Pulsatile Drug Delivery System: An Overview

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ABSTRACT

Pulsatile drug delivery systems are developed to deliver drug according to circadian behavior of diseases. This means that these systems will deliver drug at time when disease display it’s most morbid and mortal state within a circadian cycle (24 hrs.). The product follow a sigmoidal drug release profile characterized by a time period of no release (lag time) followed by a rapid and complete drug release. Thus drug can be delivered at right time, in right amount and at right site of action by use of such approach. The potential benefits of chronotherapeutics have been investigated and established for number of diseases like asthma, arthritis, cancer, diabetes, epilepsy, hypertension, ulcer, hypercholesterolemia etc. These systems are beneficial for diseases showing chronopharmacological behavior where night time dosing is required or for the drugs having high first pass effect or having site specific absorption in GIT, or for drugs with high risk of toxicity or tolerance. These systems also improve patient compliance by decreasing dosing frequency.

Key words: Pulsatile drug delivery system, Circadian rhythm, Chronotherapeutics
INTRODUCTION

Worldwide several researches are going on for the development of new drug delivery system. In conventional therapy drug is released immediately after medication. So, the drug concentration in the plasma is raised and sometimes it is more than the toxic level. The target of drug discovery is to obtain maximum drug efficacy and minimum side effect. With the advancement of technologies in the pharmaceutical field drug therapy has changed its path. Although sustained and constant release systems have been developed biological systems are not so responsive to these release systems. In addition, sustained and controlled release devices are not applicable in some cases like time-programmed administration of hormones and many drugs. Those hormones and drugs can also easily be degraded by metabolic enzymes and resistance may be developed. The living systems are predictable dynamic resonating systems which require different amounts of drug at expected times within the circadian cycle. It is not a surprise that all bodily functions from the single cell to the genome are organized and synchronized in time. Pulsatile drug delivery system has fulfilled this requirement.

Pulsatile drug release is such a system where drug is released suddenly after well-defined lag time or time gap according to circadian rhythm of disease states. No drug is released from the device within this lag time. This delivery system is true for cases where drugs including proteins and peptides undergo through large metabolic degradation. In case of chronic treatment drug resistance may grow and adverse effect may be seen. Here chances are less because the desired concentration of drug at certain time point is available. This method is good for the drugs with extensive first pass metabolism and targeted to specific site in the intestinal tract. Drug release pattern from the device with pulsatile effect is shown in Fig. 1

![Drug release profiles](image)

**Figure 1:** Conceptual in-vitro drug release profiles from Pulsatile drug delivery system: (A) Initial release followed by lag and then quick release, (B) Quick release after lag time, (C) Multiple lags & quick releases and (D) Sustained release after lag time.

This delivery is gaining lots of interest and attention because time specific and site-specific delivery of drug with actual amount is obtained from this device. Here release of drug can be controlled by circadian rhythm which regulates many body functions in human beings. High-amplitude circadian rhythms in disease pathophysiology give rise to day–night patterns in the onset and symptom exacerbation of most acute and chronic medical conditions and diseases. The synchronizer routine of most human beings is sleep in darkness from ~10–30 p.m. to ~6–30 a.m. and activity started from ~6–30 a.m. to ~10–30 p.m. Pulsatile drug delivery is related to the term “chronopharmaceutics” which is a combination of chronobiology and pharmaceutics. There are three types of mechanical rhythms in our body, “Circadian” approaches from Latin word “circa” meaning about and “dies” meaning day. Oscillations of more than one cycle per 24 h are known as **ultradian** and less than one cycle per 24 h is known as **infradian**.
suprachiasmatic nucleus synchronizes this cycle and controls almost all bodily functions. It is a paired nucleus located above the optic nerve at the base of the hypothalamus. Circadian rhythms in gastrointestinal, liver, kidney and other bodily processes and functions are of great importance for therapeutics, for example, in choosing when to administer medications in relation to rhythm influences on their pharmacokinetics, effect-duration, efficacy, adverse effect and beneficial outcomes. 

**DESIRABLE PROPERTIES**

- Drug should act locally.
- It should have absorption window in GIT.
- It should have an extensive first pass metabolism.
- It should develop biological tolerance.
- It should develop zero order release.

**ADVANTAGES**

- The system is cost effective.
- The number of dose per day can be reduced.
- Improved patient compliance.
- Adverse effect can be reduced.
- As the pharmacokinetic and pharmacodynamic profile of the most drugs are subject to circadian variation pattern effective drug level are reached which could improve the therapy outcome.
- It is useful in targeting drug delivery.
- It is useful for drug, which develop tolerance or with an excessive first pass metabolism e.g. Beta blocker.

**DISADVANTAGES**

- There may be increased toxicity due to dose dumping.
- Drug absorption is site specific.
- Capsular system requires special equipments and manufacturing steps therefore large scale production is complicated.

**DISEASES REQUIRING PULSATILE DRUG DELIVERY**

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Disease</th>
<th>Chronological Behavior Drugs Used</th>
<th>Drugs Used</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Peptic ulcer</td>
<td>Acid secretion is high in the afternoon and at night</td>
<td>H2 blockers</td>
</tr>
<tr>
<td>2</td>
<td>Asthma</td>
<td>Precipitation of attacks during night or at early morning hours</td>
<td>B2 agonist, antihistaminic</td>
</tr>
<tr>
<td>3</td>
<td>Cardiovascular diseases</td>
<td>BP is at its lowest during the sleep cycle and rises steeply during the early morning awake</td>
<td>Nitroglycerin, Calcium channel blocker, ACE inhibitors</td>
</tr>
<tr>
<td>4</td>
<td>Arthritis</td>
<td>Pain in the morning and more pain at night</td>
<td>NSAIDs, Glucocorticoids</td>
</tr>
<tr>
<td>5</td>
<td>Diabetes mellitus</td>
<td>Increase in the blood sugar level after meal</td>
<td>Sulfonylurea, Insulin, Biguanide</td>
</tr>
<tr>
<td>6</td>
<td>Hypercholesterolemia</td>
<td>Cholesterol synthesis is generally higher during night than day time</td>
<td>HMG CoA reductase inhibitors</td>
</tr>
</tbody>
</table>
Thorough understanding of the disease physiology is required before designing the pulsatile drug delivery system. A disease where rhythmic circadian organization of the body plays an important role, pharmacokinetics and/or pharmacodynamics of the drugs is not constant within 24 h. Table 1 enumerates various diseases showing such a chronological behavior. Asthma is one such disease where pulsatile drug delivery system can be useful.

### CLASSIFICATION OF PULSATILE DRUG DELIVERY SYSTEM

Pulsatile drug delivery system can be broadly classified into three classes;
1. Time controlled.
2. Stimuli induced.
3. Externally regulated.

1. Time controlled pulsatile release system

In time controlled drug delivery systems pulsatile release is obtained after a particular time interval in order to mimic the circadian rhythm. Such type of pulsatile drug delivery system contains two gears: one is of immediate release type and other one is a pulsed release type.

Various methodologies for time controlled pulsatile release systems are discussed in following section.

1.1. Delivery systems with rupturable coating layer.

![Fig. 3 Schematic diagram of Deliver systems with rupturable coating layer](image-url)
In this system, outer release controlling water insoluble but permeable coating and based on mechanically induced rupture phenomenon. In recent times different systems based on hard gelatin capsules and tablet core were illustrated, all coated by outer rupturable layer and inner swellable. The film rupture may be attained by swelling, osmotic or effervescent additives in the reservoir. By optimizing the system, drug release can be obtained at specific time interval.

1.2. Capsule shaped system provided with release controlling plug.
Capsule-based system consists of pulsincap system, which consists of an insoluble capsule body and swellable and degradable plugs made hydrophilic polymers or lipids. The lag time is controlled by plug, which is pushed away by swelling or erosion and drug is released as a pulse from the insoluble capsule, i.e., Pulsincap® (fig. 4). The composition and thickness of the polymeric membranes determine lag time of plug. A swellable hydrogel plug seals the drug contents into capsule body. When this capsule body gets in touch with dissolution medium, the hydrogel plug swells, and after the lag time, the plug pushes itself outside the capsule and rapidly releases the drug. Various types of polymer used for formulation of swellable plug include hydroxyl propyl methyl cellulose (HPMC), polyvinyl acetate and polyethylene oxide.

1.3. Delivery systems provided with erodible coating layers.
In such systems generally comprise reservoir device coated with a barrier layer. The barrier erodes after a specific lag time, after which the drug is released rapidly from the reservoir (fig 5). Time dependent release of the active ingredient can be controlled by thickness and viscosity of the outer coat.
2. Stimuli induced pulsatile systems

In these systems release of the drug is followed by any biological stimulation like temperature, pH and any other chemical.

2.1. Temperature induced systems

Temperature is most widely used triggering signal for a variety of pulsatile drug delivery system. Temperature as a signal has been justified by the fact the body temperature often deviates from the physiological temperature (37°C) in the presence of pathogens. This deviation sometimes used for the stimulation and release of active therapeutic agents from various temperature-responsive drug delivery systems. Thermo-responsive hydrogel systems have been developed for pulsatile release. Hydrogel that undergo reversible volume changes in temperature are known as thermo-responsive hydrogel. This gel shrinks at a transition temperature that is related to the lower critical solution temperature of the linear polymer from which the gel is made. Thermoresponsive hydrogel have a certain attraction for water, and thus swell at temperatures below the transition temperature, whereas they expel water and thus shrink or “Deswell” at temperature above the transition temperature. Of the many thermo-responsive polymer, poly (N-isopropyl acrylamide) (PIPAAm) is probably the most widely used.17,18

2.2. Chemical stimuli induced pulsatile systems

2.2.1. Glucose-responsive insulin release devices

In case of diabetes mellitus patients there is rhythmic increase in the levels of glucose in the body requiring injection of the insulin at proper time. Several systems have been investigated which are able to respond to changes in glucose concentration. One such system includes pH sensitive hydrogel containing glucose oxidase immobilized in the hydrogel. Glucose oxidase catalyses oxidation of glucose to gluconic acid which changes the pH of the system. This pH changes can be used to drive the swelling of pH dependent membrane and resulting into release of insulin. A double membrane system was formed. In first membrane, glucose oxidase was immobilized on cross linked polymer like polyacrylamide and this was referred to as glucose sensing membrane. Second membrane system, co-polymer membrane made up of N,N-dimethylaminoethyl methacrylate or chitosan or polyol etc., which is pH sensitive and worked as an interface between insulin reservoir and sensing membrane. Release insulin by virtue of its action reduces blood glucose level and consequently gluconic acid level also gets decreased, the pH of the barrier membrane increased and it returned to the deswelling mode thereby decreasing the insulin release. In this way, this system controlled the rhythmic changes in glucose level in blood and maintained in normal range.19

2.2.2. pH sensitive drug delivery system

Such type of pulsatile drug delivery system contains two components one is of immediate release type and other one is pulsed release which releases the drug in response to change in pH. In case of pH dependent system advantage has been taken of the fact that there exists different pH environment at different parts of the gastrointestinal tract. By selecting the pH dependent polymers drug release at specific location can be obtained. Examples of pH dependent polymers include cellulose acetate phthalate, polyacrylates, sodium carboxy methylcellulose, Eudragit E-100.

3. Externally regulated systems

For releasing the drug in a pulsatile manner, another way can be used in which drug release is obtained by external stimuli like magnetism, ultrasound, electrical effect and irradiation. Magnetically regulated system contain magnetic beads in the implant like magnetite, iron, cobalt, nickel etc. On external application of the magnetic field, drug release occurs because of magnetic beads. In case of ultrasonic modulated systems, an ultrasonic wave causes the erosion of the polymeric matrix there by modulating drug release.21

Recently available Different Chronopharmaceutical Technologies
Oros® Technology

Chronset™ is a proprietary OROS® delivery system that reproducibly delivers a bolus drug dose in a time- or site-specific manner to the gastrointestinal tract. It is nothing but osmosis based system. The active pharmaceutical is kept in a reservoir surrounded by a semipermeable membrane laser drilled with a delivery orifice and formulated into a tablet. There are two layers in this tablet comprising of one drug layer and another osmotically active agent. Upon contact with GI fluid this osmotic agent changes its characteristic from nondispensable to dispensable viscosity. As a result active pharmaceutical is pushed away through the channel due to pump effect of the osmotic agent. It is used generally for designing of extended release tablet.²²

Ceform® Technology

It produces uniformly sized and shaped microspheres of pharmaceutical Compounds. This approach is based on “melt-spinning” which means subjecting solid feedstock (i.e. biodegradable polymer/ bioactive agent combinations) to a combination of temperature, thermal gradients, mechanical forces, flow and flow rates during processing. The microspheres obtained are almost perfectly spherical, having a diameter that is typically of 150–180 mm, and allow for high drug content. The microspheres can be used in a wide variety of dosage forms including tablets, capsules, suspensions, effervescent tablets and sachets. The microspheres may be coated for controlled release with an enteric coating or may be combined into a fast/slow release combination.²³

Contin® Technology

Here cellulose polymer and a nonpolar solid aliphatic alcohol first that polymer is solvated with a polar solvent. Alcohol may be optionally substituted with an aliphatic group. This alcohol is added to the solvated polymer preferably as a melt. After addition it forms the coordination complex having utility as a matrix in controlled release formulations since it has a uniform porosity which may be varied. It is also applicable for designing of controlled release tablets. This technology has sufficient control over drug release to the blood and reduces the chances of unwanted side effects.²²,²³

Diffucaps® Technology

This technology is nothing but capsule based system containing one or more drug-containing particles (e.g. beads, pellets, granules etc.). Each bead shows pre-programmed rapid or sustained release profile with or without lag time.

Chronotopic® Technology

It is basically drug-containing core coated with an outer release-controlling layer. Both single and multiple-unit dosage forms such as tablets and capsules or mini tablets and pellets have been employed as the inner drug formulation.

Egalet® Technology

It is a delayed release form consisting of an impermeable shell with two lag plugs, enclosing a plug of active drug in the middle of the unit 24. After erosion of the inert plugs the drug is released. Time taken to erode the inert plugs determines the lag time. The shells are made of slowly biodegradable polymers (e.g. ethylcellulose) and plasticizers (such as cetostearyl alcohol), while the matrix of the plugs is a mixture of pharmaceutical excipients including polymers like polyethylene oxide (PEO).

Codas® Technology

Chronotherapeutic Oral Drug Absorption System (CODAS) technology is a multiparticular system designed for bedtime dosing. Here nonenteric coating is applied on drug-loaded beads to delay the release of drug up to 5 h. Here release controlling contains mixture of both water-soluble and water-insoluble polymers.
When this dosage form comes in contact with GI fluid water-soluble polymer gets dissolved slowly and pores are formed on the coating layer. Drug diffuses through these resulting pores. Water-insoluble polymer acting as a barrier maintains the controlled release fashion like release of verapamil 25. The rate of release is independent of pH, posture and food.

**Geoclock® Technology**

The concept is designed on the basis of Geomatrix technology. Initially a multilayer technology was recommended for constant drug release in this technology. The active core or hydrophilic matrix is coated partially on one or both bases. This partial coating adjusts the core hydration process and minimizes the surface area available for drug release. In presence of dissolution medium the barrier layer swells and becomes gel. This gelling layer is not eroded but acts as a modulating membrane to control release process. The erodible surface is instead progressively removed by the dissolution medium. Upon erosion more planar surface(s) of the active core is exposed with increasing time to outer environment which helps drug release.25

**Port® Technology**

The Programmable Oral Release Technologies (PORT) system is a uniquely coated, encapsulated system that can provide multiple programmed release of drug. It contains a polymeric core coated with a semipermeable, rate-controlling polymer. Poorly soluble drugs can be coated with solubilising agents to ensure uniform controlled release from the dosage form. In capsule form had gelatin capsule is coated with a semipermeable, rate-controlling polymer. Active medicament mixed with osmotic agent is kept inside capsule shell. A water-insoluble plug is used to seal the capsule shell. Immediate release compartment can be added according to need.24

**Three Dimensional Printing® (3DP) Technology**

It is a novel, complex oral dosage delivery system. It is based on solid free-form fabrication method. Complicated internal geometries, varying densities, diffusivities and chemicals are helpful to design such device. Immediate-extended release tablets, pulse release, breakaway tablets and dual pulsatory tablets are examples of complex dosage forms where three dimensional printing technology has been used. The enteric dual pulsatile tablets were constructed of one continuous enteric excipient phase into which diclofenac sodium was printed into two separated areas. These samples showed two pulses of release in vitro with a lag time between pulses of about 4 h. This technology is the basis of the TheriForms technology. The latter is a microfabrication process that works in a manner very similar to an “inkjet” printer. It is a fully integrated computer-aided development and manufacturing process. Products may be designed on a computer screen as three dimensional models before actual implementation of their preparation process.26, 27

**Timerx® Technology**

It is hydrogel based controlled release device. This technology can provide from zero order to chronotherapeutic release. It can provide different release kinetic by manipulating molecular interactions. The authors claimed that the “molecular engine” replaces the need for complex processing or novel excipients and allows desired drug release profiles to be “factory set” following a simple formulation development process. Basically, this technology combines primarily xanthan and locust bean gums mixed with dextrose. The physical interaction between these components works to form a strong, binding gel in the presence of water. Drug release is controlled by the rate of water penetration from the gastrointestinal tract into the TIMERx gum matrix, which expands to form a gel and subsequently releases the active drug substance.28

**Physico-Chemical Modification of the API**

Physico-chemical properties like solubility, drug lipophilicity, partition co-efficient, crystalline form, membrane permeability, melting point etc. of the API (active pharmaceutical ingredient) can be modified by introducing new substitution to the original structure to achieve chronopharmaceutical effect.29, 30
Controlled-Release Microchip

Solid-state silicon microchip is an alternative microfabrication technique like micrometer scale pumps, valves and flow channels to deliver the active medicament in pulsatile manner. It can provide controlled release of both single and multiple chemical substances according to necessity. The release mechanism is based on the electrochemical dissolution of thin anode membranes covering microreservoir filled with chemicals in solid, liquid or gel form. Proof-of-principle release studies have been performed with a prototype microchip using gold and saline as a model electrode material and release medium and revealed controlled, pulsatile release of chemical substances with this device.31,32

Current Situation and Future Scope

Now a day's pulsatile drug delivery is gaining popularity. The prime advantage in this drug delivery is that drug is released when necessity comes. As a result chance of development of drug resistance which is seen in conventional and sustained release formulations can be reduced. Furthermore, some anticancer drugs are very toxic. These drugs give hazardous problems in conventional and sustained release therapies. Now many FDA approved chronotherapeutic drugs are available in the market. This therapy is mainly applicable where sustained action is not required and drugs are toxic. Key point of development of this formulation is to find out circadian rhythm i.e. suitable indicator which will trigger the release of drug from the device. Another point is absence of suitable rhythmic biomaterial which should be biodegradable, biocompatible and reversibly responsive to specific biomarkers in rhythmic manner. Regulatory is another big question. In preapproval phase it is sometimes difficult to show chronotherapeutic advantage in clinical settings. In postapproval phase causal recreational drug abuse along with a much larger scale, by the criminal diversion of these modified formulations for profit have arisen problems. The FDA has now heavily relied on the development and implementation of risk management programs as a strategy to allow an approval of a drug to go forward while exercising some restrictions. Many researches are going on the pulsatile drug delivery to discover circadian rhythm with suitable device in the world. In future this delivery will be a leading way to deliver therapeutic agents due to its some unique characters like low chance of dose dumping, patient compliance and the above factors.

CONCLUSION

Circadian rhythm of the body is an important concept for understanding the optimum need of drug in the body. There is a constant need for new delivery systems that can provide increased therapeutic benefits to the patients. Pulsatile drug delivery is one such system that, by delivering drug at the right time, right place and in right amounts, holds good promises of benefit to the patients suffering from chronic problems like arthritis, asthma, hypertension etc. Thus designing of proper pulsatile drug delivery will enhances the patient compliance, optimum drug delivery to the target site and minimizes the undesired effects. The approaches in this article represent attempts conducted over the past decade to achieve pulsatile release. It should be pointed that these drug delivery systems are still in the early developmental stage and much research will have to be conducted for such systems become practical clinical alternatives.

REFERENCES