

## PULSATILE DRUG DELIVERY SYSTEM-CURRENT PROGRESS AND FUTURE PERSPECTIVES

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### ABSTRACT

Pulsatile drug delivery systems have emerged as a promising approach to improving drug therapy by releasing drugs at precise times that mimic the body's natural physiological rhythms. This review investigates the design, mechanisms, and applications of pulsatile drug delivery systems for improving therapeutic efficacy and reducing side effects. Various pulsatile delivery strategies, such as time-controlled, stimuli-responsive, and externally triggered systems, are evaluated for their adaptability and effectiveness in achieving desired drug release profiles. Advantages of the Pulsatile drug delivery system are reduced dose frequency; reduce side effects, drug targeting to specific site like colon and many more. Now in market varies technologies of pulsatile drug delivery system like Pulsincap, Diffucaps etc. are launched by pharmaceutical companies. Overall, this review focuses on the significant advances and future directions of pulsatile drug delivery systems, emphasizing their potential to revolutionize drug administration and improve patient outcomes.

**Keywords:** Pulsatile drug delivery systems, Circadian rhythm, Single unit, Multiple units, Lag time.

### 1. INTRODUCTION

The oral drug delivery system is the largest segment of the total drug delivery in market. It is the most commonly used method of drug administration. The oral controlled-release methods follow a predictable pattern of drug release in which the drug concentration is kept in the therapeutic window for a longer length of time, thereby ensuring sustained therapeutic activity. There are certain conditions for which such a release pattern is not suitable that demand release of drug after a lag time. In other terms, they require a pulsatile drug delivery system (PDDS).<sup>1</sup>

Pulsatile systems are gaining popularity since the drug is released completely after a predetermined lag time. Pulsatile drug delivery systems are time- and site-specific drug delivery systems that provide customized and temporal delivery and increasing patient compliance. Pulsatile drug delivery system is defined as the rapid and transient release of certain amount of molecules within a short time period immediately after a predetermined off-release period, i.e., lag time.<sup>2</sup>

Recent studies have developed that diseases have a predictable cyclic rhythm and that the timing of drug regimens can improve the outcome of a desired effect.<sup>3</sup>

Drug release as a "pulse" is required for this condition, and the system must be made so that the medicine should release completely and quickly after the lag. These devices are referred to as pulsatile drug delivery systems (PDDS), time-controlled system or sigmoidal release system.<sup>4</sup>

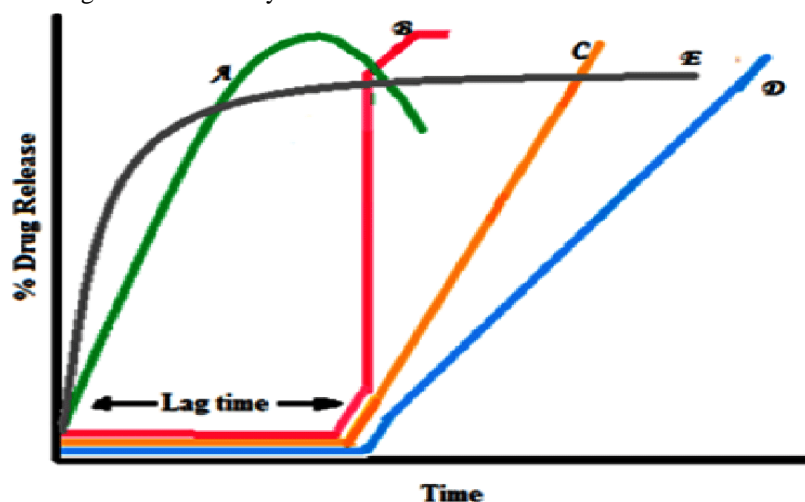


Figure 1: Schematic representation of different drug delivery systems

Where,

- a. Conventional release profile.
- b. Burst release of drug after a lag time.
- c. Delayed release profile after a lag time.
- d. Constant release profile in prolonged period after a lag time.
- e. Extended-release profile without lag time.

Pulsatile drug delivery system is importance in following situations like circadian rhythms are seen in disorders, with some of the worst symptoms occurring in the morning and others occurring at night, such as bronchial asthma, myocardial infarction, angina pectoris, rheumatic disease, ulcer, and hypertension. 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.<sup>5</sup>

#### **Classification of pulsatile drug delivery system:**

Pulsatile drug delivery system is classified into four classes:

##### **A. Time controlled pulsatile release**

###### **Single unit system**

- a) Capsular system
- b) Port system
- c) Delivery by solubility modulation
- d) Delivery by reservoir system

###### **Multi-particulate system**

- a) Pulsatile system based on rupturable coating (Time controlled expulsion system)
- b) Pulsatile delivery by change in membrane permeability
- c) Sigmoidal release system
- d) Low density floating multiparticulate pulsatile system

##### **B. Stimuli induced**

###### **a) Internal stimuli induced pulsatile system**

- a) Temperature induced system
- b) Chemical stimuli induced system
- c) pH sensitive drug delivery system

###### **b) External stimuli induced system**

- a) Electrically stimulated pulsatile system
- b) Magnetically stimulated pulsatile system
- c) Ultrasonically stimulated pulsatile system
- d) Photo chemically stimulated pulsatile system.<sup>6</sup>

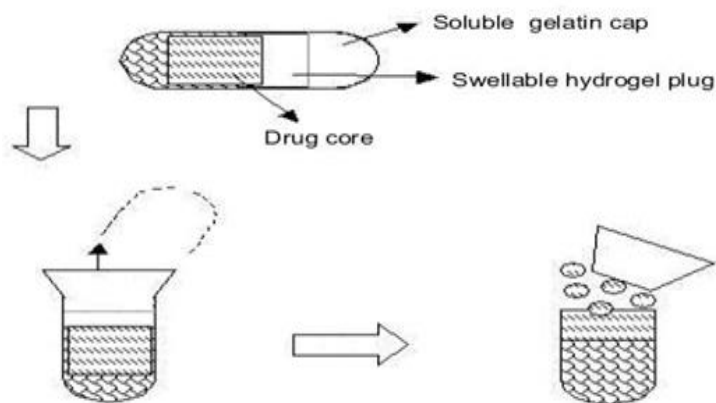
##### **A. Time controlled pulsatile release<sup>7,8,9</sup>**

###### **Single unit system**

###### **a) Capsular system**

It consists of a water insoluble capsule body filled with the drug and a cross-linked hydrogel plug which swells upon contact with dissolution medium or gastro intestinal fluids pushing it out of the capsule after a lag time as shown in **(Figure 2)**. The Pulsincap® system, which consists of a water-insoluble capsule body filled with drug formulation, is an example of such a system. The plug swells when it comes into touch with dissolving medium or gastro-intestinal fluids, eventually pushing itself out of the capsule. This is followed by a spontaneous release of the drug. The lag time can be controlled by adjusting the plug's dimension and position. Polymers used for designing of the hydrogel plug are as follows:

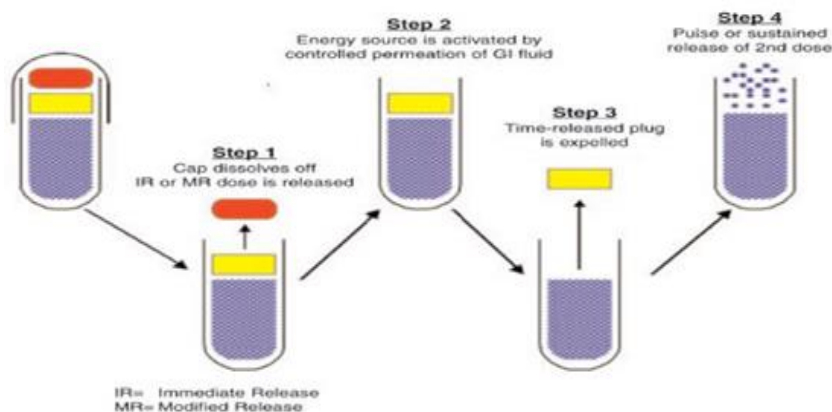
- Insoluble but permeable and swellable polymers (e.g., polymethacrylates)
- Erodible compressed polymers (e.g., hydroxypropyl methyl cellulose, polyvinyl alcohol, polyethylene oxide)
- Congealed melted polymers (e.g., saturated polyglycolated glycerides, glyceryl monooleate)
- Enzymatically controlled erodible polymer (e.g., pectin).



**Figure 2:** Capsular system

#### b) Port system (Programmable oral release technology)

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 eject the plug after a lag time that shown in **(Figure 3)**. Coating thickness controls the lag time. Such a system was utilised to deliver methylphenidate used in the treatment of attention deficit hyperactivity disorders as the pulsatile port system. This system avoided second time dosing, which was beneficial for school children during daytime.



**Figure 3.** Port system

It is further classified as –

##### 1) Based on expandable delivery orifices

It is used to deliver the drug in liquid dosage form. Osmotic pressure develops on the drug reservoir and drug release occurs through delivery orifices. The lag time is modified by changing the thickness of barrier membrane.

##### 2) Delivery by series of stops

It is for implantable capsule. It contains a drug and water absorptive osmotic engine placed in compartments separated by movable partition. Pulsatile drug delivery is achieved by series of stops. The number and frequency of stops and longitudinal placements of stop along with length of movable partition.

#### c) Pulsatile drug delivery by modulating solubility

Solubility modulator of system provides pulsed delivery of variety of drugs. Composition contains modulating agent's sodium chloride and drug. The amount of sodium chloride required is less than the amounts needed to maintain the saturated fluid enter in osmotic device. It allows for the release of pulses. A solid organic acid, inorganic salt or organic salt can be used as a modulating agent.

#### d) Delivery by reservoir systems with erodible or soluble barrier coatings

The majority of pulsatile drug delivery systems are reservoir devices with a barrier layer on top. After a specific lag period, this barrier erodes or dissolves, and the drug is swiftly released. The lag time is proportional to the thickness of the coating layer. The system's lag time is unaffected by gastrointestinal motility, PH, enzymes, or gastric residence time.

**Multi-particulate system<sup>10,11</sup>**

Multi-particulate drug delivery systems are mainly oral dosage forms, in which the active substances are present as a number of small independent subunit. This system has more benefits than single-unit system. The mechanism by which the drug is released from these systems is dependent on the type of coating, which can be insoluble under all physiological conditions or pH dependent, with solubility changing at some point in the G.I. tract and slowly eroding the coating.

**a) Reservoir systems with rupturable polymeric coating**

Drugs are coated on sugar seeds in these multiparticulate systems before being coated with an insoluble and swellable top layer. Super disintegrants such as carboxy methylcellulose, sodium starch glycolate, and L-hydroxy propyl cellulose are included in the swelling agent. Polymers such as polyacrylic acid, polyethylene glycol, and others. Upon ingress of water, the swellable layer expands, resulting in rupture the film with subsequent rapid drug release. The drug's release is unaffected by pH or solubility. Lag-time can be adjusted by varying the thickness of the coating or the amount of lipophilic plasticizers in the outermost layer. If the concentration of the osmotic agent is increased, rapid drug release after a lag time can be observed. In-vivo studies of a time-controlled explosion system with a three-hour in-vitro lag time revealed that the drug appeared in blood after three hours and reached its maximum level after five hours.

**b) Pulsatile delivery by change in membrane permeability**

The presence of different counter-ions in the medium can influence the permeability and water uptake of acrylic polymers with quaternary ammonium groups. On the basis of this ion exchange, several delivery systems have been developed. The polymer of choice for this application is said to be Eudragit RS 30D. The polymer side chain typically contains a positively polarized quaternary ammonium group, which is always accompanied by negative hydrochloride counter-ions. Because the ammonium group is hydrophilic, it helps the polymer interact with water, changing its permeability and allowing water to permeate the active core in a controlled manner. The core of these systems contains drug and sodium acetate and is coated with four different layers of Eudragit RS30D. The permeability of eudragit film is dramatically altered by a small amount of sodium acetate. Permeability increases after lag time due to increased interaction between eudragit and acetate, resulting in complete drug release within a few minutes. As thickness increases, lag time increases, but it has no effect on release.

**c) Sigmoidal release system**

Sigmoidal release pattern is therapeutically beneficial for timed release and colonic drug delivery, and observed in coated systems. Pellet cores containing drug and succinic acid are coated with ammonio-methacrylate copolymer. The rate of water influx through the polymer membrane determines the time lag.

The acid and drug in the core are dissolved by the water. In turn, the acid solution increases the permeability of the hydrated polymer film. Succinic acid, acetic acid, glutaric acid, tartaric acid, malic acid, and citric acid are some of the acids that can be used.

**d) Low density floating multiparticulate pulsatile systems**

Low density floating multiparticulate pulsatile dosage forms are only found in the stomach and are not affected by pH, local environment, or gastric emptying rate variability. These dosage forms are also advantageous for drugs that are either absorbed from the stomach or require local delivery in the stomach. These dosage forms are also advantageous for drugs that are either absorbed from the stomach or require local delivery in the stomach. In short multiparticulate pulsatile release dosage forms possessing gastric retention capabilities. A multiparticulate floating-pulsatile drug delivery system based on porous calcium silicate (Florite RE) and sodium alginate was developed for time and site-specific drug release of meloxicam for rheumatoid arthritis chrono pharmacotherapy.

**B. Stimuli induced<sup>12,13</sup>**

The drug is released in these systems after stimulation by any biological factor, such as temperature, or any other chemical stimuli. On the basis of stimulus, these systems are further classified as temperature induced systems and chemical stimuli induced systems.

**Internal stimuli induced pulsatile system****a) Temperature induced system**

For pulsatile release, thermo-responsive hydrogel systems have been developed. In these systems, the polymer goes through a swelling or deswelling phase in response to temperature, which modulates drug release when the polymer is swollen.

**b) Chemical stimuli induced system**

**1) Glucose-responsive insulin release devices**

Diabetes mellitus causes a rhythmic increase in glucose levels in the body, necessitating insulin injections at the appropriate time. Many systems are developed which are able to respond to changes in glucose concentration. One such system includes a pH sensitive hydrogel with immobilized glucose oxidase. When the concentration of glucose in the blood increases, glucose oxidase converts it to gluconic acid, which changes the pH of the system. This pH change causes the polymer to swell, resulting in insulin release. Insulin reduces blood glucose levels and, as a result, gluconic acid levels, and the system enters the deswelling mode, resulting in decreased insulin release.

**2) Inflammation-induced pulsatile release**

When any physical and chemical stress such as injury, broken bones etc occurs the various inflammatory reactions takes place at injury site. At inflammatory sites phagocytic cells like macrophages and polymorphonuclear cells, play role in healing process. During inflammation hydroxyl radicals (OH<sup>•</sup>) are generated from inflammation responsive cells. The inflammatory-induced hydroxyl radicals and designed drug delivery systems, which responded to the hydroxyl radicals and degraded in a limited manner. They used hyaluronic acid (HA) which is specifically degraded by the hyaluronidase or free radicals. Degradation of HA via the hyaluronidase is very low in a normal state of health. Degradation via hydroxyl radicals however, is usually dominant and rapid when HA is injected at inflammatory sites. Thus, it is possible to treat patients with inflammatory diseases like rheumatoid arthritis, using anti-inflammatory drug incorporated HA gels as new implantable drug delivery systems.

**c) pH-sensitive drug delivery system**

This type of pulsatile drug delivery system contains two components. The first is fast release type while the other is pulse release which releases the drug in response to change in pH. The fact that different pH environments exist at different parts of the gastrointestinal tract has been used to advantage in the case of pH dependent systems. Drug release at a specific location can be achieved by selecting pH dependent polymers. Polymers that are pH dependent include cellulose acetate phthalate, polyacrylates, and sodium carboxymethylcellulose. These polymers are used as enteric coating materials to facilitate drug release in the small intestine.

**External stimuli induced pulsatile system<sup>14,15,16</sup>**

These open-loop systems are not self-regulating. However, for drug delivery in a pulse manner, another method of drug release in a programmed pattern can be the externally regulated system. These systems are electro responsive, magnetically stimulated, ultrasonically modulated and photo stimulated.

**a) Electro responsive pulsatile release**

This system provides the drug release by action of applied electric field on rate limiting membrane and / or directly on solute, thus controls its transport across the membrane. Polyelectrolyte's (polymers with a high concentration of ionisable groups along the backbone chain) are used to make electrically responsive delivery systems, which are both pH-responsive and electro-responsive. Hyaluronic acid, chondroitin sulphate, agarose, carbomer, xanthan gum, and calcium alginate are examples of naturally occurring polymers. In general, synthetic polymers are acrylate and methacrylate derivatives such as partially hydrolysed polyacrylamide and polydimethylaminopropyl acrylamide.

**b) Magnetically stimulated pulsatile system**

One of the first methodologies investigated to develop an externally controlled drug delivery system was the use of an oscillating magnetic field to regulate drug delivery from a polymer matrix. Magnetic carriers respond to magnetic fields via incorporated materials such as magnetite, iron, nickel, cobalt, and so on. For biomedical applications, magnetic carriers must be water-based, biocompatible, non-toxic and non-immunogenic. The strategy's mechanistic approach is based on magnetic attraction, which slows the movement of oral drugs in the gastrointestinal system. This is accomplished by incorporating an additional magnetic component into capsules or tablets. An external magnet can then slow the speed of travel through the stomach and intestines at specific positions, changing the timing and/or extent of drug absorption into the stomach or intestines.

**c) Ultrasonically stimulated pulsatile system**

Pulsed drug delivery can be achieved by the on-off application of ultrasound. Repeated ultrasonic exposure releases incorporated drug molecules during polymer degradation. Ultrasound is primarily used to improve drug permeation through biological barriers such as the skin, lungs, intestinal wall, and blood vessels. Several studies



have been published that describe the effect of ultrasound on controlled drug delivery. Ultrasonic waves cause the erosion of the polymeric matrix thereby modulating drug release.

**d) Photo chemically stimulated pulsatile system**

The interaction between light and material in this system can be used to modulate drug delivery. The study material should absorb light at the desired wavelength and use the energy from the absorbed light.

**2. MARKETED TECHNOLOGIES OF PULSATILE DRUG DELIVERY<sup>17,18</sup>**

**Table 1:** Marketed technologies of pulsatile delivery system

Sr. No.	Technology	Rationale
1.	DIFFUCAPS	It consists of a capsule containing one or more drug particles as well as beads, pellets, and granules. It is an orally dissolving tablet or a rapidly dissolving tablet. It improves drug solubility. It lessens gastric mucosal irritation as well as the food effect. Its mechanism is based on a multi-particulate system.
2.	PULSINCAP	This device is made up of a non-disintegrating half capsule body that is sealed at the open end with a hydrogel plug and protected by a water-soluble cap. When this capsule comes in contact with the dissolution fluid, it swells, and after a lag time, the plug pushes itself outside the capsule and rapidly releases the drug
3.	CODAS	A chronotherapeutic oral drug absorption system is a multiunit system for dosing at bedtime. The main advantages are that it is not dependent on food or PH for drug release.
4.	DIFFUTABS	It is made up of fusing mixtures (waxes and a hydrophilic polymer). It is used to regulate drug release.
5.	OROS	As an osmotic pump system, which consists of a central drug reservoir surrounded by a semi-permeable membrane, which is surrounded by osmotically active agents in tablets with strategically laser-drilled orifices?
6.	ORBEXA	Orbexa technology is a multiparticulate system that allows for high drug loading and is suitable for granulation-required products. This technology employs granulation/extrusion and spheronization techniques to produce beads of controlled size and density.
7.	PRODAS	The PRODAS® Technology (Programmable Oral Drug Absorption System) is a multiparticulate technology that combines the benefits of tableting technology within a capsule. PRODAS® technology can be used to pre-program a drug's release rate.

**3. DISEASES REQUIRING PULSATILE DRUG DELIVERY SYSTEMS<sup>19</sup>**

**Table 2:** Diseases requiring pulsatile drug delivery systems

Disease	Chronological behavior	Drugs used
Asthma	Precipitation of attacks during night or at early morning.	B <sub>2</sub> agonist, Antihistamines
Peptic ulcer	Acid secretion high in noon and at night.	H <sub>2</sub> blockers
Cardiovascular disease	BP is at its lowest during sleep cycle and rises in early morning	Calcium channel blockers, Ace inhibitors
Diabetes mellitus	Increase in blood sugar level after meal	Sulfonyl urea, insulin.
Arthritis	Pain in the morning and more pain in the night	NSAIDS, glucocorticoids.
Hypercholesterolemia	Cholesterol synthesis is generally high during night than day	HMG COA reductase inhibitors
	The blood flow to tumours is threefold greater	

Cancer	during each daily activity phase of the circadian cycle than during the daily rest phase.	Vinca alkaloids, taxanes
Duodenal ulcer	Gastric acid secretion is highest at night, while gastric and small bowel motility and gastric emptying are all slower at night.	Proton pump inhibitors

#### 4. FUTURE PERSPECTIVES OF PDDS

The development of pulsatile-release products is very challenging since it requires the correct dose to reach the right site at the appropriate time. Multiparticulate PDDS offer more advantages when compared with the single-unit pulsatile systems since it has predictable, reproducible and short gastric empty time with no risk of dose dumping. However, the novel PDDS pays more attention on site and time-specificity. It is believed that in the near future novel PDDS will be explored in the treatment or management of some other chronic and terminal disease conditions

#### 5. CONCLUSION

Currently, oral delivery of drug is still most preferable route of drug delivery due to the high patient compliance, ease in administration and flexibility in its formulations. Generally, sustained and controlled-release products provide a desired therapeutic effect, but fall short of diseases following biological rhythms. Circadian disorders such as hypertension, osteoarthritis, asthma etc., which require chrono pharmacotherapy. PDDS can effectively tackle this problem as it is modulated according to body's circadian clock giving release of drug after a specified lag time. A variety of systems like Time, Stimuli, externally regulated, Multiparticulate regulated Pulsatile thus designing of proper pulsatile drug delivery will enhances the patient compliance, optimum drug delivery to the target site and minimizes the undesired effects. The approaches in this article represent attempts conducted over the past decade to achieve pulsatile release.

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