A Comprehensive Review of Pulsatile Drug Delivery System

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INTRODUCTION

Controlled drug delivery systems aim to maintain plasma concentration of drugs within the therapeutic window for longer period of time, thereby to ensure sustained therapeutic action and for that reason an increasing interest in their development exist. Several disease states have been proven to follow biological rhythms, expressed by short-, intermediate, and long-period oscillations. Circadian (24-h) time structure is most studied and rather the most common oscillation in a

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number of pathological cases such as asthma where the crisis are mostly happening late at night, osteoarthritis where the pain is more intense again during night, rheumatoid arthritis where the pain peaks at the morning, duodenal ulcer where the highest gastric secretion is happening in the night times, neurological disorders such as epilepsy where the oscillations are following melatonin secretion, hypercholesterolemia where the cholesterol synthesis is higher during the night and several cardiovascular diseases such as cardiac and/or platelet aggregation. Diseases with time structures other than circadian rhythm are also possible, for example, diabetes is following the secretion of insulin stimulated by meal, or tumour growth in cancer states that follows body changes in blood flow. Menstrual cycle and the corresponding hormonal flux are also following cyclic patterns. Pulsatile delivery systems aim to deliver a drug via the oral route at a rate different than constant, (i.e. zero order Pulsatile Release).^6

**Fig 1 : Possible Causes of Morning Increase in the Incidence of Coronary:**

Pulsatile Drug Delivery System are gaining a lot of significance as the drug is released completely after defined lag time. Pulsatile Delivery provides special and temporal relief increasing patient compliance.7

PDDS is being defined as the rapid and transient release of certain amount of molecules within short time period after a predetermined lag phase.8

**PDDS gaining importance / relevance in following situations:**

1. Avoidance of the degradation in upper GIT e.g. – proteins and peptides.
2. Chronopharmacotherapy of diseases showing circadian rhythms in their pathophysiology.9
3. For drugs which exhibit biological tolerance (which can’t be delivered at a constant rate since, the drug effect decreases with time of constant drug level) For drugs with extensive first-pass metabolism.
4. For time-programmed / dependent administration of hormones and many drugs such as isosorbide dinitrate.10

**ADVANTAGES of PDDS:**

1. Nearly constant drug levels at the site of action.
2. Avoidance of undesirable side effects.
3. Reduced dose.
4. Improved patient compliance.
5. Used for drugs with chronopharmacological behavior.
6. No risk of dose dumping.
7. Improved bioavailability, tolerability and reduces side effects.11

**LIMITATION:**

1. Lack of manufacturing reproducibility and efficacy.
2. Large number of process variables.
3. Multiple formulation steps.
5. Need of advanced technology.
Circadian Rhythm and Manifestation of Clinical Disease: fig 1,2:

<table>
<thead>
<tr>
<th>Diseases</th>
<th>Circadian Rhythmicity</th>
<th>Drug Used</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peptic Ulcer</td>
<td>Acid secretion is high in the afternoon and night. Pain in the morning and more pain at night. Cholesterol synthesis is during night than during day time. BP is at its lowest during the sleep cycle and rises steeply during early morning awakening period. Increase in PUPA level in the afternoon. Precipitation of attacks during night or at early morning hours.</td>
<td>$H_2$ Blockers, NSAIDS, Glucocorticoids, Biguanide, HMGCOA reductose inhibitors, Nitroglycerine, Calcium+ channel blockers, ACE inhibitors, Methylphenidate, B2agonist, antihistaminics</td>
</tr>
<tr>
<td>Arthritis</td>
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<td>Diabetes mellitus</td>
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<tr>
<td>Cardiovascular diseases</td>
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<tr>
<td>Attention deficit syndrome</td>
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<tr>
<td>Asthma</td>
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</tbody>
</table>

Methods of Development of Pulsatile Drug Delivery System:\textsuperscript{12,13}

Different approaches of Pulsatile system

- Time Controlled system
- Internally stimuli induced system
- Externally Regulated System
- Multiparticulate System

Summarization of Methods:

1. Time controlled pulsatile release system: fig 3

In time controlled drug delivery systems pulsatile release is obtained after specific time interval in order to mimic the circadian rhythm. Such type of pulsatile drug delivery system contains two components: One is of immediate release type and other one is a pulsed release type. Various methodologies that can used for time controlled pulsatile release systems are discussed in following section:\textsuperscript{13}

- By Solubilization or Erosion of Layer: In such section, the core containing drug is coated is coated with erosion or soluble polymers and drug released is controlled by dissolution or erosion of outer coat. Time dependent release of drug can
be obtained by optimizing the thickness of outer coat.\textsuperscript{14}

- **Pulsatile Delivery By Rupturing of membrane**: These systems are dependent on disintegration of coating for release of drug. The pressure necessary for rupturable coating can be achieved by swelling, disintegration, effervescent excipients, or osmotic pressure. Water permeation and mechanical resistance of the outer membrane are two important factors affecting the lag time.\textsuperscript{15,16}

- **Capsule Shaped System provided with Release Controlling Plug**: These systems contain the release controlling plug between immediate release compartment and pulse release compartment. On contact with aqueous fluids, the cap rapidly dissolves thereby releasing the immediate release component followed by pulsed release component.\textsuperscript{18,19}

- **Pulsatile System Based on Osmosis**: Osmotic System contains a capsule coated with semipermeable membrane. Inside the capsule there is an insoluble plug consisting of osmotically active agent and the drug formulation. Shown in fig 4.

**Fig 4**: Osmotic Pumps Used In Pulsatile Drug Delivery System: mechanism by Osmosis

- **Stimuli Induced System**: In these systems there is release of the drug after stimulation by any biological factor like temperature, or any other chemical stimuli. These systems are further classified into temperature induced system and chemical stimuli induced system, on the basis of stimulus. Shown in fig 5.

In these systems there is a release of drug after stimulation by any biological factor like temperature or any other chemical stimuli. These systems are further classified into Temperature Induced system and chemical stimulated Induced system on the basis of stimulus. These are of following types.\textsuperscript{20,21}

- Temperature induced Pulsatile Release
- Thermoresponsive hydrogel system
- Thermoresponsive polymeric micelle system
- Glucose responsive insulin release Devices like Pulsincap system
- pH sensitive Drug delivery system
- Inflammation induced Pulsatile release

- **pH Dependent 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 includes cellulose acetate phthalate, polyacrylates, sodium carboxymethylcellulose. These polymers are used as enteric coating materials so as to provide release of drug in the small intestine.

- **Externally Regulated System**

  For releasing the drug in a pulsatile manner, another way can be the externally regulated systems in which drug release is programmed by external stimuli like magnetism, ultrasound, electrical effect and irradiation. Magnetically regulated system contain magnetic beads in the implant. On application of the magnetic field, drug release occurs because of magnetic beads. In case of ultrasonically modulated systems, ultrasonic waves causes the erosion of the polymeric matrix thereby modulating drug release. It includes:

  - Magnetic induces release
  - Light induces release
  - Electric induces release
  - Ultrasound induces release

- **Magnetically Induced System:**

  Magnetically regulated system contain magnetic beads in the implant. On application of the magnetic field, drug release occurs because of magnetic beads. Saslawski et al. developed different formulation for in vitro magnetically triggered delivery of insulin based on alginate spheres.

- **Ultrasonically Induced System:**

  Ultrasound is mostly used as an enhancer for the improvement of drug permeation through a biological barrier, such as skin, lungs, intestinal controlled drug delivery. Kost and coworkers depicted an ultrasound-enhanced polymer.

Miyazaki et al. used ultrasound to achieve up to a 27-fold increase in the release of 5-fluorouracil from an ethylene and vinyl acetate (EVAc) matrix. Increasing the strength of the ultrasound resulted in a proportional increase in the amount of 5-fluorouracil released.

- **4.MULTIPARTICULATE SYSTEM:**

  These system are reservoir type system with either rupturable or altered permeability coating and generally housed in Capsular body. A rupturable pulsatile drug delivery system consist of (a) drug core (b) swelling layer comprising of a superdisintegrant and a binder (c) an insoluble water permeable polymeric coating.

**RECENTLY AVAILABLE CHRONOPHARMACEUTICAL TECHNOLOGIES:**

- OROS TECHNOLOGY based on osmotic mechanism
- CEFORM TECHNOLOGY
- CONTINR TECHNOLOGY
- DIFFUCAPS TECHNOLOGY-Multiparticulate system
- CHRONOTOPIC TECHNOLOGY
- Time RX TECHNOLOGY- TIME CONTROLLED SYSTEM
- PULSINCAP-Rupturable system

**COMMERCIAL PRODUCTS:**

1. Pulsys-amoxicillin-Advancis Pharm Corp.
2. Uniphyl-Theophylline-Purdue Pharm Pdts
3. Ritalin β-methylphenidate-Novartis
4. CODAS-Verapamil HCL
5. TIMER X- Oxymorphone
6. Pulsincap TM-Dofetilide
CONCLUSION

It can be concluded that Pulsatile drug delivery system offers better delivery of drugs possessing chronopharmacological behaviour, extensive first pass metabolism, necessity of night time dosing, or absorption window in GIT. Pulsatile drug delivery system shall be promising in future.

CURRENT AND FUTURE DEVELOPMENT:

The future of chronotherapeutics and more specifically the future of delivering drugs in a pulsatile manner seems to be quite promising as in certain diseases states pulsatile release exhibit several advantages over the traditional zero or first order drug delivery mechanism.

Pulsatile drug delivery system can either be time controlled or site specific single or multiple units. At a moment pulsatile release (site or time specific) most often is achieved by using different polymers in coating layers or by changing the coating thickness.

REFERENCE:


