CURRENT STATUS ON PULSATILE DRUG DELIVERY SYSTEMS – AN OVERVIEW

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ABSTRACT
A pulsatile drug release, where the drug is released rapidly after a well-defined lag-time, could be advantageous for many drugs or therapies. Pulsatile systems deliver the drug at the right site of action at the right time and in the right amount, thus providing spatial and temporal delivery and increasing patient compliance. Pulsatile release systems can be classified in single-pulse and multiple-pulse systems. A popular class of single-pulse systems is that of rupturable dosage forms. Other systems consist of a drug-containing core, covered by a swelling layer and an outer insoluble, but semipermeable polymer coating or membrane. The lag time prior to the rupture is mainly controlled by: (i) the permeation and mechanical properties of the polymer coating and (ii) the swelling behavior of the swelling layer. This review covers different pharmaceutical technologies used in development of pulsatile drug delivery systems.

INTRODUCTION
Oral controlled drug delivery systems represent the most popular form of controlled drug delivery systems for vast number of advantages over oral route of drug administration. Such systems release the drug with constant or variable release rates. The oral controlled release system shows a typical pattern of drug release in which the drug concentration is maintained in the therapeutic window for a prolonged period of time (sustained release), thereby ensuring sustained therapeutic action [1]. But there are certain conditions which demand release of drug after a lag time. i.e., chronopharmacotherapy of diseases which shows circadian rhythms in their pathophysiology like bronchial asthma, myocardial infarction, angina pectoris, rheumatic disease, ulcer, and hypertension.

- Drugs that produce biological tolerance demand for a system that will prevent their continuous presence at the biophase as this tends to reduce their therapeutic effect.
- The lag time is essential for the drugs that undergo degradation in gastric acidic medium (e.g.: peptide drugs) and irritate the gastric mucosa or induce nausea and vomiting.
- Targeting a drug to distal organs of gastro-intestinal tract (GIT) like the colon requires that the drug release is prevented in the upper two-third portion of the GIT.
- The drugs that undergo first-pass metabolism resulting in reduced bioavailability, altered steady state levels of drug and metabolite, and potential food drug interactions require delayed release of the drug to the extent possible. All of these conditions demand for a time controlled system.
therapeutic scheme releasing the right amount of drug at the right time.

- This requirement is fulfilled by Pulsatile Drug Delivery Systems [3]

  Pulsatile drug delivery system targets to release drugs in a programmed manner i.e. at appropriate time and/or at a suitable site of action as per the pathophysiological need of the disease, resulting in improved patient therapeutic efficacy and compliance and is designed for Chronopharmacotherapy (timed drug therapy) which is based on circadian rhythm [4].

**Advantages**
1. Predictable, reproducible and short gastric residence time.
2. Less inter and intra subject variability.
3. Improve bioavailability
4. Reduced adverse effects and improved bioavailability
5. Limited risk of local irritation
6. No risk of dose dumping
7. Flexibility in design
8. Improve stability
9. Improve patient comfort and compliance
10. Achieve two unique release pattern.

**Drawbacks**
1. Lack of manufacturing reproducibility and efficacy.
2. Larger no. of process variables.
3. Multiple formulation steps
4. Higher cost of production
5. Need of advanced technology [5].

**CHRONOTHERAPEUTICS**

Researchers have recently concluded that both disease states and drug therapy are affected by a multitude of rhythmic changes that occur within the human body. Chronotherapeutics refers to a treatment method in which in vivo drug availability is timed to match rhythms of disease in order to optimize therapeutic outcomes and minimize side effects. It is based on the observation that there is an interdependent relationship between the peak-to-trough rhythmic activity in disease symptoms and risk factors, pharmacologic sensitivity, and Pharmacokinetics of many drugs (Table-1) [6].

**Our body has various biological rhythms**

- **Ultradian Rhythm**
  Oscillations of shorter duration are termed ultradian rhythms (more than one cycle per 24hrs).
  Eg: 90min sleep cycle.

- **Infradian Rhythm**
  Oscillations that are longer than 24 hrs are termed as infradian rhythms (less than one cycle per 24 hrs.) Eg: monthly menstruation.

- **Circadian Rhythm**
  Circadian rhythms are self-sustaining, endogenous oscillations. (Fig-1)

There are number of diseases which required to be formulated as PDDS as like: hypercholesterolemia, asthma, cancer, duodenal ulcer, arthritis, diabetes, neurological disorders, cardiovascular diseases (e.g., hypertension and acute myocardial infarction and Colonic deliver [7].

**METHODS FOR PULSATILE DRUG DELIVERY**

**Capsular system**

Single unit systems are mostly developed in capsule form. The lag time is continued by a plug, which gets pushed away by swelling or erosion, and the drug is released as a pulse from the insoluble capsule body [8] e.g.: Pulsincap® system

In this system a water insoluble body containing the drug formulation, system is closed with a swellable hydrogel. Plugged (insoluble but permeable & swellable) at open end. Upon contact with, gastrointestinal fluid or dissolution medium the plug swells pushing itself out of the capsule after lag-time. Position & dimensions of plug, control lag-time. For rapid release of water insoluble drug effervescence or disintegrating agents are added [9]. Plug material is generally made up of following:

- Swellable materials coated with but permeable polymer (polymethacrylates).
- Erodible compressed polymer (HPMC, polyvinyl alcohol).
- Congealed melted polymer (glyceryl mono oleate).
- Enzymatically controlled erodiblepolymer (pectin).

**Pulsatile Delivery by Osmosis**

This system consists of a capsule coated with a semi permeable membrane. Inside the capsule was an insoluble plug consisting of osmotically active agent and the drug formulation [10]. This system shows good in vivo and invitro correlation in humans and used to deliver methylphenidate to school age children for the treatment of Attention Deficit Hyper activity Disorder (ADHD), e.g.: Port® System

Another system is also based on expendable orifice that contain capsular system in which liquid drug is absorbed on highly porous particles. Drug releases through orifice of a semi permeable capsule supported by an expending osmotic layer after the barrier layer is dissolved [11].

The Port® System (Port Systems, LLC) consists of a gelatin capsule coated with a semi permeable membrane (e.g., cellulose acetate) housing an insoluble plug (e.g., lipidic) and an osmotically active agent along with the drug formulation. When in contact with the aqueous medium, water diffuses across the semipermeable membrane, resulting in increased inner pressure that ejects the plug after a lag time. The lag time is controlled by coating thickness [12, 13].
Pulsatile Delivery by Solubilisation (or) Erosion of Membrane

These systems are based up on a drug reservoir surrounded with a soluble or erodible barrier layer that dissolves with time and the drug releases at once after the lag time. e.g. Time Clock® system. The Time Clock system consists of solid dosage form coated with lipid barriers such as carnauba wax & beeswax along with surfactants like polyoxyethylene sorbitan monooleate. When this system comes in contact with the aqueous medium the coat emulsifies or erodes after the lag-time depending on the thickness of coat. The lag time of system is independent of the gastrointestinal motility, PH, enzyme & gastric residence [14-18].

Pulsatile Delivery by Rupture of Membrane

These systems are based up on a reservoir system coated with a rupturable membrane. The outer membrane ruptures due to the pressure developed by effervescence agents (or) swelling agent [19-21]. Citric acid & sodium bicarbonate is incorporated as effervescence mixture in tablet core coated with ethyl cellulose, when system comes in contact with water it produces carbon dioxide gas which exerts pressure & after lag time rupture the membrane & rapid release of drug occurs [22]. A reservoir system with a semi permeable coating is proposed especially with drugs with high first pass effect in order to obtain in-vivo drug pattern similar to the administration of several immediate release doses cross carmelllose sodium starch glycolate or low substituted hydroxy propyl cellulose were used as swelling substances, which resulted in complete film rupture followed by rapid drug release. The lag time is controlled by composition of outer polymeric membrane [23-26].

Multiparticulate systems are reservoir type of devices with a coating, which either ruptures or changes its permeability. Drug is coated over sugar seeds these granules may then be packaged in a capsule or compressed with additional excipients to form a tablet. The active pharmaceutical ingredient may also be blended or granulated with polymers before coating to provide an additional level of control. However, drug loading in this type of system is low due to higher need of excipients [27-28].

Pulsatile Delivery by Rupturable Coating

Similar to single unit system, the rupturing effect is achieved by coating the individual units with effervescence (or) swelling agents. Drug deliver was controlled by the rupture of the membrane [29 -31]. The timing of release was controlled by the thickness of coating and the amount of water soluble polymer to achieve the pulsed release [32]. The swelling agent includes superdisintegrant like carboxy methyl cellulose, sodium starch glycolate, and L-hydroxy propyl cellulose. Polymers like polyacrylic acid, polyethylene glycol etc. alternatively comprising of a mixture of tartaric acid & sodium bicarbonate that used as effervescence agent [33].

Commercial Pulsatile Drug Products

OROS® or Chronoset 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 an osmosis-based system. The active pharmaceutical is kept in a reservoir surrounded by a semi permeable 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 the other, a cosmetically active agent. Upon contact with the GI fluid this osmotic agent changes its characteristic from a nondispensible to a dispensable viscosity. As a result the active pharmaceutical is pushed away through the channel due to the pump effect of the osmotic agent. It is generally used in the designing of an extended release tablet.

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, and flow and flow rates, during processing. The microspheres obtained are almost perfectly spherical, having a diameter that is typically of 150 - 180µm and they allow for high drug content. The microspheres can be used in a wide variety of dosage forms including tablets, capsules, suspensions, effervescence tablets, and sachets. The microspheres may be coated for controlled release with an enteric coating or may be combined into a fast or slow release combination.

CONTINR Technology

In this technology, molecular coordination complexes are formed between a cellulose polymer and non-polar solid aliphatic alcohol, optionally substituted with an aliphatic group, by solvating the polymer with a volatile polar solvent and reacting the solvated cellulose polymer directly with the aliphatic alcohol, preferably as a melt. This constitutes the complex having utility as a matrix in controlled release formulations, as it has a uniform porosity (semi permeable matrixes), which may be varied. This technology has concretely enabled the development of tablet forms of sustained-release aminophylline, theophylline, morphine, and other drugs. The CONTINR technology provides for closer control over the amount of drug released to the bloodstream, and benefits patients in terms of reducing the number of doses they need to take every day, providing more effective control of their disease (particularly at night), and reducing unwanted side effects.
**DIFFUCAPS® Technology**

In the DIFFUCAPS® technology, a unit dosage form, such as a capsule, is used for delivering drugs into the body in a circadian release fashion. DIFFUCAPS®, is a multiparticulate technology by Reliant Pharmaceuticals LLC, for a chronotherapeutic delivery of a combination of two drugs, Verapamil HCl and Propranolol HCl, as an extended release tablet (Innopran®). Pulsincap® system is one of the most used pulsatile systems based on capsules. It was developed by R. P. Scherer International Corporation, Michigan, US. Diffucaps®, and comprises of one or more populations of drug-containing particles (beads, pellets, granules, etc.). Each bead population exhibits a pre-designed rapid or sustained release profile, with or without a predetermined lag time of 3 - 5 hours. The active core of the dosage form may comprise of an inert particle or an acidic or alkaline buffer crystal (e.g., cellulose ethers), which is coated with an API-containing film-forming formulation and preferably a water-soluble film forming composition (e.g., hydroxpropyl methylcellulose, polyvinylpyrrolidone) to form a water-soluble or dispersible particle. The active core may be prepared by granulating and milling and / or by extrusion and spherization of a polymer composition containing the API. Such a ChrDDS is designed to provide a plasma concentration time profile, which varies according to the physiological need during the day that is, mimicking the circadian rhythm and severity or manifestation of a cardiovascular disease, predicted based on pharmacokinetinc and pharmacodynamic considerations and In vitro or in vivo correlations. This technology has been used to formulate the first and recently FDA approved propranolol-containing ChrDDS (InnopranRXL) for the management of hypertension.

**CHRONOTOPIC® Technology:**

It is also described in the system with an erodible, soluble or rupturable membrane system. It is basically a drug-containing core, coated with an outer release controlling layer. Both single and multiple unit dosage forms such as tablets and capsules or minitablets 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. 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 (e.g., cetostearyl alcohol), while the matrix of the plugs is a mixture of pharmaceutical excipients, including polymers like polyethylene oxide (PEO).

**CODAS® Technology**

Chronotherapeutics Oral Drug Absorption System (CODAS) technology is a multiparticulate system designed for bedtime dosing. Here a no enteric coating is applied on the drug-loaded beads to delay the release of the drug, up to five hours. Here release controlling contains a mixture of both water-soluble and water-insoluble polymers. When this dosage form comes in contact with the GI fluid, the water-soluble polymer gets dissolved slowly and pores are formed on the coating layer. Drug diffuses through these resulting pores. The water-insoluble polymer, acting as a barrier, maintains the controlled, fashion-like release of Verapamil. 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 the presence of the dissolution medium the barrier layer swells and becomes a gel. This gelling layer is not eroded, but acts as a modulating membrane to control the release process. The erodible surface is instead progressively removed by the dissolution medium. Upon erosion more of the planar surface(s) of the active core is exposed with increasing time to the outer environment, which helps drug release.

**PORT® Technology**

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

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

Three-dimensional printing (3DP) is a novel technique used in the fabrication of complex oral dosage delivery pharmaceuticals, based on solid freeform fabrication methods. It is possible to engineer devices with complicated internal geometries, varying densities, diffusivities, and chemicals. Different types of complex oral drug delivery devices have been fabricated using the 3DP process: immediate-extended release tablets, pulse release, breakaway tablets, and dual pulsatory tablets. The enteric dual pulsatory 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 during in vitro with a lag time between the pulses of about four hours. This technology is the basis of the TheriForm technology.

**TIMERx® Technology**

It is a hydrogel-based, controlled release device. This technology can provide from zero order to chronotherapeutic release. It can provide a different release kinetic by manipulating molecular interactions. Basically, this technology primarily combines 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 [34].

<table>
<thead>
<tr>
<th>Disease</th>
<th>Chronological behavior (category of drugs used)</th>
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<tbody>
<tr>
<td>Arthritis</td>
<td>Pain in the morning and more pain at night (NSAIDs, glucocorticoids)</td>
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<tr>
<td>Asthma</td>
<td>Precipitation of attacks during night or at early morning hour (Antihistamines and β agonist)</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>BP is at its lowest during the sleep cycle and rises steeply during the early morning awakening period (Nitroglycerine, calcium channels blockers)</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>Increase in the blood sugar level after meal (sulfonylurea, biguanide, insulin)</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>Cholesterol synthesis is generally higher during night than during day time (HMG Co-A reductase enzyme)</td>
</tr>
<tr>
<td>Peptic ulcer</td>
<td>Acid secretion is high (H2 blockers)</td>
</tr>
</tbody>
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**Table 1. Disease requiring pulsatile drug delivery**

![Schematic diagram of circadian rhythm](image1)

![Drug release profile of pulsatile drug delivery systems](image2)

![Design of Pulsincap® system](image3)
CONCLUSION

Pulsatile drug delivery system will certainly improve patient outcome and optimize disease management in the future. Research in Pulsatile drug delivery system has demonstrated the importance of biological rhythms in drug therapy and this has led to a new approach to the development of drug delivery systems. 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, 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.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

REFERENCES