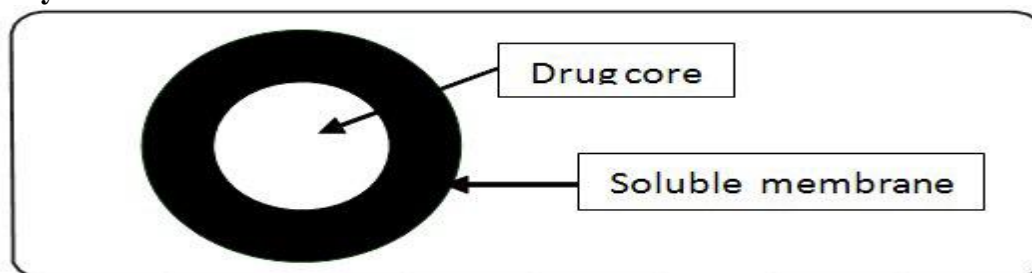


Figure (4): Delivery systems using soluble or erodible Membranes <sup>[23]</sup>.

## B- Multi-particulate Systems

These systems are based on rupturable polymer coating, soluble or eroding polymer material, and the mechanism of change in membrane permeability as shown in figure 5.

Multi-particulate drug delivery is designed to achieve controlled and delayed release. Preparation with lowest dose dumping, short period of stomach residence time and specific release patterns [24].

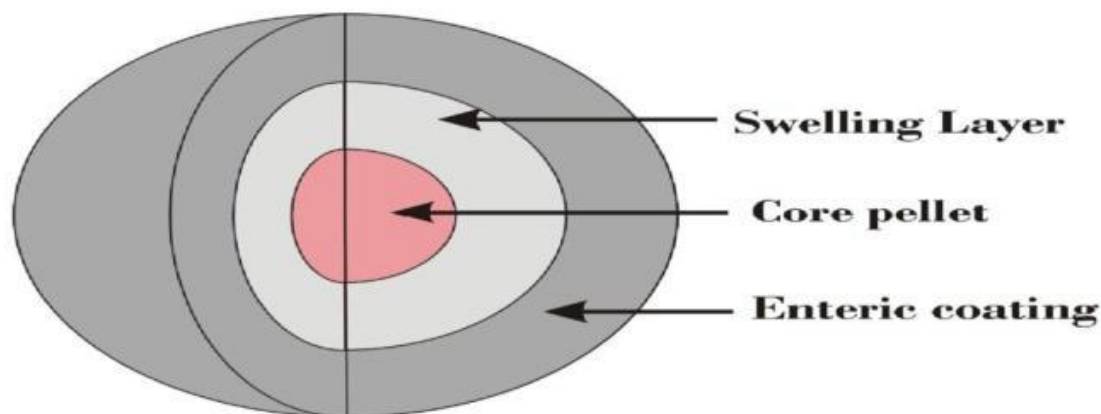


Figure (5): Multi-particulate drug delivery system [24].

## II. Stimuli induced pulsatile release system

### A-Temperature induced systems:

Thermo-responsive hydrogel methods for pulsatile drug release have been developed. In these methods, in the response to specific temperature, the polymer suffers swelling or de-swelling which in turn regulate the drugs release state of swollen. Y.H. Bae *et al* designed pulsatile indomethacin release patterns by use reversible swelling characteristics of butyryl acryl amide and iso-propyl-acryl amide co-polymers [25].

### B-Inflammation-induced Pulsatile Release:

Inflammation occurs at the injured regions, which in turn produce hydroxyl radical from the inflammation responsive cells. Yui and co-workers worked on inflammatory cells produced hydroxyl radical and developing a drug delivery system that was responded to hydroxyl radical and breaking down in a specific manner. They utilized hyaluronic acid that breaking down especially via hyaluronidase or a free radical. In a normal health status, hyaluronic acid degradation by hyaluronidase is very limited. However,

when hyaluronic acid is injected at inflammatory areas, degradation via hydroxyl radical was largely dominant and rapid. Hence, the patient with inflammatory disorders like (rheumatoid arthritis) be able to treated by utilizing anti-inflammatory drugs which incorporate with hyaluronic acid gel as modern implantable drug delivery system [26].

### C. pH Sensitive Drug Delivery Systems:

This technique of pulsatile delivery of drug includes two parts immediate release and pulsed release which release the drug in response to pH change. In this case the benefit was obtained from the fact that at different areas of the gastrointestinal tract there is distinct pH environment. Thus it is possible to achieve drug release at specific areas by selecting the pH-dependent polymers. Examples of pH dependent polymers include: polyacrylates, sodium carboxy methylcellulose, Eudragit E-100 [27].

### Chemical stimuli induced pulsatile systems

#### Glucose responsive Insulin Release Device

The patient with diabetes mellitus, glucose levels in the body rhythmically increase

and requiring insulin injection at the correct time. Many systems have been designed that can respond to alterations in the glucose concentration. One of them involves pH sensitive hydrogel comprising immobilized glucose oxidase in a hydrogel. As the concentration of glucose increases in the blood, glucose oxidase changes the glucose to gluconic acid that alters the system's pH. The change in pH causes swelling of the polymer and hence lead to insulin release. Insulin decreases blood glucose levels because of its action and subsequently the amount of gluconic acid as well decreases and the system changes to the de-swelling state thus reducing the release of insulin. Examples of the pH sensitive polymers involve: chitosan, polyol etc [28,29].

#### **Drug release from intelligent gel responding to antibody concentration**

In the body there were variety types of bioactive compounds. Lately, novel gels have been designed that responded to the alteration in bioactive compound concentration to change their (swelling and de-swelling) properties. Since this interaction is very essential, special care has been provided to the complex formation of antigen-antibody as the cross-linking units in the gel. There is a difference in constants of association between polymerized antibodies and naturally derived antibodies towards particular antigen reversible gel (swelling-deswelling) and this cause changes in drug permeation [30].

### **IV. External stimuli pulsatile release**

#### **1- Magnetically Induced Pulsatile Release**

This system involves magnetic beads in implants that result in the release of the drug upon implementation of the magnetic field. Materials such as iron, magnetite, cobalt and nickel bin beads are utilized to achieve the magnetic response. For biomedical purposes the magnetic carriers must be nontoxic, biocompatible, water

based, and no immunogenic. This technique was depends on the magnetic attraction that slow down the oral drug in the gastrointestinal tract, by incorporating an extra magnetic element to the tablets or capsules. The movement of travel across the stomach and intestine possibly slowed down at particular locations via applying exterior magnet. Hence, altering the time and the amount of drug absorption in the gastrointestinal tract [31,32].

#### **Electro Responsive Pulsatile Release**

This system is dependent on the use of polymers containing high concentration of ionizable group and pH-responsive which by the effect of electric field the swelling/de-swelling take place dependent on the location of hydrogel to electrode. The electrical responsive system is created from poly-electrolyte (polymers that comprise moderately high ionizable group concentrations along the backbone chain) and thus they are both pH responsive and electro responsive. Examples of naturally polymers involve: chondroitin sulphate, xanthan gum, calcium alginate and carbomer. The synthetic polymers are usually methacrylate and acrylate derivatives such as partially hydrolyzed polyacrylamide, and poly-dimethyl-amino-propyl acryl amide [33].

### **Conclusions**

It can be concluded that pulsatile drug delivery systems provide a key to the delivery of drugs that exhibit chronopharmacological behavior and night-time dosing requirement. Pulsatile drug delivery system is one which provides worthy promises to patients have chronic diseases as asthma, hypertension and arthritis by providing a drug at the correct time, correct site and in the correct amounts. A number of formulations with single and multiple unit systems have been designed in recent past but most lack the site specificity. From technological point of view, multiparticulate systems seem to be more efficient than single-unit dosage

forms in achieving pulsatile drug delivery and it can become even more sophisticated when coating technologies are incorporated. There is a need to comprehend the effect of the biological environment on release performance so that a successful design with expected *in-vivo* performance can be developed. Pulsatile drug delivery systems are considered as promising technology, where significant progress has been also made towards achieving pulsatile drug delivery technologies that can effectively treat diseases with non-constant dosing therapies, such as diabetes and for the delivery of active compounds for cancer treatment.

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