**Abstract**

Pulsatile drug delivery systems (PDDS) are gaining a lot of interest as they deliver the drug at the specific site at specific time as per the pathophysiological need of the disease, resulting in improved patient compliance therapeutic efficacy. Pulsatile drug delivery systems are developed to deliver drug according to circadian behaviour of diseases. This means that these systems will deliver drug at time when disease display it’s most morbid and mortal state within a circadian cycle (24 hrs.). The product follow a sigmodial drug release profile characterized by a time period of no release (lag time) followed by a rapid and complete drug release. Thus drug can be delivered at right time, in right amount and at right site of action by use of such approach. The product follow a sigmodial drug release profile characterized by a time period of no release (lag time) followed by a rapid and complete drug release. Thus drug can be delivered at right time, in right amount and at right site of action by use of such approach.

**Keywords:** Circadian rhythm, Lag time, Multiparticulate pulsatile system, Pulsatile drug delivery system, Single Unit Pulsatile System.

**Introduction**

The oral route of drug delivery is typically considered the favoured and the most having the high degree of patient compliance because of user-friendly means of drug administration. Traditionally, drug delivery systems have focused on constant/sustained drug output with the objective to optimize drug efficacy and to reduce adverse effects. A reduced dosing frequency and improved patient compliance. 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 and increasing patient compliance. The release of drug as a pulse after a lag time has to be designed in such a way that a complete and rapid drug release follows the lag time. These systems are designed according to circadian rhythm of the body. The principle rationale for the use of Pulsatile release is for the drugs where a constant drug release, zero order release is not desired. Controlled drug delivery systems have acquired very important role in pharmaceutical research and business development. These dosage forms offer many advantages over the conventional drug delivery systems; such advantages include nearly constant drug level at the site of action, prevention of peak-valley fluctuations, reduction in dose of drug, reduced dosage frequency, avoidance of side effects, and improved patient compliance.

**Pulsatile system to increase therapeutic efficacy of drug**

In recent years considerable attention has been focused on the development of pulsatile drug delivery system. Delivery system with pulsatile release pattern has gained most popular form of controlled drug delivery system because conventional systems with a continuous release are not ideal.

Oral controlled drug delivery systems are generally used due to convenient dosage form & it also releases drug in constant or variable rates. In these systems drug release generally occurs within therapeutic window for prolong period of time. Hence these systems show sustained release of drug from dosage form.

**Advantages**

- Extended day time night time activity.
- Reduce side effects.
- Reduced dosage frequency.
- Reduction in dose size.
- Improved patient compliance.
- Lower daily cost to patient due to fewer dosage units is required.
- Drug adapts to suit cardiac rhythms to body function or disease.
- Drug targeting to specific site like colon.
- Protecting of mucosa from irritating drugs.

**Limitation**

- Lack of manufacturing reproducibility and efficacy.
- Large number of process variables.
- Multiple formulation steps.
Higher cost of production.

Need of advanced technology.

Trained/ skilled personal needed for manufacturing.¹⁸

Need of Pulsatile drug delivery

1. Body function that follows circadian rhythms.
2. When circadian rhythm is altered by the hormone such as rennin, aldosterone and cortisol etc level in blood.
3. When rhythmic variation seen in acid secretion in stomach, gastric emptying, and gastrointestinal blood transfusion.
4. Disease like bronchial asthma, myocardial in fraction, angina pectoris, rheumatic disease, ulcer and hypertension display time dependence.
5. The lag time is essential for the drugs that undergo degradation in gastric acidic medium.
6. It is possible to deliver the drugs to the distal part of GIT like colon targeting with Pulsatile drug delivery.
7. Drugs that undergo extensive first-pass metabolism are administered successfully as Pulsatile drug Delivery system.²⁰

Mechanism of drug release from Pulsatile drug delivery system

The mechanism of drug release from PDDs can be occurring in the following ways:

Diffusion

Water diffuses into the interior of the particle when particle come in contact with aqueous fluids in the gastrointestinal tract and resultant drug solutions diffuse across the release coat to the exterior.

Erosion

Some coatings designed to erode gradually with time, result in the release of drug contained within the particle.

Osmosis

An osmotic pressure can be built up within the interior of the particle when water allows entering under the right circumstances. The drug is forced out of the particle into the exterior through the coating.²⁰

Methodologies for PDDS

Methodologies for the PDDS can be broadly classified into four classes;

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.¹⁶

Single unit system

a) Capsule Based

Amidon and Leesman

Described a drug delivery system for administering a drug in controlled pulse doses to an aqueous environment in the body of a living being. The formulation comprises of one or more, and preferably less than ten, individual drug-containing subunits in a unitary drug depot, such as a tablet or capsule. The individual subunits are designed to dissolve at different sites and/or times in the gastrointestinal tract to release pulse doses of drug into the portal system in an analogous manner to the rate of release from an immediate release dosage form administered according to an appropriate dosing schedule. The dissolution time of the individual subunits can be controlled by several methods including the provision of pH sensitive enteric coatings and permeability-controlled coatings. The drug delivery system has significant advantages for the oral administration of first-pass metabolized drugs which exhibit a non-linear relationship between input rate of the drug into the portal system and bioavailability.²⁸

Percel and co-workers

Described a capsule capable of delivering therapeutic agents in the body in a time controlled or position-controlled pulsatile release fashion, composed of one or more populations of multicovered particulates (beads, pellets, granules, etc.). Each bead has been prepared by coating an inert particle such as a non paralised (sugar sphere), with a drug and a polymeric binder or by preparing a drug containing particle by granulation and/or extrusion- spheronization, coating the active drug particle with a plasticized enteric coating, and coating plasticized enteric coated drug particle with a mixture of a water insoluble polymer and an enteric polymer. One of the membrane barriers is composed of an enteric polymer while the second membrane barrier is composed of a mixture of water insoluble polymer and an enteric polymer. The composition and the thickness of the polymeric membrane barriers determine the lag time and duration of drug release from each of the bead populations. Optionally, an organic acid containing intermediate membrane may be applied for further modifying the lag time and/or the duration of drug release.³¹
Jenkins et al

Described a Multi particulate modified release composition in an erodable, diffusion controlled or osmotic form designed to release the active ingredients at about six to twelve hours so that the resulting plasma profile is substantially similar to the plasma profile produced by the administration of the two or more immediate release dosage forms given sequentially. The composition can be in the form of an erodable formulation in which the structural integrity of the particulates deteriorates within the body over time, in the form of a diffusion controlled formulation in which the particulates are dispersed in a liquid medium or in the form of an osmotic controlled formulation in which the release of the active ingredient from the composition is controlled by osmosis.22

**Table 1: Diseases Requiring Pulsatile Delivery**

<table>
<thead>
<tr>
<th>Disease</th>
<th>Chronological behavior</th>
<th>Drug used</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular Diseases</td>
<td>BP is at its lowest during night or at early morning awakening period</td>
<td>Nitroglycerin, Calcium channel blocker, ACE Inhibitors</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>Increase in the blood sugar level after meal</td>
<td>Sulfonyl urea, Insulin, Biguanide Asthma</td>
</tr>
<tr>
<td>Asthma</td>
<td>Precipitation of attacks during night or at early morning hour.</td>
<td>B_2 agonist, Antihistaminics</td>
</tr>
<tr>
<td>Arthritis</td>
<td>Pain in the morning and more pain at Night</td>
<td>NSAIDS, Glucocorticoids</td>
</tr>
<tr>
<td>Peptic ulcer</td>
<td>Acid secretion</td>
<td>H2 blockers</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>

**Figure 1: Schematic diagram of capsular system**

b) Osmotic based pump capsule

Osmotic delivery capsules (“osmotic pumps”) function by virtue of walls which selectively pass water into the capsule reservoir. Absorption of water by the capsule through these walls is driven by a water-attracting agent in the capsule interior which creates osmotic pressure across the capsule wall. The water-attracting agent may be the beneficial agent itself whose controlled release is sought, but in most cases, it is a separate agent specifically selected for its ability to draw water, and this separate agent is being isolated from the beneficial agent at one end of the capsule. In either case, the structure of the capsule wall does not permit the capsule to expand, and as a result, the water uptake causes discharge of the beneficial agent through an orifice in the capsule at the same rate that water enters by osmosis.22

**Figure 2: Different type of osmotic pumps used for PDDS**

**Linkwitz and co-workers**

Proposed a drug delivery capsule where drug delivery is driven by the osmotic infusion of moisture from a physiological environment. The capsule has a delivery orifice which opens intermittently to achieve a Pulsatile delivery effect. The wall in which the orifice is formed is constructed of an elastic material (elastomer) which stretches under a pressure differential caused by the pressure rise inside the capsule as the osmotic infusion progresses. The orifice is so small that when the elastic wall is relaxed, the flow rate of drug through the orifice is substantially zero, but when the elastic wall is stretched due to the pressure differential across the wall exceeding a threshold, the orifice expands sufficiently to allow the release of the drug at a physiologically beneficial rate. The selection of the materials from which the device is constructed and the configuration of the device and its dimensions controls the length of time between pulses.23
c) Erodable Barrier System

**Kim:** Described a formulation of coated Donut Shaped Tablet (DST) and multi-layer DST so that immediate release or time-delayed release can be achieved Figure 2. Both zero order or first order extended release kinetics is possible, depending on the excipients and types of drugs in the tablet formulation. The coating layer for time delay is made of high molecular weight water soluble polymers so that the dose dumping can be minimized even when the hydrated surface of the DST and MLDST peels off. Low molecular weight water soluble polymer coatings having a drug dispersed may be employed to provide a Pulsatile release of a drug.\(^{24}\)

**Figure 3:** a) Coated Donut Shaped Tablet (DST) and b) multi-layer DST MLDST's so that immediate release or time-delayed release of a drug proposed by Kim.

**Kohn and co-workers**

Uses the degradation products of one polymer to trigger the release of the active compound from another polymer. The delayed release of the active compound was achieved without using a barrier system that requires complex and sophisticated formulation techniques.\(^{25}\)

**Table 2:** Drug formulated as Pulsatile drug delivery system \(^{22}\)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage form</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diclofenac sodium13</td>
<td>Pulsatile tablet</td>
</tr>
<tr>
<td>Ranitidine HCL14</td>
<td>Floating Pulsatile tablet</td>
</tr>
<tr>
<td>Aceclofenac15</td>
<td>Floating Pulsatile tablet</td>
</tr>
<tr>
<td>Aceclofenac16</td>
<td>Floating Pulsatile Multi particulate System.</td>
</tr>
<tr>
<td>Theophylline17</td>
<td>Pellets</td>
</tr>
<tr>
<td>Meloxicam18</td>
<td>Multi particulate System For Pulsatile release</td>
</tr>
<tr>
<td>Theophylline19</td>
<td>Pulsatile Tablet</td>
</tr>
<tr>
<td>Salbutamol Sulphate 20</td>
<td>Pulsatile Tablet</td>
</tr>
<tr>
<td>Verapamil HCL21</td>
<td>Floating Pulsatile tablet</td>
</tr>
<tr>
<td>Metoprolol Tartarate 22</td>
<td>Floating Pulsatile tablet</td>
</tr>
<tr>
<td>Propranolol23</td>
<td>Time Controlled Pulsatile release tablet</td>
</tr>
<tr>
<td>Atenolol24</td>
<td>Enteric Press Coated Tablet for pulsatile delivery</td>
</tr>
<tr>
<td>Nizatidine25</td>
<td>Floating Pulsatile Tablet</td>
</tr>
</tbody>
</table>

**B) Multiple Units**

**a) Systems Based on Change in Membrane Permeability**

Numerous pharmaceutical forms with delayed release for oral administration are available. As already mentioned the release of the drug must be controlled according to therapeutical purpose and the pharmacological properties of the active ingredient. In consequence, it is not always desirable the blood levels to be constant. On the contrary, in order to avoid any habituation and in order to limit the side effects provoked by the active ingredient, it would be absolutely advantageous for the plasmatic rate to follow the metabolic rhythm and the specific needs of the patient during certain periods. For instance, in order to diminish the nocturnal symptoms or the symptoms upon awakening in the case of certain chronic diseases such as ischemic heart disease, asthma and arthritis, the drugs should be administered in such a way that the desired therapeutical plasmatic level is reached only at the desired moment, i.e. during sleep or at the moment of awakening dosage form for Pulsatile release proposed by Chen 53 containing a plurality of different pellets composed with a core and several coating layers.

**Chen**

Described a dosage form for delivering drugs into the body in a series of sequential, Pulsatile releasing events. The system can be used with drugs which cannot be released by diffusion through a porous coating, such as water insoluble drugs. A plurality of populations of pellets is provided within a unit dosage form such as a capsule or tablet.\(^{27}\)

**CONCLUSION**

Oral drug delivery is the largest, oldest and most preferred route of administration. Circadian disorders such as hypertension, osteoarthritis, asthma etc, which require chronotherapy. PDDS can easily solve this problem as it is modulated according to body’s circadian clock giving release of drug after specified lag time. Pulsatile drug delivery systems offer a solution for delivery exhibiting chronopharmacological behaviour, extensive first-pass metabolism, necessity of night time dosing. The development of pulsatile-release products is very challenging since it requires correct dose to reach the right site at the appropriate time. However, the novel PDDS pays more attention on site and time specificity.

**REFERENCES**


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