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 site of action, at the right time and in the right amount, as per the pathophysiological needs of the diseases, resulting in increasing patient compliance. The purpose of writing this review on pulsatile drug delivery systems (PDDS) is to compile the recent literatures with special focus on the different types and approaches involved in the development of the formulation. PDDS are gaining importance in the field of pharmaceutical technology as these systems deliver the right dose at specific time at a specific site. Some of the disease conditions wherein PDDS are promising include duodenal ulcer, cardiovascular diseases, arthritis, asthma, diabetes, neurological disorder, cancer, hypertension and hypercholesterolemia. PDDS can be classified into time controlled systems wherein the drug release is controlled primarily by the delivery system, stimuli induced PDDS in which release is controlled by the stimuli, such as the pH or enzymes present in the intestinal tract or enzymes present in the drug delivery system and externally regulated system where release is programmed by external stimuli like magnetism, ultrasound, electrical effect and irradiation. This review also summarizes some current PDDS already available in the market. These systems are useful to several problems encountered during the development of a pharmaceutical dosage form.

KEYWORDS: Pulsatile drug delivery system, circadian rhythm, pulsatile release of Pulsincap.

INTRODUCTION

Oral controlled drug delivery systems represent the most popular form of controlled drug delivery system for the obvious advantages of oral route of drug administration. Such systems release the drug with constant or variable release rates. The oral controlled release system shows a typical pattern of drug release in which the drug concentration is maintained in the therapeutic window for a prolonged period of time (sustained release), therapy ensuring sustained therapeutic action. But there are certain conditions which demand release of drug after a lag time.e.g. Chonopharmacotherapy of diseases which show circadian rhythms in their pathophysiology. Recent studies have revealed that diseases have predictable cyclic rhythms and that timing of medication regimens can improve outcome in selected chronic condition.

There are many condition that demand pulsatile release like a) many body function that follow circadian rhythm.e.g. secretion of hormones, acid secretion in stomach, gastric emptying, and...
gastrointestinal blood transfusion. b) chronopharmatherapy diseases which shows circadian rhythms in their pathophysiology like bronchial asthma, myocardial infarction, angina pectoris, rheumatatic disease, ulcer, and hypertension. c) Drug that produce biological tolerance demand for a system that will prevent their continuous presence at the biophase as this tends to reduce their therapeutic effect. d) The lag time is essential for the drugs that undergo degradation in gastric acidic medium (e.g. Peptide drugs) and irritate the gastric mucosa or induce nausea and vomiting. e) targeting a drug to distal organs of gastro-intestinal tract (GIT) like the colon requires that the drug release is prevented in the upper two-thirds portion of the GIT. f) the drugs that undergo first-pass metabolism resulting in reduced bioavailability, altered steady state level of drug and metabolite, and potential food drug interactions require delayed release of the drug to the extent possible. All of these condition demand for a time controlled therapeutic scheme releasing the right amount of drug at the right time. This requirement is fulfilled by pulsatile drug delivery system (1, 2, 3, 4).

![Drug Release Profile of Pulsatile Drug Delivery Systems](image)

**Fig 1: Drug release profile of pulsatile drug delivery systems**

**Advantage of Pulsatile Drug Delivery System**

There are many advantages of pulsatile dosage form over conventional dosage form.

1. Extended day time night time activity.
2. Reduce side effects.
3. Reduce dosage frequency.
4. Reduction in dose size
5. Improved patient compliance.
6. Lower daily cost to patient due to fewer dosage form.
7. Drug adapts to suit cardiac rhythms to body function or disease.
8. Drug targeting to specific site like colon.
9. Protecting of mucosa from irritating drugs \(^{(1, 10, 11, 12, 13)}\).

**Disadvantages of Pulsatile Drug Delivery system**
1. Lack of manufacturing reproducibility and efficacy.
2. Wide range of process variable.
3. Various formulation steps.
4. Production cost is higher.
5. Need of advanced technology.
6. Trained person is required for manufacturing \(^{(1,14, 15, 16, 17, 18)}\).

**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. Drug that undergo extensive first-pass metabolism are administered successfully as pulsatile drug delivery system.

**Mechanism of drug release from pulsatile drug delivery System**\(^{(2)}\)
The mechanism of drug release from PDDS can be occurring in the following ways:

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

Some coating 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 or the particle when water allows entering under the right circumstances. The drug is forced out of the particle into the exterior through the coating.

**Disease Required for Pulsatile Drug Delivery** \(^{(3, 6, 7, 8, 9)}\)

The list of diseases which are required for pulsatile release given in table

<table>
<thead>
<tr>
<th>Disease</th>
<th>Chronological Behaviour</th>
<th>Drug Used</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthma</td>
<td>Precipitation of attacks during night or at early morning</td>
<td>(\beta_2) agonist, antihistamines</td>
</tr>
<tr>
<td>Peptic ulcer</td>
<td>Acid secretion is high in the afternoon and at night</td>
<td>H2 blockers</td>
</tr>
<tr>
<td>Cardiovascular diseases</td>
<td>BP is at its lowest during the sleep cycle and rises steeply during the early morning</td>
<td>Nitroglycerin, calcium channel blocker, ACE inhibitors</td>
</tr>
<tr>
<td>Arthritis</td>
<td>Pain in the morning and more pain at night</td>
<td>NASIDs, glucocorticoids</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>Increase in the blood sugar level after meal</td>
<td>Sulfonylurea, insulin</td>
</tr>
<tr>
<td>hypercholesterolemia</td>
<td>Cholesterol synthesis is generally higher during night than day time</td>
<td>HMG CoA reductase inhibitor</td>
</tr>
</tbody>
</table>

**Methodologies for PDDS** \(^{(4, 24)}\)

PDDS can be divided into main 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
I. Time controlled pulsatile release system

These time-controlled systems can be divided into single unit and multiple unit system.

A. Single unit systems

Capsular Systems

A general design of such systems consists of an insoluble capsule body housing a drug and a plug. The plug is removed after a predetermined lag time due to 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 body is closed at the open end with a swellable hydrogel plug.

Figure 2: Capsule Based System

The capsule contact with dissolution medium or gastro-intestinal fluids, the plug swells, pushing itself out of the capsule after a lag time. This is followed by a spontaneous release of the drug. The lag time can be controlled by manipulating the dimension and the position of the plug. For water insoluble drugs, a spontaneous release can be ensured by inclusion of effervescent agents or disintegrants. The plug material consists of insoluble but permeable and swellable polymer, erodible compressed polymers, congealed melted polymers. These formulations are well tolerated in animals and healthy volunteers, and there have been no reports of gastro-intestinal irritation. However, there was a potential problem of variable gastric residence time, which was overcome by enteric coating the system to allow its dissolution only in the higher pH region of small intestine \(^{(25, 26, 27)}\).

Osmosis Based System

This system contains a drug and a water-absorptive osmotic agent that is placed in compartments separated by a 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. This system was used to deliver...
porcine somatotropin. 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 \(^{(28, 29)}\).

a) **Port® System**: The Port®System consists of a gelatin capsule coated with a semi permeable membrane (e.g., cellulose acetate). Inside the capsule were an insoluble plug and an osmotically active agent along with the drug formulation. When this capsule came in contact with the dissolution medium, water diffuses across the semi permeable membrane, resulting in increased pressure inside that ejects the plug after a predetermined lag time. The lag time is controlled by coating thickness \(^{(30)}\).

![Port® System](image)

**Fig 3: Port system**

b) **Delivery System with Soluble or Erodible Membranes**: In such systems the drug release is controlled by the dissolution or erosion of the Outer coat which is applied on the core containing drugs. Time dependent release of the active ingredient can be obtained by optimizing the thickness of the outer coat. E.g. chronotropic system which
consists of a drug containing core layered with HPMC optionally coated with an outer enteric coating.

![Diagram of delivery system with soluble or erodible membranes](image)

**Fig. 4: Delivery system with soluble or erodible Membranes**

The lag time prior to drug release is controlled by the thickness and the viscosity grade of HPMC layer. Solid dosage form coated with lipid barriers such as carnauba wax & beeswax along with surfactants like polyoxyethylene sorbitan monooleate. When this system comes in contact with the aqueous medium the coat emulsifies or erodes after the lag-time depending on the thickness of coat $^{31, 32, 33}$.

c) **Delivery System with Repturable Coating**

These systems are based up on a reservoir system coated with a rupturable membrane. The outer membrane ruptures due to the pressure developed by effervescent agents (or) swelling agent. Citric acid & sodium bicarbonate is incorporated as effervescent mixture in tablet core coated with ethyl cellulose, when system comes in contact with water it produces carbon dioxide gas which exerts pressure & after lag time rupture the membrane & rapid release of drug occurs. A reservoir system with a semi permeable coating is proposed especially with drugs with high first pass effect in order to obtain in-vivo drug pattern similar to the administration of several immediate release doses croscarmellose sodium starch.
Fig. 5: Delivery system with Repturable Coating

Glycollate or low substituted hydroxyl propyl cellulose were used as swelling substances, which resulted in complete film rupture followed by rapid drug release. The lag time is controlled by composition of outer polymeric membrane (34).

B. Multi-particulate system

Systems Based on Change in Membrane Permeability:

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 (35).

II. Classification of PDDS based on stimuli induced

1. Temperature induced system

Thermo-responsive hydrogel system have been developed for pulsatile release. In these system the polymer undergoes swelling or deswelling phase in response to the temperature which modulate drug release in swollen state (36).

2. Chemically induced system

There has been much interest in the development of stimuli-sensitive delivery systems that release a therapeutic agent in presence of specific chemical moieties like enzyme or
protein. One of the good example is Glucose-responsive insulin release devices in which insulin is release on increasing of blood glucose Level. In 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 developed 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. This pH change induces swelling of the polymer which results in insulin release. Insulin by virtue of its action reduces blood glucose level and consequently gluconic acid level also gets decreased and system turns to the deswelling mode thereby decreasing the insulin release (37, 38, 39, 40).

III. Externally Induced System

For releasing the drug in a pulsatile manner, another way can be the externally regulated systems in which drug release is programmed by external stimuli like magnetism, ultrasound, electrical effect and irradiation (41).

1. Electrically stimulated

Electrically responsive delivery systems are prepared by poly electrolytes (polymers which contain relatively high concentration of ionisable groups along the backbone chain) and are thus, pH-responsive as well as electroresponsive. Under the influence of electric field, electro responsive hydrogels generally bend, depending on the shape of the gel which lies parallel to the electrodes whereas deswelling occurs when the hydrogel lies perpendicular to the electrodes (42, 43).

2. Magnetically stimulated

Magnetically regulated system contains magnetic beads in the implant. On application of the magnetic field, drug release occurs because of magnetic beads. Magnetic carriers receive their magnetic response to a magnetic field from incorporated materials in beads such as magnetite, iron, nickel, cobalt etc (44, 45).

IV. Pulsatile release system 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 (46). The frequency of the booster shots, and hence the exact immunization- schedule is antigen dependent. Also, co-administration of vaccine adjuvant is often required to enhance the immune response to achieve protective immunity.
PDDS offer the possibility of single-shot vaccines if initial booster release of the antigen can be achieved from one system in which timing of booster release is controlled (47).

**Evaluation**

1. **Pre-compression study:**

   a) **Angle of repose:** powder will allow to flow through the funnel and fixed to a stand at found height (h). The angle of repose will then calculate by measuring the height and radius of the heap of granules will be form.

   \[
   \tan \theta = \frac{h}{r} \\
   \theta = \tan^{-1} \frac{h}{r}
   \]

   Where, \( \theta \) = angle of repose, \( h \) = height of the cone, \( r \) = radius of the cone

   b) **Bulk density:** Both density loose bulk density (LBD) and tapped bulk density (TBD) will determine. A quantity of 10 g of powder from each formulation will introduced into a 10 ml measuring cylinder. Initial volume will observe, the cylinder will allow tapping. The tapping will continue until no further change in volume is noted. Bulk density and tapped density are calculated by using formula

   \[
   \text{Bulk density} (\rho_b) = \frac{\text{Bulk volume of the powder}}{\text{Weight of the powder}} \\
   \text{Tapped density} (\rho_t) = \frac{\text{Tapped volume of the powder}}{\text{Weight of the powder}}
   \]

   c) **Carr’s index:** The carr’s index of the powder will determine by using formula

   \[
   \text{Carr’s index} (%) = \frac{\text{TBD} - \text{LBD}}{\text{TBD}} \times 100
   \]

   Where, \( \text{LBD} = \frac{\text{weight of the powder}}{\text{volume of the packing}} \)

   \( \text{TBD} = \frac{\text{weight of the powder}}{\text{tapped volume of the packing}} \)

   d) **Hausner’s ratio:**

   \[
   \text{Tapped density} \div \text{Bulk density}
   \]

**EVALUATION OF MODIFIED PULSINCAP** (49)

- **Solubility study of treated capsule**
  The capsule bodies were expose to formaldehyde solution in varying time intervals. The exposed capsule bodies were dried in hot air oven. The solubility of bodies was test in 0.1 N HCl. Then time at which the capsule dissolved or forms a soft fluffy mass is noted.

- **Qualitative test for free formaldehyde:**
Standard used is formaldehyde solution and sample solution is formaldehyde treated bodies. Treated body cut into small pieces and taken into a beaker containing distilled water. This was stirred for 1 hrs with a magnetic stirrer. The solution was then filtered into a 50ml volumetric flask, washed with distilled water and volume was made up to 50ml with the washing.

**Method**

1ml of sample solution and 9ml of water was added. 1ml of resulting solution was taken into a test tube and mixed with 4ml of water and 5ml of acetone reagent. The test tube was warmed in water bath at 40°C and allowed to stand for 40 min. the solution was less intensely colored than a reference solution prepared at the same time and same manner using 1ml of standard solution in place of the sample solution.

- **Weight variation**
  
  10 capsule are selected randomly from each batch and weight individually for weight variation.

- **Drug content**

  Weight accurately a quantity of the mixed contents of 5 capsule containing about drug, shake for 10min with 150ml of methanol. Allow to stand, dilute 10ml of the supernant liquid to 100ml with methanol and measure the absorbance of the resulting solution at the maximum $\lambda_{max}$.

- **In –vitro release profile**

  Dissolution study were carried out by using USP type I dissolution test apparatus (Basket) method. Capsule were placed in a basket so that capsule should be immersed completely in dissolution media. In order to stimulate pH change along the GI tract, 3 dissolution media with pH were sequentially used referred to sequential pH change method. 900ml of the dissolution medium was used at each time. Rotation speed is 50 rpm and temperature was maintained at $37\pm 0.5^\circ$C. 5ml of sample withdrawn at predetermined time intervals and replaced with fresh dissolution media. The withdrawn samples were analysed by UV absorption spectroscopy.
Marketed Technologies of Pulsatile Delivery

Table 2: Marketed formulation of PDDS

<table>
<thead>
<tr>
<th>Technology</th>
<th>Mechanism</th>
<th>Proprietary name and dosage form</th>
<th>API</th>
<th>Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>OROS</td>
<td>Osmotic Mechanism</td>
<td>Covera-HS; XL,tablet</td>
<td>Verapamil HCl</td>
<td>Hypertension</td>
</tr>
<tr>
<td>Three dimensional printing</td>
<td>Externally regulated system</td>
<td>Their form</td>
<td>Diclofenac sodium</td>
<td>Hypertension</td>
</tr>
<tr>
<td>DIFFUCAPS</td>
<td>Multiparticulates</td>
<td>Innopran; XL,tablet</td>
<td>Verapamil HCl</td>
<td>Hypertension</td>
</tr>
<tr>
<td>Pulsincap\textsuperscript{TM}</td>
<td>Rupturable system</td>
<td>Pulsincap\textsuperscript{TM}</td>
<td>Propranolol HCl Dofetilide</td>
<td>Hypertension</td>
</tr>
<tr>
<td>CODAS</td>
<td>Multiperticular pH dependent system</td>
<td>Verelan PM; XL release capsule</td>
<td>Verapamil HCl</td>
<td>Hypertension</td>
</tr>
</tbody>
</table>

**CONCLUSION**

Oral drug delivery is the largest, oldest and most prime 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 and night time dose is required. 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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