Chronotherapeutic Drug Delivery Systems

Pandiyan Shanmugan and Ramu Bandameedi*
Department of Pharmacy, Mewar University, Chittorgarh, Rajasthan, India

Abstract

Recent advances in chronotherapeutics led to the development of pulsatile drug delivery systems which effectively delivered the drug at specified time. Diseases like asthma, arthritis, cancer, diabetes, hypertension, ulcer, hypercholesterolemia, congestive heart failure, stroke etc. show different day night pattern in onset and symptoms exacerbation. Pulsatile drug delivery systems deliver the drug at right time in desired levels providing the multiple benefits over the conventional dosage forms. According to the circadian rhythms of the body drug is facilitated to completely release after a lag time especially for drugs eliciting higher first pass effect and where nocturnal dosing is required these systems are highly beneficial. This review epitomizes the special focus on chronotherapeutics, various approaches in chronotherapeutic drug delivery and applications.

Keywords: Chronotherapeutics; Pulsatile drug delivery; Circadian rhythms

Introduction

Master circadian clock of the body, the suprachiasmatic nucleus regulates the endogenous circadian rhythms present inside the human body [1-3]. Major global market of drug delivery systems is occupied by the oral drug delivery systems where the drug release pattern is within the therapeutic window assures the sustained therapeutic action some conditions demands release of drug after a lag time, i.e., a period of no drug release, where pulsatile drug delivery releases the drug completely after a lag time with increased patient compliance [4-7] shown in Figure 1. Lag time is essential for site specific drug delivery to colon requiring the prevention of drug in G.I.T excessive first pass metabolism, drug degrade in gastric acid medium in stomach, which results in bioavailability. Human body functions such as metabolism, behavior sleep patterns, hormone production regulated by circadian rhythms. Reports suggests that more chances of heart attacks in the early morning hours, high levels of cortisol levels, blood pressure were also high early morning than drops off in the night [8-11]. Nocturnal asthma increased responsiveness in early hours of morning, sudden surge of gastric acidity in the mid night. High cholesterol synthesis in night than in the day light all these events associated with the circadian rhythms definitely reveals the importance for designing time specific drug delivery.

Chronobiology

Study of biological rhythms and their mechanism is known as chronobiology. There are three types of mechanical rhythms in our body [12,13].

➢ Ultradian rhythms: generally last for shorter period less than 24 hrs.
➢ Infradian rhythms: have a frequency range greater than a day and last until a week.
➢ Circadian rhythm: Franz Harberg coined the term circadian which mean approximately one day. The series of events usually experienced in our day to day life shown in Figure 2.

Ideal characteristics for chronotherapeutic drug delivery systems should

• Be biocompatible and biodegradable.
• Non-toxic with the usage of delivery systems.
• Self-regulated and adaptive capability to circadian rhythms

Advantages

• Reduced frequency in dosage schedule
• Improved patient acceptability and compliance
• Minimization of side effects
• Biological tolerance
• Protection of stomach mucosa from gastric irritation drugs
• Drugs with high first pass effects can be delivered efficiently without loss of drug
• Drug targeting to specific sites such as colon is possible

Limitations of pulsatile drug delivery system

• Multiple manufacturing steps in multiparticulate pulsatile drug delivery system.
• Low drug load.
• Incomplete release.
• In-vivo variability in single unit pulsatile drug delivery system.

Classification of pulsatile drug delivery systems [14]

Pulsatile drug delivery system is classified into four classes:

Time controlled pulsatile release

*Corresponding author: Ramu Bandameedi, Department of Pharmacy, Mewar University, Chittorgarh, Rajasthan India, Tel: +919989078708; E-mail: bandameedi.ramu@gmail.com

Received October 11, 2015; Accepted December 07, 2015; Published December 17, 2015


Copyright: © 2015 Shanmugan P, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.
Single unit system
i. Capsular system
ii. Port system
iii. Delivery by solubility modulation
iv. Delivery by reservoir systems

Multi-particulate system
i. Pulsatile system based on rupturable coating (Time controlled expulsion system)
ii. Pulsatile delivery by change in membrane Permeability
iii. Sigmoidal release system
iv. Low density floating multiparticulate pulsatile systems

Stimuli induced

Internal stimuli induced pulsatile system
i. Temperature induced system
ii. Chemical stimuli induced system
iii. pH sensitive drug delivery system

External stimuli induced system
i. Electrically stimulated Pulsatile system
ii. Magnetically stimulated Pulsatile system
iii. Ultrasonically stimulated Pulsatile system

Pulsicap system: It consists of a water insoluble capsule body filled with the drug and a cross-linked hydrogel plug which swells upon contact with dissolution medium or gastro intestinal fluids pushing it out of the capsules shown in Figure 3 [15,16].

Port systems: It consists of a gelatin capsule in a cellulose acetate semi permeable membrane and inside insoluble plug and osmotically active ingredient along with the drug. When it imbines the gastric fluids resulting in increased inner pressure that ejects the plug after a lag time shown in Figure 4 [17].

Delivery by solubility modulation: Systems composites of modulated agents sodium chloride and drug, lesser amounts of NaCl is required to maintain saturated fluid entering the osmotic device which facilitates pulse release [18].

Delivery by reservoir system with erodible or soluble barrier coatings: Barrier layer was coated over to the reservoir device of pulsatile drug delivery where the barrier erodes or dissolves after a specific lag period enabling the drug to get released rapidly from the reservoir core [19].

Multiparticulate system: Drug release from these systems depends on parameters such as type of coating, pH dependent coating, insoluble coating under all physiological conditions influences the solubility changes at some point in G.I. tract and facilitates slow erosion [20].

Reservoir with rupturable polymeric coating or time controlled explosion system: Super-disintegrants incorporated in as swelling agents facilitating the time burst release of particulates upon ingress of water. Initially the drug coated on non-peril seeds followed by a swellable layer and an insoluble top layer coating [21,22]. In vitro in vivo correlation studies reported that time controlled explosion systems with a lag time of 3 hrs appearance of drug in blood and maximum release noted after 5 hrs [23].

Sigmoidal release systems: It consists pellets comprising of different acids such as succinic acid, acetic acid, glutamic acid, malic acid, citric acid, coated with ammonia methacrylate copolymer usp/nf type b. water influx turns the drug core to acid solution in turn increases the permeation of the hydrated polymer film [24].

Low density floating multiparticulate pulsatile systems: Especially for the drugs having absorption window in the stomach low density floating micro particle pulsatile dosage forms retain the drug in stomach for a longer period and not influencing by the pH fluctuations and gastric emptying [25].

Thermoresponsive pulsatile release: Hydrogels at their transient temperatures undergo substantial reversible volume changes in response to change in temperature. Among the various polymers available N-isopropylacrylamide is probably the most extensively used [26].

Chemical stimuli induced pulsatile release: Stimuli sensitive delivery systems release the drug in presence of biological factors like enzymes, pH or any other chemical stimuli example; Development of a gel composed of poly-N-isopolycrylamide with phenylboronic acid moieties that showed a remarkable change in the swelling induced by glucose [27].

pH sensitive drug delivery systems: pH dependent polymers enabled the drug to release in the desired pH range such as eudragit, phthalates, carboxy methyl cellulose, methacrylic acid especially polymers like eudragit I. and S favoured the colon targeting [28,29].
Electro responsive pulsatile release: Drug release is facilitated by the action of applied electric field on rate controlling membrane containing polyelectrolytes [30-32].

Magnetically induced pulsatile system: With the incorporation of magnetic materials such as magnetite, iron, nickel, cobalt in to capsule or tablets by the external influence of magnetic field shown in Figure 5. We can position drug at a specific place or slow down its access to unwanted sites thus changing the time or extent of drug absorption in to stomach or intestine [33-35].

Ultrasonically stimulated: Interaction of Ultrasound With biological tissues, improving the drug permeation through biological barriers, such as skin. Mechanism mainly involved here is the absorption of acoustic energy by the fluids or tissues and oscillating bubbles cause non thermal effect along with the non cavitational effects such as radiation pressure, radiation torque and acoustic streaming [36] (Table 1, 2 and 3).

Evaluation of pulsatile drug delivery system

Tablet thickness and diameter: Thickness and diameter of tablets were important for uniformity of tablet size. Thickness and diameter were measured using Vernier calipers [63,64].

Hardness: This test is used to check the hardness of a tablet which may undergo chipping or breakage during storage, transportation and handling. In this six tablets were selected at random and the hardness of each tablet was measured with Monsanto hardness tester. The hardness is usually measured in terms of kg/cm$^2$ [65,66].

Friability: The friability test was carried out to evaluate the hardness and stability instantly in Roche Friabilator. The percent loss in weight or friability (F) was calculated by the formula [67,68].

$$F= (1-W/Wo) \times 100$$

$F =$ friability

$Wo =$ initial weight

$W =$ final weight

Weight variation: This test is performed to maintain the uniformity of weight of each tablet which should be in the prescribed range. This is done by sampling randomly and weighing 20 tablets and average weight is calculated.

Content uniformity: This test is performed to maintain the uniformity of weight of active ingredient in each tablet which should be in the prescribed range according to the Indian Pharmacopoeia. This test is performed by taking twenty tablets randomly, weighed and powdered. A quantity of powdered tablet was dissolved in 0.1 N HCl in 100ml volumetric flask. It was diluted and the absorbance was measured at fixed wave length using 0.1 N HCl as blank and the % drug content was estimated.

In vitro buoyancy determination: The floating characteristics of the GFDDS are essential, since they influence the in vivo behaviors of the drug delivery system. However there seemed to be no threshold value for the floating system to remain afloat under a physiological condition due to the latter’s complication.

Floating lag time: The time taken by the tablet to emerge onto the surface of the liquid after adding to the dissolution medium at pH 1.2, temperature 37 ± 0.5°C, paddle rotation at 50 rpm.

Total floating time: The time taken by the tablet to float constantly on the surface of the Gastric fluid without pepsin, at pH 1.2, temperature 37 ± 0.5°C, paddles rotation at 50 rpm.

In vitro dissolution studies [69]: Dissolution studies were carried out using USP XXIV dissolution apparatus (rotating paddle method-2). The collected samples were suitably diluted with dissolution fluid wherever necessary and were analyzed for the drug by using a double beam UV spectrophotometer.
The controlled release is achieved by constructing a multilayered tablet made of two basic key components: 1) hydrophilic polymers such as hydroxypropyl methylcellulose (HPMC) and 2) surface controlling barrier layers. Active loaded core surface that is available for drug release when exposed to the fluid is controlled by barrier layers.

Table 1: Marketed products of chronotherapeutic drug delivery systems [37].
Pulsating transdermal drug delivery system

Diabetes mellitus and cancer provide electrophoretic/electro-osmotic transdermal drug delivery system that rhythmically delivers a therapeutic compound in response to application of current pulsations to the system [48,49].

Hydrogel system

Pulsatile drug delivery device using stimuli sensitive hydrogel (US 5226902)

Diabetes mellitus, invention relates to delivery of drug laden hydrogels which Deswell and gives pulsatile release of drugs in response to external or internal stimuli such as temperature or pH changes, or chemical reactions [50].

Table 2: Summarizes the patents involving different types of pulsatile delivery systems with advanced formulation approaches.

<table>
<thead>
<tr>
<th>Disease</th>
<th>Chronological behavior</th>
<th>Drugs used</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peptic ulcer</td>
<td>Acid secretion high in noon and at night</td>
<td>H₂ blockers [51]</td>
</tr>
<tr>
<td>Asthma</td>
<td>Precipitation of attacks during night or at early morning</td>
<td>β₂ agonists, antihistamine [52-54]</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>BP is at its lowest during sleep cycle and rises in early morning</td>
<td>Nitroglycerine, calcium channel blockers, ACE inhibitors [55-58]</td>
</tr>
<tr>
<td>Arthritis</td>
<td>Pain in the morning and more pain in the night</td>
<td>NSAIDS, glucocorticoids [59,60]</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>Increase in blood sugar level after meal</td>
<td>Sulfonyl urea, insulin, bioguanide [61].</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>Cholesterol synthesis generally high during night than day</td>
<td>HMG COA reductase inhibitors [62].</td>
</tr>
</tbody>
</table>

Table 3: Diseases requiring pulsatile drug delivery systems.

Water uptake study: The % water uptake of pulsatile release tablets was determined in medium filled container placed in a horizontal shaker (100 ml of 0.1 N HCl, 37.5°C, 74 rpm n=3) at predetermined time points, the tablets were removed from the dissolution medium. Then were then carefully blotted with the tissue paper to remove surface water, then weighed and then placed back in the medium up to the time when the coating of the tablet ruptured. The % water uptake was calculated as follow:

\[
\text{% Water uptake} = \left(1 - \frac{W_t}{W_0}\right) \times 100
\]

where, Wt: Weight of tablet at time t and Wo: is weight of dry tablet.

Swelling index: The individual tablets were weighed accurately and kept in 50 ml of double distilled water. Then tablets were taken out properly after 60 min., then blotted with filter paper so as to remove the water present on the surface and weighed accurately. Percentage swelling index (SI) was calculated by using the formula

\[
\text{SI} = \left(\frac{W_{\text{wet}} - W_{\text{dry}}}{W_{\text{dry}}}\right) \times 100
\]

Rupture test: The Rupture test on coated tablets was carried out using USP paddle apparatus. Here all other parameters were same as In-Vitro Dissolution Method. The time at which the outer coating layer starts to rupture is called as lag time. This was determined by Rupture test [71,72].

Conclusion

Rapid development in the field of drug delivery has led to the formulation of pulsatile drug delivery system, which delivers the drug at right time, place and amount in the patient’s body. Significant modification in the conventional delivery systems in the form of pulsatile delivery system ensures the time-controlled pulsatile release of bioactive compounds which is prerequisite for chronotherapy. Sustained and controlled delivery keep the in vivo drug concentration in the therapeutic level for a prolonged period of time and this is essential but not sufficient for treatment of circadian rhythm diseases. Chronotherapy goal is to provide perfect therapy by strictly targeting the drug to specific site at most appropriate time. To correlate the biological rhythms the pulsatile drug delivery systems will play a key role by maintaining optimal concentrations at diseased state when required. Since the timing of drug administration in disease therapy has significant impact on treatment, chronopharmacodynamics emerges as an important tool to overcome drug delivery problems and present a greater patient compliance.

References


