A COMPREHENSIVE REVIEW OF PULSATILE DRUG DELIVERY SYSTEMS
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Article Received on: 11/02/12 Revised on: 18/03/12 Approved for publication: 22/03/12

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ABSTRACT
Pulsatile drug delivery systems are gaining popularity in the field of pharmaceutical formulation, research and development. The prime advantage in this drug delivery is that the drug is released as per the pathophysiological need of the disease. As a result the change of development of drug resistance which is seen in conventional and sustained released formulations can be reduced. This therapy is mainly applicable where sustained action is not required and the drugs are toxic. Basic point of development of this formulation is to find out the circadian rhythms that is a suitable indicator that will trigger the release of drug from the device. Clock genes are the genes that control the circadian rhythms in human physiology. Pulsatile drug delivery systems are promising in case of asthma, cardiovascular diseases, peptic ulcers, arthritis, and hypercholesterolemic conditions.

Key words: circadian rhythms, chronopharmaceutics, pulsatile delivery, multi particulate delivery

INTRODUCTION
Pulsatile drug delivery system is defined as the rapid and transient release of certain amount of molecules within a short time period immediately after a predetermined off-release period, i.e., lag time[1]. A pulse has to be designed in such a way that a complete and rapid drug release is achieved after the lag time so as to match body’s circadian rhythms with the release of drug which increases the efficacy and safety of drugs by proportioning their peak plasma concentrations during the 24 hours in synchrony with biological rhythm. Now a days concept of chronopharmaceutics has emerged wherein, research is devoted to the design and evaluation of drug delivery systems that release a therapeutic agent at a rhythm that ideally matches.

Generation of Circadian Rhythms
"Circadian rhythm" was first described by Halberg and Stephens in 1959. Suprachiasmatic nucleus (SCN), present in brain acts as a biological clock which creates biological rhythms under the control of clock genes and coordinate peripheral oscillators, for functions including cell proliferation and cellular metabolism. The cycle duration generated at the SCN is calibrated by the alternation of light / darkness, both directly and through melatonin secretion by the pineal body. Many body functions that follow circadian rhythm, ie, their activity waxes and wanes with time. A number of hormones like rennin, aldosterone, and cortisol etc, levels in blood may alter with circadian rhythms[3]. Acid secretion in stomach, gastric emptying, and gastro-intestinal blood transfusion[5] may varies rhythmically. Diseases like bronchial asthma, myocardial infarction, angina pectoris, rheumatic disease, ulcer, and hypertension display time dependence[6]. The lag time is essential for the drugs that undergo degradation in gastric acidic medium. It is possible to deliver the drugs to the distal parts of GIT targeting with pulsatile drug delivery systems that undergo extensive first-pass metabolism,are administered successfully as pulsatile delivery systems

Advantages of pulsatile drug delivery systems
1. Improves bioavailability, tolerability and Reduce adverse effects
2. Limited risk of local irritation
3. No risk of dose dumping
4. Improves patient comfort and compliance
5. Achieves a unique release pattern
Fig2: Circadian changes in human

Table1: Diseases requiring pulsatile drug delivery

<table>
<thead>
<tr>
<th>Disease</th>
<th>Chronobiological behavior</th>
<th>Drugs used</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthma</td>
<td>Precipitation of attacks during night or at early morning hours</td>
<td>Anti asthmatics, β2 agonists</td>
</tr>
<tr>
<td>Peptic ulcers</td>
<td>Acid secretion is high at afternoons</td>
<td>H2 blockers</td>
</tr>
<tr>
<td>Cardio vascular diseases</td>
<td>BP is at its lowest during the sleep cycle and rises steeply during the early morning</td>
<td>Nitroglycerin, Calcium channel blockers</td>
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<tr>
<td>Arthritis</td>
<td>Pain in the morning and more pain at night</td>
<td>NSAIDs, Glucocorticoids</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>Increase in the blood sugar level after meal</td>
<td>Sulfonlurea, Insulin, Biguanide</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>Cholesterol synthesis is generally higher during night than during day time</td>
<td>HMG CoA reductase inhibitors</td>
</tr>
</tbody>
</table>

EFFECT OF CIRCADIAN RHYTHMS ON PHARMACOKINETICS OF DRUGS

Drug absorption
In humans orally administered drugs are mostly affected with circadian changes. Gastric acid secretion and pH, motility, gastric emptying time, and gastrointestinal blood flow vary according to the time of the day. Such changes may contribute to the dosing time-dependent difference of drug absorption. Circadian changes of pH may induce modifications of drug ionization, lipophilicity or hydrophilicity of drugs. The circadian changes in drug absorption are significant in lipophilic drugs, than in hydrophilic drugs. Drug absorption by other than an oral route of administration is also influenced by biological rhythms.

Drug distribution
Drug distribution in biological fluids and body tissues vary with the circadian changes. Blood flow depends on sympathetic and parasympathetic activities, these activities turn circadian time-dependent with a predominant diurnal effect of the sympathetic system. Thus, a diurnal increase and nocturnal decrease of blood flow may occur. Plasma proteins such as albumin or Alpha-glycoproteins are circadian time-dependent.

Drug metabolism
Metabolism of many drugs depends upon hepatic enzymes and hepatic blood flow, both shows circadian time dependent variations. Several metabolic reactions including conjugation, hydrolysis, and oxidation show a circadian time-dependent difference.

Drug elimination
Most of the drugs are excreted by kidneys. Renal physiological functions such as glomerular filtration, renal blood flow, and tubular reabsorption urinary pH etc shows circadian time-dependent differences with higher values during daytime, which in turn results in circadian dependent changes in renal excretion of drugs.

METHODS OF DEVELOPMENT OF PULSATILE DRUG DELIVERY SYSTEMS
Different approaches of pulsatile systems include:
1. Time controlled systems
2. Internal stimuli induced systems
3. Externally regulated systems
4. Multiparticulate systems.

1. Time controlled systems
In time controlled drug delivery system, drug is released in pulsatile manner after specific time interval in order to coincide the drug with proper site, thus mimic the circadian rhythm. These are obtained as follows.

a) By Solubilisation or Erosion of layer
In such systems, the core containing drug is coated with the soluble or erodible polymer as outer coat and drug release is controlled by the dissolution or erosion of the outer coat. Time dependent release of the drug can be obtained by optimizing the thickness of the outer coat.

b) Pulsatile Delivery by Rupture of Membrane
In place of swelling or eroding, these systems are dependent on the disintegration of the coating for the release of drug. The pressure necessary for the rupture of the coating can be achieved by the swelling, disintegrants, effervescence
exciipients, or osmotic pressure. Water permeation and mechanical resistance of the outer membrane are major factors affecting the lag time.  

**c) Capsule shaped system provided with release controlling plug**  
These systems contain release controlling plug between immediate release compartment and pulsed release compartment. On contact with aqueous fluids, the cap rapidly dissolves thereby releasing the immediate release component followed by pulsed release component.  

**d) Pulsatile System Based On Osmosis**  
Osmotic system consists of capsule coated with the semipermeable membrane. Inside the capsule there is an insoluble plug consisting of osmotically active agent and the drug formulation.  

**2) Internal Stimuli induced pulsatile systems**  
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 systems and chemical stimuli induced system, on the basis of stimulus. These are of following types:  

a) Temperature–induced pulsatile Release  
b) Thermoresponsive hydrogel Systems  
c) Thermoresponsive polymeric micelle systems  
d) Glucose-responsive insulin release Devices  
e) pH sensitive drug delivery system  
f) Inflammation-induced pulsatile Release  
g) Drug release from intelligent gels responding to antibody concentration  

**3) Externally regulated pulsatile release System**  
This system is not self-operated, but instead requires externally generated environmental changes to initiate drug delivery. These can include magnetic fields, ultrasound, electric field, light, and mechanical force. It includes:  

a) Magnetic induces release  
b) Electric field induces release  
c) Ultrasound induces release  
d) Light induces release  

**4) Multipaticulate system**  
These systems are reservoir type with either rupturable or altered permeability coating and generally housed in capsular body. A rupturable pulsatile drug delivery system consists of:  

- (i) a drug core;  
- (ii) a swelling layer, comprising a superdisintegrant and a binder; and  
- (iii) an insoluble, water-permeable polymeric coating  

**Recently Available Chronopharmaceutical Technologies**  
- OROS technology based on osmotic mechanism  
- CEFORM technology  
- CONTINR technology  
- DIFFUCAPS technology- multi particulate system  
- CHRONOTOPIC technology  
- TIME Rx technology- timed controlled system  
- Pulseincap- rupturable system  
- CODAS-multi particulate pH dependent systems  

**CONCLUSION**  
It can be concluded that pulsatile drug delivery systems offer better delivery of drugs exhibiting chronopharmacological behavior, extensive first-pass metabolism, necessity of nighttime dosing, or absorption window in GIT. There are various technologies present in the market based on the various methodologies. Pulsatile release systems should be promising in the future.  

**REFERENCES**  

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**Fig3:** multi particulate system