PULSATILE DRUG DELIVERY SYSTEM: A REVIEW
*
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ABSTRACT:
Pulsatile Drug Delivery Systems are gaining a lot of interest as they deliver the drug at the right place at the right time and in the right amount, hence providing temporal delivery and increasing patient compliance. Pulsatile drug delivery systems are designed according to the circadian rhythm of the body. Thus the principle rationale for the use of pulsatile release of the drugs is where a constant drug release is not required. A pulse has to be designed in such a way that a complete and rapid drug release is achieved after the definite lag time. Pulsatile systems are beneficial for the drugs having chronopharmacological behavior where night time dosing is desired, such as antiasthmatic, antihypertensive and antiarrhythmic. Current review article discussed the development of pulsatile drug delivery system, types of disease in which pulsatile release is required, advantages, disadvantages, classification, limitation, evaluation and work done on pulsatile drug delivery system.

Keywords: Pulsatile drug delivery, Circadian Rhythm, Chrono-pharmacological, Lag time.

INTRODUCTION
Over the last 30 years, numerous technical advancements have occurred in the formulations, biodegradable polymers and understanding of pharmacokinetics has resulted in new techniques of drug delivery. Apart from the targeted, prolonged, controlled, sustained and targeted delivery systems, a new drug delivery systems known as pulsatile delivery system has drawn attention of the scientists, which is based on the concept of chrono-therapeutics. A pulsatile drug delivery system is one that delivers drug molecule in a rapid and transient manner within a short time period immediately after a predetermined off release (lag time) period. The rationale for use of proposed system is to deliver drug at a time when disease condition is in the most morbid and mortal state during 24 hours. The particular rhythm in the onset and amount of symptoms were seen in diseases such as bronchial asthma, rheumatic disease, angina pectoris, ulcer, diabetes, hypercholesterolemia, neurological disorder and hypertension. Several pulsed release formulations have been developed, where tablets/capsules are the basis of pulsatile formulation that addresses emerging chronotherapeutic requirements. PDDS aims to release drug on programmed pattern that is at appropriate time and at appropriate site of action. The pulsatile effect, that is, 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 should follow the lag time^1^-^5^.

Control release systems for 12 or 24 hr drug release are not suitable for diseases, which follow circadian variation and in such conditions there is requirement for time or pulsatile drug delivery system. Long-term constant drug concentration exposed in blood and tissues may induce many problems such as tolerance of drug and activation of physiological system. These systems are beneficial for the drugs having chronopharmacological behaviour (where night time dosing is required), first pass effect and having specific site of absorption in gastrointestinal tract (GIT). Most
pulsatile drug delivery systems are reservoir devices covered with a barrier coating. The barrier may erode, dissolve or rupture during/after a certain lag time after which the drug is released quickly from the inner reservoir. The lag time prior to the rupture is mainly controlled by: (i) the permeation and mechanical properties of the polymer coating and (ii) the swelling behavior of the swelling layer. The rupturing of the barriers is induced by an expanding core upon water penetration through the barrier coating. The expansion can be caused by effervescent excipient or swelling agents. Pulsatile tablet formulations are manufactured with a rapid-release core (reservoir) encased in a barrier layer formed by rupturable press coating or liquid coating of erodible and swelling polymer. Polymers like various grades of Eudragit® or ethyl cellulose have been tested as film coating to achieve the desired lag time.

Drug release profile of pulsatile drug delivery systems is shown in fig. 1.

Drug release profile of pulsatile drug delivery systems

**Advantages**

1. Extended daytime or night time activity.
2. They reduce the dose size and dose frequency, which reduces side effects and hence cost is reduced thereby improving patient compliance.
3. Drug adapts to suit circadian rhythms of body functions or diseases.
4. Drug targeting to specific site like colon.
5. Protection of mucosa from irritating drugs.
6. Drug loss is prevented by extensive first pass metabolism.
7. This system helps to prevent the continuous presence of some drugs (e.g. salbutamol sulphate) that produce biological tolerance and thus they increase their therapeutic effect.
8. They provide constant drug levels at the site of action and prevent the peak-valley fluctuation.

**Disadvantages**

1. Lack of manufacturing reproducibility and efficacy.
2. Large number of process variables.
3. Multiple formulation steps.
5. Need of advanced technology.

**Limitations**

1. Multiple manufacturing steps in case of Multiparticle drug delivery system.
2. Low drug loading capacity and incomplete release of drug.
3. In vivo variability in single unit pulsatile drug delivery system.
4. Drug dose manipulation in case of child and elder patients is not possible.
5. Immediate withdrawal of drug is not possible.

**Necessity of Pulsatile drug delivery system**

1. Follow Circadian rhythm
2. Protection from gastric environment
3. To achieve localized action
4. First-pass metabolism can be overcome
5. For drugs having short half life

**CLASSIFICATION OF PULSATILE DRUG DELIVERY SYSTEM (PDDS):**

(I) Time controlled pulsatile release

(A) Single unit system
1. Osmotic pressure based systems
   - Based on expandable orifice
   - Based on solubility modifications
   - PORT systems
2. Capsular systems
3. Pulsatile system with rupturable coating
4. Pulsatile system with erodible or soluble barrier coatings

(B) Multi-particulate system
1. Time controlled explosion systems
2. Osmotic based rupturable coating system
3. Rupturable coating systems
4. Pulsatile Delivery by Change in Membrane Permeability
5. Sigmoidal release systems.

(II) Stimuli Induced

(A) Thermo-responsive pulsatile release
1. Temperature controlled systems
(B) Chemical stimuli induced pulsatile systems
1. Inflammation induced systems
2. Glucose sensitive systems
3. pH based systems
4. Gel based systems
Dolly et al, ARPB, 2014; Vol 4 (III)

(III) Externally regulated pulsatile release

(A) Electro responsive pulsatile release
(B) Micro electro mechanical systems (MEMS)
(C) Magnetically induced pulsatile release
(D) Ultrasounds.
(E) Mechanical force
(F) Electric field
(G) Light

(IV) Pulsatile release systems for hormone products and vaccine.

(I) Time controlled pulsatile release:

(A) Single unit system

1. Capsular systems: The general structure of this system consists of an insoluble capsule body containing a drug and a plug which is swelling, soluble or erodible after a predetermined lag time. Eg. Pulsincap system

2. Osmosis based capsular system (PORT System): This system consists of a gelatin capsule coated with a semi permeable membrane (eg. cellulose acetate). Inside this capsule there is an in-soluble plug, an osmotically active agent along with the drug formulation. When this cap comes in contact with the GI fluids, water diffuses across the semi permeable membrane resulting in increased pressure inside that ejects the plug after a predetermined lag time.

3. System with erodible or soluble barrier coating: This system consists of a reservoir device coated with a barrier layer. The barrier dissolves after a specific lag time (no drug release), after that drug was released quickly. This lag time depends on the coating layer’s thickness.

4. System with rupturable coatings: In this system, coating disintegrates to release the drug. Pressure necessary for the rupture of the coating can be achieved by disintegrating, swelling, osmotic pressure or by effervescence excipients

(B) Multiparticulate systems: These systems are reservoir type of devices with a coating which either ruptures or changes its permeability. Sugar beads are coated by drug; these granules are then packaged in a capsule or compressed with additional excipients to form a tablet. The drug may also be blended or granulated with polymers before coating to provide an additional level of control. Eg: beads, pellets.

(II) Stimuli induced: In Pulsatile systems the drug is released after stimulation by any biological factor like temperature, or any other chemical stimuli.

(III) Externally regulated pulsatile release: For the drug release in a pulsatile way, the externally regulated systems in which the release of drug is programmed by external stimuli like electric effect, ultra sound, magnetism and irradiation. Magnetically regulated system contains magnetic beads in the implant. On application of the magnetic field, the release of drug occurs because of the magnetic beads.

Table 1: List of drugs formulated as single and multiple unit forms of PDDS

<table>
<thead>
<tr>
<th>Capsules</th>
<th>Metoprolol tartrate, Propranolol Hcl, Diclofenac sodium, Actaminophen, Ibuprofen, Metoprolol tartrate, Mesalazine, Diltiazem Hydrochloride, Nifedipine, Valsartan, Doxetilide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pellets</td>
<td>Aceclofenac, Diltiazem Hcl, Indomethacin, 5-aminosalicylic acid, Propranolol Hcl, Sosoride-5-mononitrate, Diclofenac sodium.</td>
</tr>
<tr>
<td>Microspheres</td>
<td>Salbutamol sulfate (pH-sensitive ion exchange resins), Theophylline, 5-aminosalicylic acid, Diltiazem hydrochloride</td>
</tr>
<tr>
<td>Tablets</td>
<td>Verapamil HCl, Propranolol HCl, Chlorpheniramine maleate, Felodipine, Salbutamol sulphate, Ranitidine HCl, Acetaminophen, Theophylline, Buflomedil hydrochloride, Isoniazid, Ketoprofen, Nifedipine, Antipyrine, Pseudoephedrine hydrochloride, Diclofenac sodium.</td>
</tr>
<tr>
<td>Beads</td>
<td>Meloxicam, Dicoicosenacid sodium, Theophylline, Acceclofenac,</td>
</tr>
<tr>
<td>Micelles</td>
<td>Diflunisal, Doxorubicin</td>
</tr>
<tr>
<td>Thermo-responsive hydrogel</td>
<td>Gentamicin, Indomethacin, Sulonamide, Diltiazem hydrochloride</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 2: Polymers employed in PDDS

<table>
<thead>
<tr>
<th>Synthetic</th>
<th>Natural</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPMC K4M</td>
<td>Sodium alginate</td>
</tr>
<tr>
<td>HPMC K 15M</td>
<td>Pectin</td>
</tr>
<tr>
<td>HPMC K100M</td>
<td>Karaya gum</td>
</tr>
<tr>
<td>Eudragit</td>
<td>Gelatin</td>
</tr>
<tr>
<td>Ethyl cellulose</td>
<td>Xanthan gum</td>
</tr>
<tr>
<td>Cellulose acetate phthalate</td>
<td>Chitosan</td>
</tr>
<tr>
<td>Polymethacrylic acid</td>
<td>Guar gum</td>
</tr>
</tbody>
</table>
Dolly et al., ARPB, 2014; Vol 4 (III)
(REVIEW ARTICLE)

Table 3: Marketed Technologies of Pulsatile Delivery

<table>
<thead>
<tr>
<th>Technology</th>
<th>Mechanism</th>
<th>Proprietary name and dosage form</th>
<th>KPI</th>
<th>Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>DROS*</td>
<td>Osmotic mechanism</td>
<td>Covera-5H5; XL</td>
<td>Verapamil</td>
<td>Hypertension</td>
</tr>
<tr>
<td>Three dimensional</td>
<td>Externally regulated system</td>
<td>Their Form*</td>
<td>Diclofenac sodium</td>
<td>Inflammation</td>
</tr>
<tr>
<td>DIFFUCA*</td>
<td>Multiparticle system</td>
<td>Imopran*; XL tablets</td>
<td>Verapamil HCL</td>
<td>Hypertension</td>
</tr>
<tr>
<td>CODAS®</td>
<td>pH dependent system</td>
<td>Verelan®; PM tablets</td>
<td>Verapamil HCL</td>
<td>Hypertension</td>
</tr>
<tr>
<td>PULSYSTM</td>
<td>Multiparticle system</td>
<td>Moxatag® tablets</td>
<td>Imoxicillin</td>
<td>Infection</td>
</tr>
<tr>
<td>TIMEX®</td>
<td>Erodible/soluble barrier coating</td>
<td>OPA®; ER tablets</td>
<td>Acetylsalicylic acid</td>
<td>Pain management</td>
</tr>
<tr>
<td>Pulsincap®TM</td>
<td>Rupturable system</td>
<td>Pulsicap®</td>
<td>Dofetilide</td>
<td>Hypertension</td>
</tr>
</tbody>
</table>

Table 4: Diseases requiring PDDS

<table>
<thead>
<tr>
<th>Chronological behavior</th>
<th>Drugs used</th>
<th>Diseases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acid secretion is high in afternoon and at night</td>
<td>H2 blockers</td>
<td>Peptic ulcer</td>
</tr>
<tr>
<td>Precipitation of attacks during night or at early morning</td>
<td>32 agonist, Antihistamines</td>
<td>Asthma</td>
</tr>
<tr>
<td>BP is at its lowest during the sleep cycle and rises steeply during the early morning</td>
<td>Calcium channel blocker, ACE inhibitors, Nitroglycerin</td>
<td>Cardiovascular diseases</td>
</tr>
<tr>
<td>Pain in the morning and more pain at night</td>
<td>NSAIDs, Glucocorticoids</td>
<td>Arthritis</td>
</tr>
<tr>
<td>Increase in the blood sugar level after meal</td>
<td>Sulfonylurea, Insulin</td>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>Cholesterol synthesis is generally high during night than day time</td>
<td>HMG CoA reductase inhibitors</td>
<td>Hypercholesterolemia</td>
</tr>
</tbody>
</table>

Table 5: Weight variation limit

<table>
<thead>
<tr>
<th>5. No. Average weight of tablet (mg)</th>
<th>Maximum difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>80 mg or less</td>
</tr>
<tr>
<td>2</td>
<td>More than 80 mg but less than 250 mg</td>
</tr>
<tr>
<td>3</td>
<td>More than 250 mg or more</td>
</tr>
</tbody>
</table>

3. Friability: Friability of tablet was found to be USP friability. First of all tablet batch was weighed and placed in friabilator for 100 revolution in 4 minutes. The % friability was calculated by
\[ F = \frac{(Wt-Wi)}{Wi} \times 100 \]
Where, Wi = initial weight
Wf = final weight

4. Weight variation test: The USP weight variation test was done by weighing 20 tablets individually calculating average weight and comparing the individual weight to the average.

5. Lag time and Drug release: The lag time and drug release studies was carried out in gastric and intestinal fluids at body temp. This test is performed in USP dissolution apparatus, in this test the tablet was placed in dissolution media and the sample was withdrawn at specific time interval and after that analyzed in UV spectroscopy.

6. 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.

7. Drug content: In this test accurately weight amount of powder was dissolved in water and filtered. After that the absorbance was measured at fixed wave length by UV spectrophotometer.

8. 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±0.5°C, 74 rpm n=3) at predetermined time points, the tablets were removed from the dissolution medium. They 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 update was calculated as follow:
\[ \% \text{Water uptake} = \left(\frac{(Wt-Wo)}{Wo}\right) \times 100 \]
where, Wt- weight of tablet at time t and
Wo - is weight of dry tablet

9. 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
\[
SI = \frac{(\text{Wet weight} - \text{Dry weight})}{\text{Dry weight}} \times 100
\]

**CONCLUSION**

Circadian rhythm of the body is an essential concept for understanding the optimum need of drug in the body. Pulsatile drug delivery is one such system that by delivering of drug at the right time, right place and in right amt., holds promising benefits for the patients suffering from chronic problems like arthritis, asthma, hypertension etc. A significant progress has been made towards designing Pulsatile drug delivery system (PDDS) that can effectively treat diseases with non-constant dosing therapies and hence, enhance patient compliance, optimal delivery of the drug to the site of target while minimizing the undesired effects. Pulsatile release systems should be promising in the future.

**Work done on pulsatile drug delivery system:** There are following tables no. 6 and 7 that represents the recent work done.

**Table 6:** Work done on pulsatile drug delivery system

<table>
<thead>
<tr>
<th>S. No</th>
<th>Author</th>
<th>Drug</th>
<th>Method/Polymer</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Zhang Z et. al. (2014)</td>
<td>Enalapril Maleate</td>
<td>Fluid bed coating technology</td>
<td>Drug release in pulsatile manner</td>
</tr>
<tr>
<td>3.</td>
<td>Huang H et.al. (2013)</td>
<td>Glipizide</td>
<td>wet granulation method</td>
<td>Peroral controlled release delivery system of water-insoluble drugs</td>
</tr>
<tr>
<td>4.</td>
<td>Sokar M.S et. al. (2013)</td>
<td>Valsartan</td>
<td>Direct compression method</td>
<td>Optimize the drug release after a certain lag time expecting an improvement in its bioavailability.</td>
</tr>
<tr>
<td>5.</td>
<td>Kumar S et.al.(2013)</td>
<td>Metoprolol tartrate</td>
<td>Direct compression method</td>
<td>Prolong gastric residence time and increase the drug bioavailability</td>
</tr>
<tr>
<td>6.</td>
<td>Dandale SS et.al.(2013)</td>
<td>Nifedipine</td>
<td>Direct compression method</td>
<td>Rapid release of the drug after a lag time</td>
</tr>
<tr>
<td>7.</td>
<td>Sandeep M et.al.(2013)</td>
<td>Lansoprazole</td>
<td>Wet granulation method</td>
<td>lag time prior to drug release was highly affected by the plug position</td>
</tr>
<tr>
<td>8.</td>
<td>Prasad V et.al. (2013)</td>
<td>Ramipril</td>
<td>Direct compression method</td>
<td>Pulsatile release of the drug after a lag time</td>
</tr>
<tr>
<td>10.</td>
<td>Patel S et.al. (2012)</td>
<td>Meloxicam</td>
<td>wet granulation method</td>
<td>Drug can be released in upper GI tract after a lag phase</td>
</tr>
<tr>
<td>11.</td>
<td>Garg B.K et.al. (2012)</td>
<td>Rosuvastatin calcium</td>
<td>Direct compression method</td>
<td>levels of ethylcellulose coating retarded water uptake and thus prolonged the lag time</td>
</tr>
<tr>
<td>15.</td>
<td>Patil S et.al. (2011)</td>
<td>Aceclofenac</td>
<td>Direct compression method</td>
<td>Relief of morning stiffness in patients with rheumatoid arthritis</td>
</tr>
<tr>
<td>17.</td>
<td>Yadav D et.al. (2011)</td>
<td>Propranolol</td>
<td>extrusion–spheronization technique</td>
<td>lag time could be modified by level of swelling layer and rupturable coating</td>
</tr>
<tr>
<td>18.</td>
<td>Patil A.S et.al. (2011)</td>
<td>Naproxen</td>
<td>rupturable coating method</td>
<td>Release the drug after a desirable lag time</td>
</tr>
<tr>
<td>19.</td>
<td>Sadaphal K.P. et. al. (2011)</td>
<td>Theophylline</td>
<td>Direct compression method</td>
<td>deliver the drug rapidly and completely after a lag time</td>
</tr>
</tbody>
</table>
| 22.   | Liu F et.al. (2010) | Prednisolone | wet granulation method | Double-coating of Eudragit for improved pH-
Nayak U.Y et al. (2009) valsartan hydroxypropyl cellulose (L-HPC) rapid release of the drug after a lag time

Lin H.L et al. (2008) Doxazosin mesylate HPMC E50 desired lag time can be adjusted by the thickness and the hydrophilicity of the coated membrane

Qureshi J et al. (2008) salbutamol sulphate direct compression method osmotic pumping effect eventually lead to the drug release.

Schellekens R.C.A et al. (2008) Mesalazine Eudragit S100 Coating enables pulsatile delivery of the content to the lower parts of the intestines.

Qureshi J et al. (2008) salbutamol sulphate direct compression method osmotic pumping effect eventually lead to the drug release.

Badve S et al. (2007) diclofenac sodium pectin Increase the gastric residence of the dosage form

Ghimire M et al. (2007) Theophylline glyceryl behenate (GB), L-HPC The lag time can be modulated by varying the weight ratio of GB to L-HPC

Sharma S et al. (2006) Meloxicam ionotropic gelation method Pulse release of drugs in upper part of small intestine

Table 7: Patents on PDDS

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Author</th>
<th>Drug</th>
<th>Method/polymer</th>
<th>Inferences</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Mullen A et al. (2013)</td>
<td>Active drug substances</td>
<td>Low-substituted hydroxypropyl cellulose (L-HPC),</td>
<td>Delayed release of active agent followed by a pulsed delivery of the agent.</td>
<td>62</td>
</tr>
<tr>
<td>2.</td>
<td>Matharu AS et al. (2011)</td>
<td>Valsartan</td>
<td>Polymeric hydrogel</td>
<td>Improved residence time in the GIT and a pulsatile release profile.</td>
<td>63</td>
</tr>
<tr>
<td>3.</td>
<td>Holmlund JT et al. (2010)</td>
<td>Gossypol</td>
<td>Lyophilizing processes</td>
<td>Inhibiting the activity of anti-apoptotic Bcl-2 family proteins.</td>
<td>64</td>
</tr>
<tr>
<td>4.</td>
<td>Muthusamy R et al. (2010)</td>
<td>Active drug substances</td>
<td>Dry granulation method</td>
<td>Pulsatile release of the therapeutic agent after a lag time</td>
<td>65</td>
</tr>
<tr>
<td>5.</td>
<td>Gandhi AS et al. (2008)</td>
<td>Valsartan</td>
<td>Eudragit L30</td>
<td>Increasing the bioavailability of an ARB by administering solubilized ARB in pulses</td>
<td>66</td>
</tr>
<tr>
<td>7.</td>
<td>Schellekens RCA et al. (2007)</td>
<td>Active drug substances</td>
<td>Sodium starch glycolate</td>
<td>Pulsatile release of drug in response to a change in pH</td>
<td>68</td>
</tr>
<tr>
<td>10.</td>
<td>Devane JG et al. (2005)</td>
<td>Methylphenidate HCl</td>
<td>Hydrophilic and hydrophobic polymers</td>
<td>Delivers drug in a pulsed or bimodal manner.</td>
<td>71</td>
</tr>
<tr>
<td>11.</td>
<td>Ting R et al. (2004)</td>
<td>Isosorbide-5-mononitrate</td>
<td>Hydrophilic and hydrophobic polymers</td>
<td>Overcome the “first pass” effect</td>
<td>72</td>
</tr>
</tbody>
</table>
REFERENCES


