PULSATILE DRUG DELIVERY SYSTEM: ADVANCED AND NOVEL APPROACH

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ABSTRACT

Chronotherapeutics is a method of treatment in which in-vivo drug availability is timed to match rhythms of disease, in order to optimize therapeutic outcomes and minimize side effects. From past several decades pulsatile delivery system has gained a lot interest as dosage form. Pulsatile delivery system aims to release drugs in planned pattern which means at appropriate time or at appropriate site. Several controlled release preparations are available which maintains constant drug concentration in the blood and tissues but it is not desired all the time as it has some side effects such as resistance, tolerability and drug side effects. Diseases wherein pulsatile drug delivery systems are effective include asthma, peptic ulcer, cardiovascular diseases, arthritis, attention deficit syndrome in children, and hypercholesterolemia. For preparing pulsatile delivery system, various design strategies have been proposed, most of them are time controlling, stimuli induced, externally regulated and multiparticulate formulations. Pulsatile delivery system is very much useful in case of drugs having chronopharmacological behavior, for the drug having high first pass metabolism effect and for those drugs which have specific site of adsorption in the GIT. Various polymeric materials are used in order to achieve desired lag time in pulsatile release dosage forms. The present article covers findings about the diseases which follows circadian rhythm and can be treated effectively by pulsatile delivery system. Here we also covered various methods of novel pulsatile drug delivery systems that might be able to release the therapeutic agents after proper lag time and at specific site of GIT.

Keywords: Pulsatile Delivery, Chronotherapeutics, Circadian Rhythm.

Introduction:[1-5]

For the treatment of various diseases oral route is the most preferred route and conventional dosage forms are widely used for treatment. The oral route of drug delivery is typically considered the favored and the most having the highest degree of patient compliance because of user-friendly means of drug administration. Conventional drug delivery systems have targeted on constant or sustained drug output with the objective to optimize drug efficacy and to reduce adverse effects. Such dosage forms release drugs with constant or variable drug release. Diseases are being treated through delivery of the drug to the patient in the form of various conventional dosage forms. All these dosage forms have to be administered repetitively for maintaining the drug concentration within therapeutically effective range. Controlled release medication deliver drug at constant level not as and when necessary. If diseases symptoms occur during specific time of day or night conventional dosage forms are unable to fulfill necessities of conditions. Modified release dosage form preparations are expected to provide reduce dosing frequency and improved patient compliance. There are other several problems regarding modified dosage form preparations such as resistance, drug tolerance, activation of physiological systems due to long term constant drug concentration in the body. This challenge has been met by pulsatile dosage forms. Pulsatile release dosage forms are useful when constant plasma drug levels are not desired and that an optimum therapeutic effects comes from a periodically fluctuating drug concentration. Pulsatile systems are gaining a lot of interest as they 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 delivery system developed in order to fulfilling condition of rapid drug release after lag time. Circadian rhythm is the main factor affecting on development of pulsatile drug release. Pulsatile delivery system is very much useful when constant drug release e.g. zero order drug release is not desired. Pulsatile delivery system is also known as time controlled release system as it is independent of pH, enzymes, gastrointestinal motility etc.

Many disease shows circadian rhythms in their pathophysiology. It is observed that diseases have predictable cyclic rhythms and that the timing of medication regimens can improve outcome in selected chronic conditions. For understanding concept of chronotherapeutics, it is necessary to understand following concepts:

- **Chronobiology:** It is the science concerned with the biological mechanism of the diseases according to a time structure.
- **Chronopharmacology:** Chronopharmacology is the science concerned with the variations in the pharmacological actions of various drugs over a period of time.
- **Chronopharmacokinetics:** Chronopharmacokinetics involves study of changes in drug absorption, distribution, metabolism and excretion. Pharmacokinetic parameters, which are conventionally considered to be constant time, are influenced by different physiological functions displaying circadian rhythm. Circadian changes in gastric acid secretion, gastrointestinal motility, gastrointestinal blood flow, drug protein binding, liver enzyme activity, renal blood flow and urinary pH can play role in time dependent variation of drug plasma concentrations.
- **Chronotherapy:** Co-ordination of biological rhythms and medical treatment is called chronotherapy.
- **Chronotherapeutics:** Chronotherapeutics is the discipline concerned with the delivery of drugs according to inherent activities of a disease over a certain period of time. It is becoming increasingly more evident that the specific timethat patients take their medication may be even more significant than was recognized in the past. Chronopharmacists consist of two words chronobiology and pharmacists. Chronobiology is the study of biological rhythms and their mechanisms.

There are three types of mechanical rhythms in our body:[7, 8]

1. **Circadian:** This word comes from Latin word —circa means about and—dies means day.
2. **Ultradian:** Oscillation of shorter duration are termed as ultradian (more than one cycle per 24h) less than one cycle per day.
3. **Infradian:** Oscillations that are longer than 24 h (less than one cycle per day).

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Figure 1: Schematic diagram of circadian rhythm showing diseases require PDDS

Table:1 Influence of circardian rhythm on physiological functioning [10]

<table>
<thead>
<tr>
<th>Sr. no.</th>
<th>Physiological function</th>
<th>Changes in functioning</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Body temperature</td>
<td>Decrease in sleep, Increase in wakefulness</td>
</tr>
<tr>
<td>2</td>
<td>Breathing</td>
<td>Decrease in sleep, Increase in wakefulness</td>
</tr>
<tr>
<td>3</td>
<td>Blood pressure</td>
<td>Decrease in sleep, Increase in wakefulness</td>
</tr>
<tr>
<td>4</td>
<td>Growth hormone</td>
<td>At 11 pm secretion increase</td>
</tr>
<tr>
<td>5</td>
<td>Adrenaline</td>
<td>At 11 pm secretion increase</td>
</tr>
<tr>
<td>6</td>
<td>Heart rate</td>
<td>Decrease in sleep, Increase in wakefulness</td>
</tr>
<tr>
<td>7</td>
<td>Catecholamines</td>
<td>Increase in morning</td>
</tr>
<tr>
<td>8</td>
<td>Plasma aggregability</td>
<td>Increase in morning</td>
</tr>
<tr>
<td>9</td>
<td>Fibrinolytic activity</td>
<td>Decrease in morning</td>
</tr>
<tr>
<td>10</td>
<td>Gastric acid secretion</td>
<td>Highest in evening</td>
</tr>
<tr>
<td>11</td>
<td>Gastric emptying</td>
<td>Increase in morning</td>
</tr>
</tbody>
</table>

Figure 2: Drug Release Patterns: A) Pulsatile B) And C) Other Conventional Extended Release Dosageforms [9]

Requirements Of Pulsatile Delivery Systems:[11-13]
Sustained delivery systems are not always able to fulfill all the needs of some diseases at that time dosage form that can release drugs after lag time or not releasing drugs in early phase of drug administration. In such case pulsatile delivery is the most effective way of treatment.

1. Many body functions follow circadian rhythm, i.e., their activity increases or decreases with time. A number of hormones like rennin, aldosterone, and cortisolshow daily as well as timely
fluctuations in their blood levels. Circadian effects are also observed in case of pH and acid in these cases pulsatil delivery system is the preferred one.

2. salbutamol sulphate is the drug which develop tolerance in the human body when given assustained release dosage form. Many patients are required to upgrade their dosage regimen after one-year under treatment using transdermal clonidine patches. Arterial pressure in patients exceeds the pretreatment value during the 3–7 days following removal of their previous transdermal nitroglycerin patch. All these conditions can be treated effectively by pulsatile delivery systems.

3. some drugs undergo extensive first pass metabolism such as beta blocker, salicylamide and require fast drug input in order to saturate metabolizing in order to minimize pre systemic metabolism. Thus a constant/sustained oral method of delivery would result in reduced oral bioavailability.

4. Circadian rhythms in certain physiological functions are well established. It has been recognized that many symptoms and onset of disease occur during specific time periods of the 24 hr period day. E.g.: asthma and angina pectoris attacks occur generally in early morning.

5. Local treatment: In order to obtain effective drug treatment for local disorders such as inflammatory bowel disease delivery of compounds to the site of inflammation with no loss due to absorption in the small intestine is highly desirable to achieve the therapeutic effect and to minimize side effects.

6. Protection from gastric environment is essential for the drugs that undergo degradation in gastric acidic medium (e.g., peptide drugs), irritate the gastric mucosa (NSAIDs) or induce nausea and vomiting. These conditions can be satisfactorily handled by enteric coating, and in this sense, enteric coating can be considered as pulsatile drug delivery system.

Advantages:[14-16]
- Predictable, reproducible and short gastric residence time
- Less inter- and intra-subject variability
- Bioavailability improved
- Reduction of local irritation
- No dose dumping observed
- Flexibility in design
- Stability gets improved

Disadvantages:[17, 18]
- Lack of manufacturing reproducibility and efficacy
- Numbers of process variables are high
- Cost of production is high
- Trained/skilled personnel are needed for manufacturing
- Less inter- and intra-subject variability
- Improve patient comfort and compliance
- Achieve a unique release pattern
- Extend patent protection, globalize product, and overcome competition
- Reduced adverse effects and improved tolerability

Diseases targeted for Pulsatile Drug Delivery System:[19-24]
Diseases targeted by pulsatile delivery systems are hypercholesterolemia, asthma, ulcer, arthritis, diabetes, neurological disorders, cardiovascular disease and colonic delivery.

Hypercholesterolemia
A circadian changes are observed during hepatic cholesterol synthesis. Therefore cholesterol synthesis occurs higher in concentration during night than day time particularly early in the morning.

Asthma
The chronotherapy of asthma has been widely studied. Airway resistance increases progressively at night or early morning in asthmatic patients. Normal lung function showscircadian changes which reaches a low point in the early morning hours. Broncho constriction and worsening of symptoms observed in circadian fashion so chronotherapy is well suited for asthma.

Arthrities
The chronobiology, Chronopharmacology and chronotherapeutics of pain have been widely studied. Circadian rhythm observed in interleukin 6 and c reactive protein of patients with arthritis. Patients with osteoarthritis shows less pain in the morning and more at night while patients suffering with rheumatoid arthritis shows less pain in the night and more pain in the early morning. Chronotherapy has been selected in such a way that highest drug level observed at the right time for effective treatment of diseases.

Diabetes
The circadian variations of glucose and insulin in diabetes have been extensively studied. The goal of insulin therapy is to mimic the normal physiologic pattern of endogenous insulin secretion in healthy individuals, with continuous basal secretion as well as meal-stimulated secretion.

Neurological disorders
Central mechanisms of epilepsy showscircadian rhythm. Various convulsive events shows circadian rhythm and chronotherapy is the considered one for effective treatment.

Cardiovascular diseases
Several functions such as, Blood pressure (BP), heart rate, stroke volume, cardiac output, blood flow of the cardiovascular system is subject to circadian rhythms. For instance, capillary resistance and vascular reactivity are higher in the morning and decrease later in the day. Platelet aggregability is increased and fibrinolytic activity is decreased in the morning, leading to a state of relative hypercoagulability of the blood. It was postulated that modification of these circadian triggers by pharmacologic agents may lead to the prevention of adverse cardiac events. BP is at its lowest during the sleeping period and rises steeply during the early morning period. Most patients with essential hypertension have a similar circadian rhythm of BP as do normotensive persons, although hypertensive patients have an upward shift in the profile

Colonic delivery
There is low proteolytic activity observed at site of colon so it is the preferred absorption site for absorption of protein and peptide drugs. A colon specific delivery system prevent drug release in stomach and small intestine and upon entry in colon sudden drug release in pulsatile fashion occurs. Colon targeted delivery system also named as time specific delivery system. Here in this case lag time is the time required for the dosage form to reach at colon. All these diseases require to deliver drugs in right amount and at right time and site. Pulsatile delivery system is the only dosage form which can fulfill the needs of these diseases.

Methodologies for the PDDS can be broadly classified into four classes:[24]

I. Time controlled pulsatile release
A. Single unit system
B. Multi-particulate system

II. Stimuli induced
A. Thermo-Responsive pulsatile release
B. Chemical stimuli induced pulsatile systems

III. External stimuli pulsatile release
A. Electro responsive pulsatile release
B. Magnetically induced pulsatile release
IV. Pulsatile release systems for vaccine and hormone products

Table: 2 Diseases treated by pulsatile delivery systems

<table>
<thead>
<tr>
<th>NO.</th>
<th>Diseases</th>
<th>Conditions</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Peptic ulcer</td>
<td>Acid secretion is high in afternoon and night</td>
<td>(H_2) blockers</td>
</tr>
<tr>
<td>2</td>
<td>Duodenal ulcer</td>
<td>Gastric secretion high at night while gastric and small bowel motility and gastric emptying are slower at night</td>
<td>Proton pump inhibitors</td>
</tr>
<tr>
<td>3</td>
<td>Neurological disorder</td>
<td>Central pathophysiology of epilepsy and behavioural classification of convulsive events in</td>
<td>MAO-B inhibitors</td>
</tr>
<tr>
<td>4</td>
<td>Attention deficient disorder</td>
<td>Increase DOPA in afternoon</td>
<td>Methyl phenidate</td>
</tr>
<tr>
<td>5</td>
<td>Hypercholesterolemia</td>
<td>Cholesterol synthesis high in night</td>
<td>HMG CoA reductase inhibitors</td>
</tr>
<tr>
<td>6</td>
<td>Diabetic mellitus</td>
<td>Increase blood sugar level after meal</td>
<td>Sulfonluryl urea, Insulin</td>
</tr>
<tr>
<td>7</td>
<td>Osteoarthritis</td>
<td>Level of pain increase in night and decrease throughout day</td>
<td>NSAIDS, Glucocorticoids</td>
</tr>
<tr>
<td>8</td>
<td>Rheumatoid arthritis</td>
<td>Level of pain increase in early morning and less at night</td>
<td>NSAIDS, Glucocorticoids</td>
</tr>
<tr>
<td>9</td>
<td>Asthma</td>
<td>Precipitation of attack in night and early morning</td>
<td>(\beta_2) agonist, Anti histamines</td>
</tr>
<tr>
<td>10</td>
<td>Cardiovascular disease</td>
<td>BP (Blood pressure) is lowest at sleep cycle and raised sharply during early morning</td>
<td>Nitroglycerine, calcium channel blocker, ACE inhibitors</td>
</tr>
<tr>
<td>11</td>
<td>Cancer</td>
<td>The blood flow to tumours three fold greater during each daily activity phase of the circadian cycle than during the daily rest phase</td>
<td>Vinca alkaloid, taxanes</td>
</tr>
</tbody>
</table>

I. Time controlled pulsatile release

A. Single unit system [25]

A.1 capsular system

Different single-unit capsular PDDS are available. A general design of such systems consists of an insoluble capsule body consisting of a drug and a plug. The plug is removed after a predetermined time lag due to various mechanisms such as swelling, erosion, or dissolution. The Pulsincap® system is an example of such a system that is made up of a water-insoluble capsule body filled with drug formulation. The plug material consists of various polymeric materials such as insoluble but permeable and swellable polymers (e.g.: polymethacrylates), erodible compressed polymers (e.g.: hydroxypropylmethyl cellulose, polyvinyl alcohol, polyethylene oxide), congealed melted polymers (e.g.: saturated polyglycolated glycerides, glyceryl monooate and enzymatically controlled erodible polymer (e.g.: pectin)).

A.2. Port systems

The Port System 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 it comes in contact with the aqueous medium, water diffuses across the semi permeable membrane resulting in increased inner pressure that ejects the plug after a lag time. Thickness of semi permeable membrane determines the lag time. Port system shows the good correlation between in vivo and in vitro experiments.

Figure 1: Capsular System
A.3 Delivery by a series of stops:
Implantable capsules are the example of such systems. The capsule contains a drug and a water-absorptive osmotic agent that are placed in compartments separated by movable partition. The pulsatile delivery is achieved by a series of stops along the inner wall of the capsule. These stops obstruct the movement of the partition but are overcome in succession as the osmotic pressure rises above a threshold level. Porcine and somatotropine have been delivered by this system.

A.4 Delivery by solubility modulation:
Solubility modulators are available for pulsatile delivery of variety of drugs. Salbutamol sulphate is the best example. This system comprises the drug (salbutamol sulphate) and a modulating agent, sodium chloride (NaCl). The amount of NaCl was such that it was less than the amount needed to maintain saturation in a fluid that enters the osmotic device. The pulsed delivery obtained based on solubility of drugs.

A.5 Delivery by reservoir systems with erodible or soluble barrier coatings:
Reservoir devices coated with a barrier layer are the most widely observed pulsatile drug delivery systems. Most of the pulsatile drug delivery systems are. This barrier erodes or dissolves after a specific lag period, and the drug is subsequently released rapidly. Thickness of the coating layer decides the lag time of system. The Time Clock® system consists of a solid dosage form coated with lipid barriers containing carnauba wax and bees wax along with surfactants, such as aspolyoxylhexenylsorbitanmonoleate. This coat erodes prematurely in the aqueous environment in a time proportional to the thickness of the film, and the core is then available for dispersion. The Chronotropic® system consists of a drug-containing core coated by hydrophilic swellable hydroxypropylmethyl cellulose (HPMC), which is responsible for a lag phase in the onset of drug release.

B. Multiparticulate Systems
Multi-particulate drug delivery systems are mainly oral dosage forms consisting of amultiplicity of small discrete units, in which the active substance is present as anumber of small independent subunits. There are different types of multiparticulate systems and these are enumerated and explained below:

B.1 Pulsatile System Based on Rupturable Coating:
This is a multiparticulate system in which drug is coated on nonpareil sugar seeds followed by a swellable layer and an insoluble top layer. Superdisintegrants like sodium carboxymethyl cellulose, sodium starch glycollate, L-hydroxypropyl cellulose, etc are used as swelling agents. Expansion of swellable layer occurs after ingress of water, resulting in rupture of film with subsequent rapid drug release.

B.2 Time controlled expulsion system:
Combination of osmotic and swelling action is used for time controlled expulsion system. The core contains the drug, a low bulk density solid and/or liquid lipid material (e.g., mineral oil) and a disintegrant. Cellulose acetate is further used for coating of core. Upon immersion in aqueous medium, water penetrates the core displacing the lipid material. After the depletion of lipid material, internal pressure increases until a critical stress is reached, which results in rupture of the coating material.

B.3 Pulsatile Delivery by Change in Membrane Permeability:
The permeability and water uptake of acrylic polymers with quaternary ammonium groups can be influenced by the presence of different counter-ions in the medium. Several delivery systems based on this ion exchange have been developed. Eudragit RS 30D is reported to be a polymer of choice for this purpose.
**B.4 Sigmoidal Release System:**

This consists of pellet cores comprising drug and succinic acid coated with ammonium methacrylate copolymer USP/NF type B. Water influx through permeable membrane determines the lag time. The water dissolves acid and the drug in the core. The acid solution in turn increases permeability of the hydrated polymer film.

**B.5 Low density floating multiparticulate pulsatile systems:**

Conventional multiparticulate pulsatile release dosage forms mentioned above are having longer residence time in the gastrointestinal tract and due to highly variable nature of gastric emptying process may result in in vivo variability and bioavailability problems. In contrary, low density floating multiparticulate pulsatile dosage forms reside only in stomach and not affected by variability of pH, local environment or gastric emptying rate. Drugs either absorbed from the stomach or requiring local delivery in stomach these dosage forms are also specifically advantageous for delivery of those types of drugs.

**II. Stimuli induced [26-28]**

A. **Temperature induced systems**

Thermo-responsive hydrogel systems have been developed for pulsatile delivery systems. In these systems the polymer undergoes swelling or deswelling phase in response to the temperature which modulate drug release in swollen state.

B. **Chemical stimuli induced pulsatile systems** [29, 30]

B.1 **Glucose-responsive insulin release devices:**

In case of Diabetes mellitus there is rhythmic increase in the levels of glucose in the body, requiring injection of the insulin at proper time. Several systems have been designed which are able to respond to changes in glucose concentration. One such system includes pH sensitive hydrogel containing glucose oxidase immobilized in the hydrogel. When glucose concentration in the blood increases glucose oxidase converts glucose into gluconic acid which changes the pH of the system. Swelling of the polymer observed due to pH change which results in insulin release. Examples of the pH-sensitive polymers include N,N-dimethylaminoethyl methacrylate, chitosan, polyolefins.

B.2 **Inflammation-induced pulsatile release:**

On receiving any physical or chemical stress, such as injury, fracture etc., inflammation take place at the injured sites. Hydroxyl radicals are produced due to inflammation from these inflammation-responsive cells. Degradation via hydroxyl radicals however, is usually dominant and rapid when Hyaluronic Acid gel is injected at inflammatory sites. These gels are used for delivery of drugs to particular inflamed sites.

B.3 **Drug release from intelligent gels responding to antibody concentration:**

There are numerous kinds of bioactive compounds which exist in the body. Recently, new gels were developed which responded to the change in concentration of bioactive compounds to alter their swelling/deswelling characteristics. Antigen-antibody complex formation as the cross-linking unit in the gel gained special attention, since such interaction is very specific.

**B.4 pH sensitive drug delivery system:**

This type of PDDS contains two components. The first is fast release type and the 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. Examples of pH dependent polymers include cellulose acetate phthalate, polyacrylates, and sodium carboxymethylcellulose.

**III. External stimuli pulsatile release** [31-33]

This system was divided into three subparts and is discussed below.

A. **Electro responsive pulsatile release**:

Polyelectrolytes (polymers which contain relatively high concentration of ionisable groups along the backbone chain) are used for preparing electrically responsive delivery systems and are thus, pH-responsive as well as electro-responsive. Examples of naturally occurring polymers include hyaluronic acid, chondroitin sulphate etc.

B. **Micro electro mechanical systems (MEMS):**

A micro fabricated device has the ability to store and release multiple chemicals substances on demand by a mechanism devoid of moving its parts. The digital capabilities of MEMS may allow greater temporal control over drug release compared to traditional polymer-based systems. The micro chip is the other development in the MEMS. The microchip consists of an array of reservoirs that extend through an electrolyte impermeable substrate.

C. **Magnetically induced pulsatile release:**

The use of an oscillating magnetic field to modulate the rates of drug release from polymer matrix was one of the old methodologies. Magnetic carriers receive their magnetic response to a magnetic field from incorporated materials such as Magnetite, Iron, Nickel, Cobalt etc. For biomedical applications, magnetic carriers must be water based biocompatible, non-toxic and non-immunogenic mechanistic approach.

**IV. Pulsatile release systems for vaccine and hormone products**

Vaccines are traditionally administered as an initial shot of an antigen followed by repeated booster shots to produce protective immunity. The frequency of the boosters, and hence the exact immunization schedule is antigen dependent. Also, coadministration of vaccine adjuvant is often required to enhance the immune response so achieve protective immunity. PDDS offer the possibility of single-shot vaccines.
Recent Techniques of Oral Time Controlled Pulsatile Technology

Currently, pharmaceutical companies have been focused on developing and commercializing PDDS that fulfill unmet medical needs in the treatment of various diseases. Recently developed technologies are SODAS® Technology, IPDAS® Technology, CODAS™ Technology, GEOCLOCK® Technology, PULSYS™ Technology, and Eurand’s pulsatile and Chrono Release System, Magnetic Nanocomposite Hydrogel.

Conclusion

Sustained delivery system is not beneficial particularly in case of treating diseases which follows circadian rhythm but in this case pulsatile delivery system is very much useful. For determining optimum need of drug in the body circadian rhythm of the body is an important concept. Pulsatile delivery system is the system which provides drug release at right amount, right time and at right place. Chronotropic systems are an emerging approach to drug delivery. In this review article we describe advantages of pulsatile delivery system and also recent marketed preparations available as pulsatile dosage forms. There are various technologies present in the market based on the various methodologies. Thus, development of proper pulsatile drug delivery will enhance the patient compliance, optimum drug delivery to the target side & minimizing the side effects.

REFERENCES


