REVIEW ON RECENT TRENDS AND APPROACH FOR PULSATILE DRUG DELIVERY SYSTEMS

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ABSTRACT
Pulsatile drug delivery aims to release drugs on a programmed pattern i.e.: at appropriate time and/or at appropriate site of action. Currently, it is gaining increasing attention as it offers a more sophisticated approach to the traditional sustained drug delivery i.e.: a constant amount of drug released per unit time or constant blood levels. Technically, pulsatile drug delivery systems administered via the oral route could be divided into two distinct types, the time controlled delivery systems and the site-specific delivery systems. The simplest pulsatile formulation is a two layer press coated tablet consisted of polymers with different dissolution rates. Homogeneity of the coated barrier is mandatory in order to assure the predictability of the lag time. The disadvantage of such formulation is that the rupture time cannot be always adequately manipulated as it is strongly correlated with the physicochemical properties of the polymer. Gastric retentive systems, systems where the drug is released following a programmed lag phase, chronopharmaceutical drug delivery systems matching human circadian rhythms, multiunit or multilayer systems with various combinations of immediate and sustained-release preparation, are all classified under pulsatile drug delivery systems. On the other hand, site-controlled release is usually controlled by factors such as the pH of the target site, the enzymes present in the intestinal tract and the transit time/pressure of various parts of the intestine. In this review, recent patents on pulsatile drug delivery of oral dosage forms are summarized and discussed.

KEYWORDS: Pulsatile release, chronotherapeutics, time controlled systems, pH target release.

INTRODUCTION
Master circadian clock of the body, the suprachiasmatic nucleus regulates the endogenous circadian rhythms present inside the human body. 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 shown in fig 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 suggest 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. 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.

Fig 1. Drug release profile of pulsatile drug delivery systems.

Chronobiology: Study of biological rhythms and their mechanism is known as chronobiology. There are three types of mechanical rhythms in our body.
Ultradian rhythms: generally last for shorter period less than 24 hrs.

Infradian rhythms: have a frequency range greater than a day and last until to 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 fig 2.

Ideal characteristics for chronotherapeutic drug delivery systems should:
- Associate with real time and specific triggering biomarkers for a given disease state.
- 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 with out loss of drug
- Drug targeting to specific sites such as colon is possible.

Limitations of pulsatile drug delivery system
1. Multiple manufacturing steps in multiparticulate pulsatile drug delivery system.
2. Low drug load.
3. Incomplete release.
4. 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.

A. Time controlled pulsatile release
   1. Single unit system
      i. Capsular system
      ii. Port system
      iii. Delivery by solubility modulation
      iv. Delivery by reservoir systems.

II. 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.

B. Stimuli induced
   I. Internal stimuli induced Pulsatile system
      i. Temperature induced system
      ii. Chemical stimuli induced system
      iii. pH sensitive drug delivery system
   II. 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 crosslinked hydrogel plug which swells upon contact with dissolution medium or gastrointestinal fluids pushing it out of the capsules shown in fig 3.[15, 16]

Port systems
It consists of a gelatine capsule in a cellulose acetate semi permeable membrane and inside insoluble plug and osmotically active ingredient along with the drug. When it imbibes the gastric fluids resulting in increased inner pressure that ejects the plug after a lag time shown in fig 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
Superdisintegrants 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 L 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 fig 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. \(^{33, 34, 35}\)

Sonochemistry induced pulsatile release:- 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 cavitations effects such as radiation pressure, radiation torque and acoustic streaming. \(^{36}\)

**Fig 4. Port systems**

**Fig 5 Drug release from magnetically induced pulsatile systems.**
**Table 1. Marketed products of chronotherapeutic drug delivery systems**

<table>
<thead>
<tr>
<th>Technology</th>
<th>Rationale</th>
<th>Products</th>
<th>Company</th>
</tr>
</thead>
<tbody>
<tr>
<td>CONTIN®</td>
<td>Drug blended with hydrophilic cellulose, then hydrated with polar solvent and fixed with a higher aliphatic alcohol to produce a semi-permeable matrix with uniform porosity.</td>
<td>Uniphyl® once daily theophylline MS Contin® and Oxycontin® for use in pain management.</td>
<td>Purdue Frederick, Norfolk, CT, USA</td>
</tr>
<tr>
<td>CODAS®</td>
<td>Chronotherapeutical oral drug absorption system consisting of drug loaded beads that are coated with release-controlling polymer. Polymer consists of water-soluble and water-insoluble polymers to induce a lag time.</td>
<td>Verelan® PA containing verapamil for use in hypertension.</td>
<td>Elan Drug Technologies, San Francisco, CA, USA</td>
</tr>
<tr>
<td>CEFORM®</td>
<td>Biodegradable polymers/bioactives are subjected to varying temperature, thermal gradients and flow processes to produce microspheres of uniform size and shape (150-180μm)</td>
<td>Cardizem® LM containing diltiazem for use in hypertension.</td>
<td>Fuisz Technologies, Chantilly, VA, USA</td>
</tr>
<tr>
<td>DIFFUCAPS®</td>
<td>A multiparticulate system consisting of an inactive core, coated with an active pharmaceutical ingredient mixed with a water-soluble composition. This may be in the form of beads, pellets or granules.</td>
<td>Innopran® XL containing Propranolol for use in hypertension.</td>
<td>Eurand Pharmaceuticals LTD, Dayton, Ohio, USA</td>
</tr>
<tr>
<td>GEOMATRIX®</td>
<td>The controlled release is achieved by constructing a multilayered tablet made of two basic key components; 1) hydrophilic polymers such as hydroxypropyl methycellulose (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.</td>
<td>Sular® (nisoldipine CR) &amp; Coruno® (molsidomine)</td>
<td>SkyePharma, Muttenz, Switzerland</td>
</tr>
<tr>
<td>TIMERx®</td>
<td>A novel polysaccharide system that adopts the use of xanthan gum and locust bean gum in the presence of secondary and tertiary components, to form water-soluble granules.</td>
<td>‘Tablet within a tablet’ to obtain different chronotherapeutic profiles. Geminex® is an improvement which provides the potential for dual therapy.</td>
<td>Penwest Pharmaceuticals, Danbury, CT, USA</td>
</tr>
<tr>
<td>OROS®</td>
<td>As osmotic pump system comprising a central drug reservoir surrounded by a semi-permeable membrane, which is surrounded by osmotically active agents in tablets with a strategically laser-drilled orifice.</td>
<td>Covera® HS containing verapamil for use in hypertension</td>
<td>Alza Corporation, Mountainview, CA, USA</td>
</tr>
<tr>
<td>PULSINCAP®</td>
<td>Consists of a drug reservoir housed within a water-soluble capsule body. The open end is plugged with swellable polymers that are pushed out when in contact with fluid, releasing drug from the reservoir.</td>
<td>A versatile system that can create lag times as well as allowing tablets/minitablets, solutions or beads to be housed within the capsule body.</td>
<td>R.P. Scherer International Corporation, Troy, MI, USA</td>
</tr>
<tr>
<td>PULSYSTM</td>
<td>A novel pulsatile release technology that consists of one immediate-release and two delayed-release components with the use of soluble and insoluble coatings.</td>
<td>MoxatagTM containing amoxicillin for use in antibiotic therapy.</td>
<td>Middlebrook Pharmaceuticals, Westlake, Texas, USA</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Mode of drug delivery</th>
<th>Title (number)</th>
<th>Rationale for chronotherapy and features of patented systems</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral tablet based</td>
<td>IR gastrointestinal drug delivery system (US6531152)</td>
<td>Diseases of alimentary tract, system able to release drug at specific locations within GIT[39]</td>
</tr>
<tr>
<td>Oral tablet based</td>
<td>Pulsatile particles drug delivery system (US5260069)</td>
<td>Hypertension, unit dosage form for delivering drugs into the body in a series of sequential, pulsatile fashion. The system can be used with drugs that cannot be released by diffusion through a porous coating such as Water-insoluble drugs[40]</td>
</tr>
</tbody>
</table>
Table 3. Diseases requiring pulsatile drug delivery systems.

<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[^31]</td>
</tr>
<tr>
<td>Asthma</td>
<td>Precipitation of attacks during night or at early morning hours</td>
<td>β₂ agonists, antihistamine[^52-54]</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>B.P 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[^99,100]</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 is generally high during night than day</td>
<td>HMG COA reductase inhibitors.[^102]</td>
</tr>
</tbody>
</table>

**Evaluation of pulsatile drug delivery system**

**Table 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$^2$.

**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.$^{[67,68]}$

\[ F = \frac{W - W_0}{W_0} \times 100 \]

F= friability
W= 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 wavelength 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.

**a) 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.

**b) 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.

**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. 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

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

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

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

**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.$^{[71]}$

**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, chronopharmacology emerges as an important tool to overcome drug delivery problems and present a greater patient compliance.

**REFERENCES**


42. Jagoteg AG. Pharmaceutical tablet suitable to deliver the active substance in subsequent and predetermined times. US6294200; 2001.


