



# PULSATILE DRUG DELIVERY SYSTEMS- AN OVERVIEW

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## Abstract

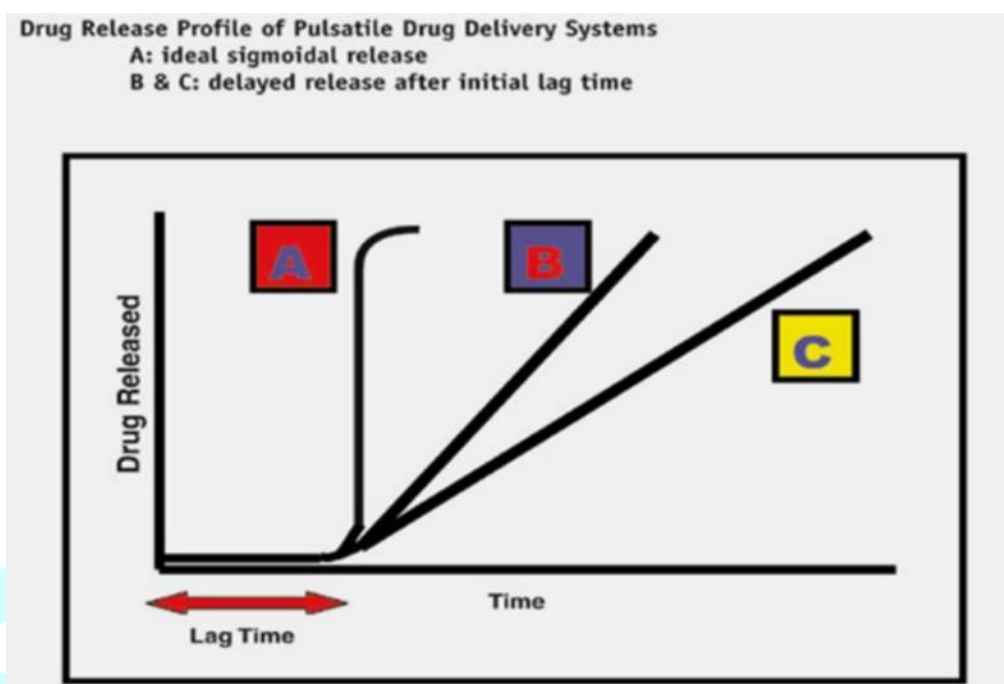
Pulsatile delivery systems getting more attention as they delivered the medication in the desired concentration at the right time, and at the right place results in increases, patient compliances due to it provide spatial, temporal, and smart delivery of a drug. Pulsatile drug delivery is based on the biological rhythm of the body as well as disease rhythm. A pulse should be configured to do so after the lag time, the complete and quick release of drug is achieved. A release of drug from pulsatile drug delivery is mainly achieved by diffusion, erosion, and osmotic mechanism. These systems are useful for those drugs which show chronopharmacological nature such as the drugs used in the treatment of cardiovascular diseases, bronchial asthma, osteoarthritis, diabetic mellitus, ankylosing spondylitis, and peptic ulcer. The first part of this article deals with the chronobiology of the body and diseases, benefits and limitations, reason behind the development of this system. The last part of the article deals with marketed technologies, methods of development of pulsatile delivery systems, and its characterization.

**Keywords:** Capsular System, Pulsatile Drug Delivery System, Pulse, Rupturable Coating, Chronotherapy.

## Introduction

Pulsatile drug delivery systems (PDDSs) are increasingly important due to the dependence on the circadian rhythm of the body. They have therapeutic significance by providing scope for controlled release dosage system. After pulsatile drug delivery system study, the specific time at which patient take medicines become more significant than previous [1]. Pulsincap (single unit system) developed by R. R. Scherer (International Corporation, Michigan, US) [2]. Pulsatile drug delivery is the main issue in personalized pharmacotherapy, especially in chronopharmacotherapy, where dosing interval becomes specific to enhance patient compliance [3-6]. The rapid and transitional release within a short span of the default time of certain drug molecules is known as pulsatile drug release [7-9]. For the treatment of disease, the drug concentration requires to maintain at a therapeutic level. It is desirable for active agent pulsatile release [10, 11]. PDDS(s) are prompt drug delivery systems. Pulsative mechanisms for drug delivery are programmed to follow the rhythms across the body to achieve the site and time-specific drug delivery [12]. PDDS may be built as a drug core coated with a hydrophilic polymer that, when in contact with watery liquids, undergoes a glassy, erodic rubber transformation to delay drug release starting [13]. The principle of PDDS is that a certain amount of medicines is released rapidly within a short period i.e. lag time [14]. This new drug delivery is designed for: (i) Time-controlled hormones and other medicines such as isosorbide dinitrate to prevent the removal of normal

hormones from the corpse which can be interrupted by continuous hormone release from the administered dosage form and resistance development [15,16]; (ii) prevent active ingredient degradation e.g. proteins and peptides, in upper GI tract [17]; (iii) chronopharmacotherapy of a disease whose pathophysiology displays circadian patterns [18]; (iv) to prevent pharmacokinetic interactions between drugs which simultaneously administered, etc. [14, 19]



**fig 1:** drug release profile of pulsatile drug delivery systems [20, 21].

## Chronobiology

Studies on biological processes and their mechanisms are called chronobiology [22]. In our body, mechanical rhythms have three types such as Circadian, Ultradian, and Infradian. The most widely studied rhythm is circadian. The physical, mental and behavioral changes that follow a period of about 24 hrs. are circadian rhythms [23].

### 1. Circadian Rhythms

Franz Halberg coined the term “circadian” the word “circa” is derived from the Latin meaning “in” and “dies” means “day”. It is oscillations in our body which completed in 24 hrs. [24].

### 2. Ultradian Rhythms

It is oscillations of shorter duration (for 24 hours, more than one cycle) For example sleep cycle of 90 min. [25].

### 3. Infradian Rhythms

It is oscillations that are longer than 24 hrs. (For 24 hours, less than one cycle). Disease in which constant concentrations of medicines are not required but require regular therapeutic pulses that accelerate the development of the “Pulsatile Drug Delivery System” [26].

# THE CIRCADIAN BODY

Contrasting Vitruvian Man's traditional "anthropometric scale of proportions", the Circadian Body is modelled on the "neural patterns" found in chronobiology, a science which examines the biological effects of the 24-hour cycle on human biochemistry, physiology and behaviour.

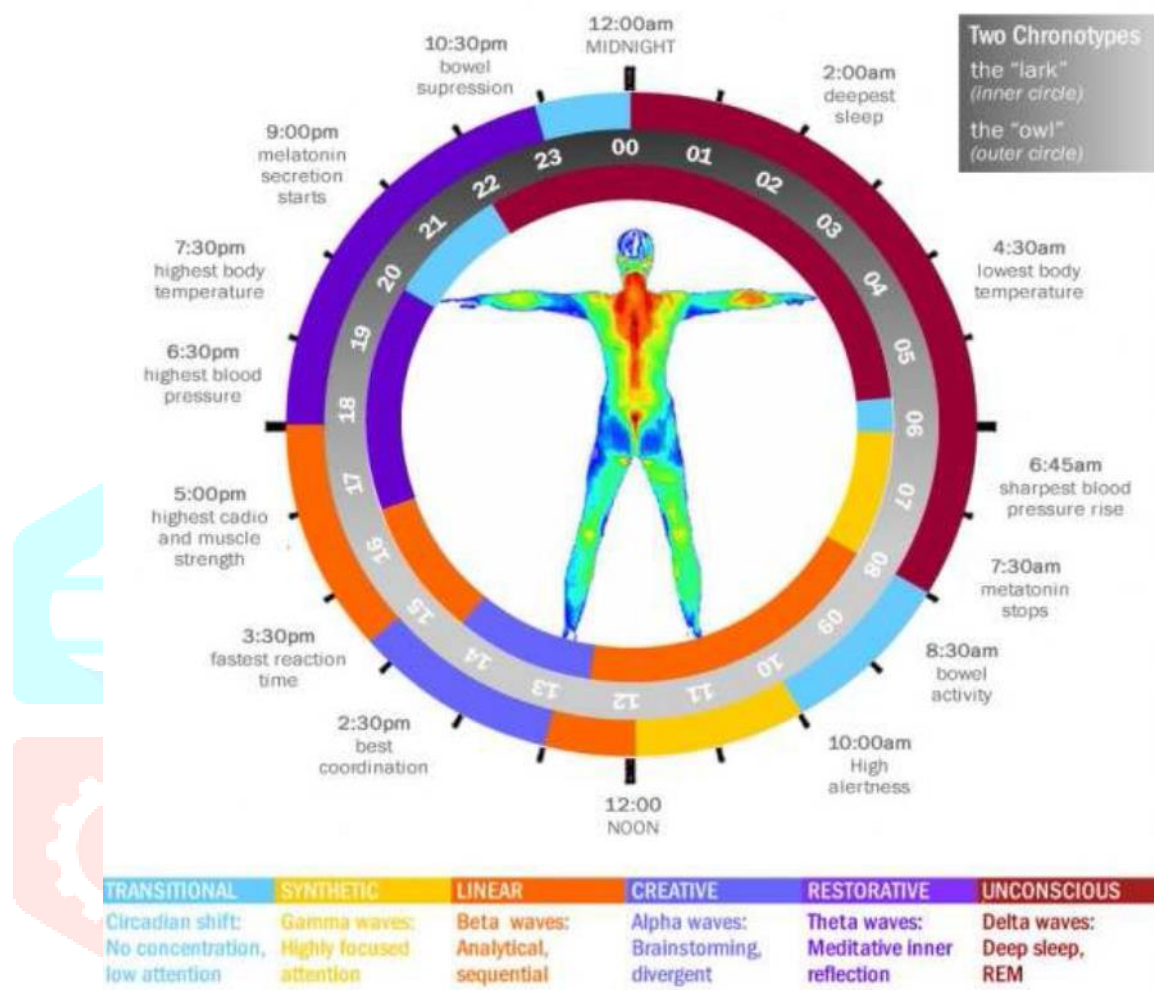


Figure 1: Diseases displaying circadian rhythm [25].

Target diseases in chronotherapy [24].

Diseases	Chronological behavior and symptoms	Drugs used
Diabetes mellitus	After taking a carbohydrate-containing meal, the blood glucose level increased.	Insulin, Sulfonylurea
Bronchial asthma	Attack precipitation after midnight or early morning.	Salbutamol (Beta-agonists), Desloratadine (antihistaminics)
Attention deficiency disorder	In the afternoon, the DOPA level increases.	Methylphenidate
Cardiovascular diseases	Blood pressure decreases during the sleep cycle but increases steeply in the early morning.	Amlodipine (calcium channel blockers), Nitroglycerin
Rheumatoid arthritis	The concentration of interleukin-6 and c-reactive protein increases in blood. Dolor in the early hours of the day.	Celecoxib (NSAIDs), Prednisone (glucocorticoids)
Peptic ulcer	Increases in acid secretion in the afternoon and night.	Omeprazole (Proton pump blockers)
Hyperlipidemia	During the night, cholesterol synthesis increases.	Atorvastatin (HMG CoA Reductase inhibitors)

### Advantages of pulsatile drug delivery [29-31]

1. The activity extended over the day or night.
2. Fewer side effects.
3. The frequency of dosage decreased.
4. The reduced dose sizes.
5. Enhanced patient compliance.
6. Due to the reduced frequency of dosage, the daily cost of medicines in therapy decreased.
7. Target specific action.
8. Mucosal protection from irritating drugs.
9. There is no first-pass effect.

### Disadvantages of pulsatile drug delivery [32, 33]

1. No reproducibility and efficacy of the manufacturing process.
2. Lots of process variables.
3. Due to multiple steps, it is a complex process.
4. High production cost.
5. Need sophisticated technology.
6. For manufacturing, well trained, and an experienced person needed.

### Ideal characteristics of PDDS [34]

1. Non-toxic when taken within the limit.
2. For a given disease, it should have a reliable and real-time biomarker.
3. It should have a feedback control.
4. Mainly for administration by the parenteral route, it should be biocompatible and biodegradable.
5. To increase patient compliance, it should be easy to use.

## The need of pulsatile drug delivery [35, 36]

1. Body activity which works according to circadian rhythms.
2. Useful to maintain hormone levels such as renin, aldosterone, and cortisol. Because imbalance in hormone level results in altered circadian rhythm.
3. A disease that shows time dependence such as myocardial infarction, bronchial asthma, angina pectoris, ulcer, rheumatic disease, and hypertension.
4. For the degradation of the drug in gastric acid medium, lag time is necessary.
5. The drugs targeting the distal part of GIT (colon) that can be delivered by PDDS.
6. Drugs that become inactive due to the first-pass metabolism that can be administered by PDDS.

## The drug-release mechanism from the pulsatile drug delivery system [37]

PDDS drug-release process can occur in the following ways.

### Diffusion

When the particulate matter comes into the contact with the aqueous fluid of the gastrointestinal tract then water diffuses into the particle and the resulting medicament spread outwards across the release coat.

### Erosion

Some coatings are prepared for the release of particles containing drugs by destroying the coat gradually with time.

### Osmosis

In that water enter into the particles after building up the osmotic pressure and then the drug is pushed out from the coating of the sample.

## METHODS OF DEVELOPMENT OF PULSATILE DRUG DELIVERY SYSTEM [38- 40]

PDDS can be broadly classified into the following classes-

### 1. Time controlled Pulsatile release

It again divided into two classes –

1. Capsular system.
2. Multi-particulate system.

### 2. Stimuli induced Pulsatile release

It contains two classes –

1. Thermo-responsive.
2. Chemical stimuli induced.

### 3. External stimuli Pulsatile release

It mainly divided into two classes –

1. Electro responsive.
2. Magnetically induced.

## 4. Pulsatile Release Systems for Hormone Products and Vaccine

### 1. TIME CONTROLLED PULSATILE RELEASE

#### a. Capsular System (Single Unit System)

Capsule form is mainly preferred in a single unit system. In that, the medication is released from the insoluble body of the capsules as a pulse by swelling or erosion and continues the lag time.

**Pulsincap**® method can be prepared by closing the water-insoluble body containing the drug into a swelling hydrogel and plugged to the open end (insoluble but permeable and swellable). After a lag, the plug is swollen from the capsule after contact with the gastrointestinal fluid or dissolving media. Add effervescent or disintegrating agents to the rapid release of water-insoluble drugs [41].



### **Delivery by Solubility Modulation**

In those systems for the pulsed delivery of different drugs, the solubility modulators are mounted. The release of the pulse is depended on the solubility of the drugs. Primarily, the salbutamol sulphate distribution system has been established. This formula includes the medication (salbutamol sulphate), sodium chloride (NaCl), and a modulating agent. The less amount of sodium chloride may be important to maintain saturation in a fluid that is less than expected in the osmotic system. There are various types of modulators are used like inorganic salt or organic salt, and solid organic acid.

### **Delivery with Erodible or Soluble Barrier Coatings by Reservoir Systems**

In most of pulsatile drug delivery system, the barrier-coated reservoir devices are used. Drug releases in the system depend on a particular lag period when the barrier coat is disrupted or dissolved. This particular lag period is dependent on the thickness of the barrier coat [39].

## **b. Multi-particulate system:**

### **Membrane Permeability-Based Systems**

There are various dosage forms for oral administration, with delayed-release. According to the therapeutic activity and the pharmacological action of the active ingredient, the release of the drug can be monitored. Consequently, the blood levels are not always ideal to be stable. On the other hand, to maintain the patient's metabolic and basic needs during certain cycles to prevent any habituations and to reduce the unwanted effects caused by the drug the plasma output should be entirely desirable. For example, the desired therapeutic plasma level can only be achieved at the right time, that is, when sleeping, or when waking up, for to decrease the indications upon arousing for some chronic illnesses, for example, bronchial asthma, cardiac heart failure, and inflammation of a joint, drugs should be administered to consist of two or more systems of pellets or particles populations, and those systems as defined by Chen as a large number of pellets. Every pellet contains a core drug and an osmotic water solution agent in a water-permeable and water-insoluble polymer film. The film requires a hydrophobic water-insoluble agent affecting the polymer film permeability. The swelling of the pellets and regulation of the rates of spread of the substance to the atmosphere after the dissolution of the osmotic agent into the water. Since pellets release each population medicines consecutively in the atmosphere, the number of the pulsatile medicines are taken from one dosage form. In most pulsatile medicaments, the barrier-coated reservoir systems are used. Drug release in this device depends on a specific lag period by destroying or dissolving the barrier coat and this specific lag period depends on the thickness of the barrier coat [39].

## **2. STIMULI INDUCED PULSATILE RELEASE**

### **a. Thermo- Responsive -**

For the pulsatile release, the thermo-responsive hydrogel systems were developed. In that, the polymer has to swell or decompose state and according to the temperature which is a swollen state modifies the release of drugs. Y.H. Bae et al established that Indomethacin pulsative patterns are used to release butyrylacrylamide and the acrylamide copolymer N-Isopropyl at temperatures between 200C and 300C. As drug carriers for treating cancer, Kataoka et al. developed a thermo-sensible polymer micelle. To prepare corona micelle use of endfunctionalized poly (N isopropyl acrylamide) (PIPAAm) which shows higher temperature hydration and dehydration [43, 44].

### **b. Chemical stimuli -**

It was of great interest to establish stimulation-sensitized delivery that releases therapeutical products in front of certain chemical motility such as enzymes and proteins. For example, insulin is released on increasing blood glucose levels through a Glucose-responsive insulin release system. Blood glucose levels in the body rhythmically increase in diabetes mellitus, for decreasing the blood glucose level require insulin injection at the proper time. Therefore, various systems were established for altering the concentration of blood glucose. The pH-sensitive hydrogel is one of the systems in that the glucose oxidase is immobilized into the hydrogel. After increasing the blood glucose level in the body, Oxidase glucose transforms into gluconic acid, and this conversion changes the pH of systems. Due to this change in pH, the polymer can swell which increases insulin production. Insulin lowers blood glucose levels because of its action and thus the level of gluconic

acid also decreases and the system shifted towards the deswelling mode thus reducing the release of insulin [45]

### **3. EXTERNAL STIMULI PULSATILE RELEASE**

#### **a. Electrically Stimulated**

Polyelectrolyte (i.e. polymers that contain ionizable groups relatively high in the backbone) is used for electrically responsive supply systems and the system is both sensitive to pH and electro responsive. The electrically stimulated method was designed by R. V. Kulkarni et al. for ketoprofen transdermal delivery by using hydrogel (PAAm-g-XG) poly(s). Electroresponsive hydrogels typically bend under the influence of the electric field, based on the gel that is perpendicular to electrodes while the hydrogel is perpendicular. While deswelling is taking place [46].

#### **b. Magnetically Stimulated**

Magnetically operated implant device includes magnetic beads. Drug release occurs due to magnetic poles when applying the magnetic field [47]. Magnetic carriers derive their magnetic response from magnetic fields in which materials such as Nickel, iron, magnetite, cobalt, etc. are integrated. Magnetically hydrogels described by Tingyu Liu, et al that was effectively manufactured as a cross-linking agent by chemical crosslinking of iron (II, III) oxide and gelatin hydrogels nanoparticles (approx. 40–60 nm) from genipin (GP). Saslawski et al. [44] developed various formulations based on alginate spheres for the in vitro magnetically activated insulin delivery. In an experiment, insulin powder and microparticles of ferrite (1µm) were scattered in a viscous solution of sodium alginate. Insulin alginate ferrite suspension was subsequently reduced to an aqueous solution of calcium chloride which forms of cross-linked alginate spheres and again connected with watery poly (ethylene imine) or poly (L-lysine) solutions. Due to microparticles of ferrite, the magnetic feature retained and the media of the polymer with mechanical properties may contribute to the management of the insulin system's release rates [48].

### **4. PULSATILE RELEASE SYSTEMS OF HORMONE PRODUCTS AND VACCINE**

Traditionally, an antigen and a regular booster injection are the main vaccines for protecting the immunity [49]. The duration of the booster dose is dependent on antigen, and thus the exact immunization schedule. Adjuvant vaccine co-administration is also often necessary to reinforce the immune response to protecting immune [50]. It permits single-shot vaccines if the initial antigen release booster from a managed booster release control system can be achieved. GnRH, used in nutritionally anesthetic cows, developed a higher luteal activity frequency by 13 days in 2 mg of pulses administered over 5 minutes in an hour than cows receiving continuous infusion or pulses per 4 Hr. Viscarra et al. [40].

## marketed technologies of pulsatile drug delivery system.

Sr No.	Technology	Mechanism	Proprietary name and dosage form	API	Disease	References
1	CODAS®	Multiparticular pH-dependent system	Verelan® PM; XL	Verapamil HCL	Hypertension	51
2	Pulsincap™	Rupturable system	Pulsincap™ M	Dofetilide	Hypertension	52
3	Three-dimensional printing®	Externally regulated system	TheirForm®	Diclofenac Na	Inflammation	53
4	OROS®	Osmotic Mechanism	Covera-HS®; XL	Verapamil HCL	Hypertension	54
5	Pulsys®	Timed-controlled System	Timed-controlled System	Amoxicillin	Pharyngitis/tonsillitis	55
6	DIFFUCAPS®	Multiparticulate System	Innopran®; XL	Verapamil HCL, Propranolol HCL	Hypertension	56, 57
7	TIMERx®	Erodible/soluble barrier coating	OPANA® ER tablets	Oxymorphone	Pain management	58

**Characterization of PDDS****Differential scanning calorimetry**

DSC evaluated the probability of some interaction between TP, polymers, and other excipients. The sample thermogram was collected by scanning speed of 10 °C / minute over a spectrum of 0° C to 350 ° C under an inert air at a rate of 20 ml/minute flushed with nitrogen [59].

**Friability Test**

By using Roche friabilator, the friability test is carried out. 20 tablets are weighed and put in a plastic chamber, rotates this chamber at 25rpm for 4 minutes. After that, the tablets are weighed again and calculate percent friability by using the following formula.

$$\% F = (\text{loss in weight}/\text{initial weight}) \times 100$$

Whereas,

% F is the percent friability

As per Indian Pharmacopeia, this test was carried out [60].

**Hardness**

Different hardness testers are available to determine the hardness of tablets but the Monsanto tester is most commonly used to measure the hardness of tablets. Select randomly six tablets from the batch and measure the hardness of it; it is measured in kg/cm<sup>2</sup> [61].



**Density**

The density of the powder can affect the compressibility, dissolution, flowability, and porosity of the powder.

**Bulk density**

It is calculated by using the following formula

$$\rho_b = \frac{m}{v_b}$$

Whereas,

P<sub>b</sub> is the bulk density

M is the mass of powder

v<sub>b</sub> is the Bulk Volume.

**Tap density**

It is used to measure the void space between the powders and is calculated by pouring the pre-weighed amount of powder in a measuring cylinder. The volume is measured before and after 50 tappings of measuring cylinder. By using the following formula, it is calculated

$$\rho_t = \frac{m}{v_t}$$

Whereas,

ρ<sub>t</sub> is tapped density.

m is the mass of powder.

v<sub>t</sub> is tapped volume.

**Carr's Index**

It is based on the particle size distribution, cohesiveness, and flow properties of powdered materials. To measure the compressibility index of powdered materials, a bulk density as well as tapped density is an important parameter.

It is determined by the following equation

$$\text{Carr's index (\%)} = \frac{\rho_t - \rho_b}{\rho_t} \times 100$$

Whereas,

ρ<sub>t</sub> is tapped density, ρ<sub>b</sub> is bulk density.

**Hausner's Ratio**

It is commonly used to determine the compressibility of powdered materials.

$$\text{Hausner's Ratio} = \text{Tapped Density} / \text{Bulk Density}$$

**Angle of Repose**

Various methods are used to measure the angle of repose but the funnel method is most common. The desired amount of powdered materials pours in the funnel. Adjust the height of the funnel that is appropriate two cm from the plane surface to the tip of the funnel and allow it to flow from it. Measure the angle of response by calculating the following parameters.

$$\tan \theta = \frac{h}{r}$$

Whereas,

θ is the angle of repose

h is the height of the pile of powder

r is the radius of the cone base [62].

**Solubility study for formaldehyde exposed the body of the capsule**

By the different time intervals, the bodies of capsules were exposed to a solution of 15 percent formaldehyde. Then exposed bodies of capsules were dried in an oven of hot air. And 0.1N HCl measured the solubility of capsule bodies [63]

## Stability Studies

The rapid Analysis of Stability was performed. Following ICH instructions, the elevate formulation was subject to stabilization studies for not less than three months. The samples were wrapped in an aluminum foil inserted in a high-density polyethylene bottle which is tightly closed and held at  $40\pm 20^{\circ}\text{C}/75\% \pm 5\% \text{RH}$ . The tablets were collected and tested for the duration of floating, in vitro drug release, appearance, drug content, hardness, thickness, diameter, and floating lag time of capsule after the three months [64].

## Weight variation

From each batch randomly collect 10 Capsules and separately weight for weight variation [65].

## Conclusion

Rapid advancement and newer developments in the field of drug delivery have led to the formulation of the pulsatile drug delivery system, which, on one hand, can be formulated with ease and, on the other hand, provides a significant amount of therapeutic benefits. These systems deliver the drug at right time, place and amount in the patient's body. Chronopharmaceutics will certainly improve patient outcome and optimize disease management in the future. Hence this system play major role in treating various diseases according to chronopharmacotherapy and gives sustained or controlled release therapy.

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