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# PULSATILE DRUG DELIVERY SYSTEMS - A REVIEW

**P. S. S. Prasanna Kumar*[1], T. Anjali[1], Srinivas Nandyala[2], P. Vanitha[1], T. Srihitha[1], M. Yamini Saraswathi[1], S. K. Dilshad[1], K. Madhuri[1] and N. Nikitha[1]**

[1]Department of Pharmaceutics, A.K.R.G College of Pharmacy, Nallajerla, A.P-534112.

[2]Department of Pharmacology, A.K.R.G College of Pharmacy, Nallajerla, A.P-534112.

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***Corresponding Author**
**P. S. S. Prasanna Kumar**
Department of Pharmaceutics, A.K.R.G College of Pharmacy, Nallajerla, A.P-534112.

## ABSTRACT

The pulsatile drug delivery system has carried off a lot of importance in drug delivery technology in the last 30 years. In this type of drug delivery systems, the devices deliver the right dose, at a specific location at a particular time in the field of pharmaceutical industry. Under this pulsatile drug delivery system, some conditions show positive result. It includes duodenal ulcer, cardiovascular disease, arthritis, asthma, diabetes, neurological disorder, cancer, hypertension, and hypercholesterolemia. For chronopharmaceutical drug delivery some technologies such as time-controlled, pulsed, triggered and programmed drug delivery devices have been developed and extensively studied in recent years. When compared to conventional dosage form this system has more multiple benefits. These pulsatile drug delivery systems gaining more importance in the field of pharmaceutical technology. Recent trends comprise multi particulate drug delivery systems which are especially suitable for attaining controlled release oral formulations with a property of dose dumping and flexibility to attain different release patterns as well as reproducible and short gastric residence time. There are different methods and different marketed technologies are available for pulsatile drug delivery systems like Pulsincap TM, Diffucap, CODAS, OROS etc.

**KEYWORDS:** Pulsincap TM, Diffucap, CODAS, OROS etc.

## INTRODUCTION[1]

It is a most convenient method of oral controlled drug release. This system follows the pulse pattern method. PDDS provides better patient compliance. When compared to conventional dosage forms it has multiple benefits. Based on the circadian rhythm of the body this system

was designed and the drug is release rapidly, completely as a pulse after a lag time. PDDS(s) is a system in which it was modulated for delivery of drugs within respective time. These systems are designed as body's circadian rhythm to accomplish time-specific and site-specific delivery of drugs. Pulsatile systems have chronopharmacological behavioral of drugs. It follows the lag time.

This system was focused on constant, variable, sustain drug release and targeting the therapeutic agent to a specific site or tissue or organ. To introduce the concept of chronotherapeutics, it is important to define the following concepts.

**Chronobiology:** Chronobiology is the science which is concerned with the biological mechanism of the diseases according to a time structure. "Chrono" means time and "biology" means science of life.

**Chronopharmacology:** Chronopharmacology is a branch of science which is concerned with the variations in the pharmacological actions of various drugs over a period of time in a day.

**Chronopharmacokinetics:** It involves study of temporal changes in drug ADME (Absorption, Distribution, Metabolism and Excretion).

**Chronotherapy:** It is defined as Co-ordination of biological rhythms and medical treatment is known as chronotherapy.

**Chronotherapeutics:** It is the discipline which is concerned with the delivery of drugs according to inherent activities of a disease over a particular period of time.[2-4]

## 2. BIOLOGICAL RHYTHMS[5]

**1. Ultradian Rhythms:** Ultradian Rhythms have shorter duration of oscillations (more than one cycle per 24 hrs). ex:90 minutes sleep cycle.

**2. Infradian Rhythms:** If the rhythms longer than 24 hours then they are known as Infradian Rhythms (less than one cycle per 24hours). ex: Monthly Menstruation.

**3. Circadian rhythms:** oscillations of a day. Self-sustaining, endogenous oscillations are known as circadian rhythms.

**Table 01: Disease, Chronological behaviour, Drug treatment.[5]**

| Disease | Chronological Behavior | Drugs Used |
|---|---|---|
| Asthma | It is usual in sleep. It can also attack at mid night or morning hours | Antihistamines<br>β2 agonist |
| Allergic rhinitis | Inconvenient during morning | Antihistamines |
| Duodenal ulcer | The gastric acid secretion is high during night. | Proton pump inhibitors Ex: Pentaprazole, Rabeprazole |
| Cancer | The passage of blood to tumour is high and it is according to circadian cycle | Vinca alkaloids, Toxins |
| Cardiovascular disease | Hypertension is low at sleep period and it raises in the morning | Calcium channel blockers,acetyl choline enzyme inhibitors, copper nitroglycerine |
| Rheumatoid arthritis | Pain level increases at night | Glucocorticoids , NSAIDS |
| Diabetis mellitus | Blood glucose level increases after meal | Insulin , sulfonyl urea |
| Attention deficiency syndrome | DOPA level increases in afternoon | Methyl fenidate |
| Hypercholestramia | Synthesis of cholesterol is high at night when compared to day time | HMG CoA reductase inhibitors |
| Mental disorders | It causes epilepsy and behavioural changes | MAO-B inhibitor |

## ADVANTAGES[6,7]

- It Improve bioavailability.
- It has less adverse effects.
- It reduces dose size.
- It reduces dosage frequency.
- Improves patient compliance.
- It protects mucosa from irritating drugs.
- It extends day time, night time activity.
- It has a specific drug target.
- It has high hepatic metabolism.
- Less dose dumping.
- No first pass metabolism.
- Site of action.
- Prevent fluctuations.

## DISADVANTAGES[6,7]

- Content of drug is low.
- Incomplete release of drug.

- Immediate withdrawal of drug is not possible.
- Numerous manufacturing steps are involved.

## CLASSIFICATION OF PULSATILE DRUG DELIVERY SYSTEMS[8-10]

Pulsatile drug delivery system can be classified into three classes.

I. Time controlled pulsatile drug delivery

II. Stimuli induced pulsatile drug delivery

III. Externally regulated pulsatile drug delivery

### I. Time Controlled pulsatile drug delivery

A. Single unit pulsatile systems

1. Capsule based systems- E.g. Pulisincap system

2. Capsular system based on Osmosis

a. 'PORT' System

b. System based on expandable orifice

c. Delivery by series of stops.

d. Pulsatile delivery by solubility modulation

3. Pulsatile system with Erodible or soluble barrier coatings.

a. The chronotropic system

b. 'TIME CLOCK' System

c. Compressed tablets

d. Multilayered Tablets

4. Pulsatile system with rupturable coating

B. Multi particulate / Multiple unit systems:

1. Pulsatile system with rupturable coating- E.g. Time –controlled Explosion system (TCES)

2. Osmotic based rupturable coating system- E.g. Permeability controlled system

3. Pulsatile delivery by change in membrane permeability- E.g.Sigmoidal release system.

### II. Stimuli induced

1. Temperature induced type

2. Chemical induced stimuli type

a) Glucose responsive insulin release

b) Inflammation induced

c) Release of drug from intelligent gels responding to antibody concentration

d)Electrical stimuli response pulsatile

e) PH sensitive type of drug delivery

**III. EXTERNAL REGULATED**

1. Electro responsive to drug release
2. Stimulation by ultrasonic method
3. Stimulation by the magnetically induced method

**I. TIME CONTROLLED PULSATILE DELIVERY SYSTEM**

**A. Single unit pulsatile systems**[11,12]

**1. Capsule based systems:** These are present in the form of capsule in which the lag time is managed by a plug, and it is pushed by swelling/erosion. So, that the drug is released as a "Pulse" from the insoluble capsule body. Change in the dimension and the position of the plug the lag time is managed.

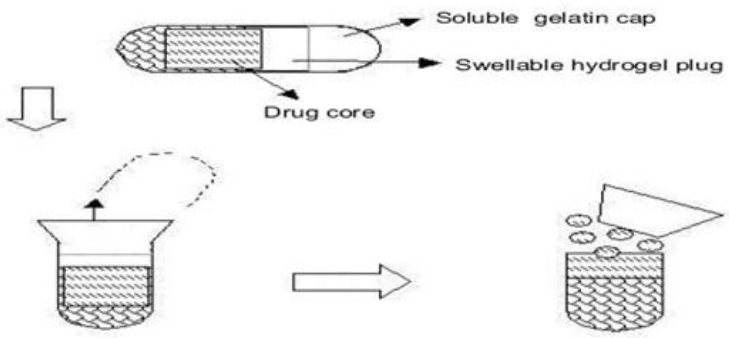


**Fig 1: Design of Pulsincap system.**

The polymers used for designing of the hydrogel plug are as follows,

1) Insoluble but permeable and swellable polymers- (e.g., polymethacrylates)

2) Erodible compressed polymers- (e.g., hydroxy propyl methyl cellulose, Polyethylene oxide)

3) Congealed melted polymers- (e.g., saturated poly glycolated glycerides, glyceryl mono oleate)

4) Enzymatically controlled erodible polymer- (e.g., pectin)

**2. Capsular system based on Osmosis**[13]

**a. 'PORT' System:** It was enlarged by the "Therapeutic system research laboratory". It consists of a capsule with a semipermeable coating membrane. A plug was present inside the capsule having active agent, which is insoluble and osmotic. The semipermeable membrane

allows water, when the capsule dissolves with the dissolution fluid, the pressure was developed and the insoluble plug was expelled after a lag time.

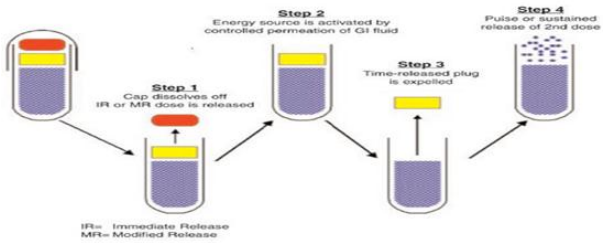


**Fig 2: Drug release mechanism from PORT system.**

**b. System based on expandable orifice:** To deliver the drug in liquid form, an osmotically capsular system was developed by the osmotic drive and the liquid drug is noticed into highly porous particles and the system releases the drug through an orifice which is supported by an expanding osmotic layer after the barrier layer is dissolved. The drug releases through the orifice when the elastic wall is stretched out beyond threshold value, the orifice increases according to need and allows the drug to release at a rate of drug required. E.g. Elastomers, such as styrene-butadiene copolymer.

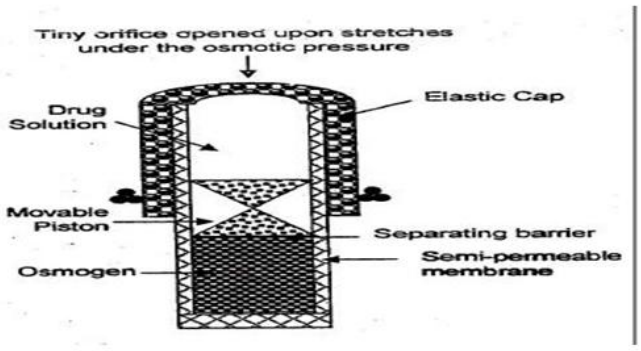


**Fig 3: System based on expandable orifice.**

**c. Delivery by series of stops[14]:** These are implantable capsules. It involves a drug and a water of absorptive osmotic engine that are kept in compartments and are separated by a movable partition. The pulsatile drug delivery and the inner wall of the capsule is gained by a series of stops. These stops obstruct the movement of the partition but are overcomed by succession, as the osmotic pressure rises above a threshold level.

**d. Pulsatile delivery by solubility modulation[14]:** It contains a modulator which is soluble for pulsed delivery of various drugs. It is specially developed for salbutamol sulphate

delivery. It contains the drug (salbutamol sulphate) and a modulating agent (sodium chloride). The amount of sodium chloride was less than the amount which is neccessary to maintain soak in a fluid which enters the osmotic device. The pulsed delivery is mainly based on drug solubility.

**3. Pulsatile system with Erodible or soluble barrier coatings[15,16]:** These are reservoir devices and are coated with a barrier layer. Later a particular lag time and the drug is released rapidly from reservoir core by barrier erodes. The lag time depends on the thickness of the coating layer.

**a. The chronotropic system[15,16]:** It contains a drug with a core and they are coated by hydrophilic swellable hydroxypropylmethyl cellulose (HPMC), and they are accountable for the onset of release by the lagphase. The gastric emptying time is overcomed by the applying of outer gastric-resistant enteric film, and a colon-specific release can be gained relying on the relative reproducibility of small intestinal transit time. The lag time is controlled by Through thickness and viscosity of HPMC. Both tablets and capsules are suitable for this type of system.

**b. 'TIME CLOCK' System:** The lag time was controlled by differentiating the by thickness of the film. After the lag time, immediately it releases the drug by the core. It shows reproducible reports in invitro and in vivo. By using gamma scintigraphy, the low calorie and high calorie meal on the lag time was affected and it was studied.

**c. Compressed Tablets:** The core and coat were directly compressed, and coating solutions was involved. Hydrophilic cellulose derivates are used. The compression is easy. The major drawback is, it needs large amounts of coating materials.

Press-coated pulsatile drug delivery systems use.

1. This is used for hydroscopic protection.
2. It is easy and available in low cost.
3. Core and the coat are directly compressed.
4. Hydrophobic, hydrophilic materials are used.
5. It releases drug after "lag-time".
6. It achieves sustained release.

**d. Multilayered Tablets[16]:** The two pulses were acquired from a three-layered tablet which contains two drug containing layers and are separated by a drug-free gellable polymeric barrier layer.

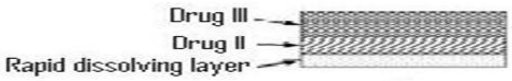


**Fig.4: Multilayered Tablet.**

**4. Pulsatile system with rupturable coating:** It is based on disintegration of the coating. It involves release of drug. The pressure is main for rupturing of the coat and it is attained by the effervescent excipients, swelling agents, or osmotic pressure. The release of drug turn on the mechanical property of the coating layer.

**B. MULTIPARTICULATE SYSTEM[16]**

**a) Pulsatile system based on rupturable coating:** The multi-unit system, in which the drug is coated on non-pareil sugar seeds and it is followed by a swellable layer and an insoluble top layer. The swelling agents and superdisintegrants like sodium carboxymethyl cellulose, sodium starch glycollate, L hydroxypropyl cellulose. Polymers like polyvinyl acetate, polyacrylic acid, polyethylene glycol, etc. are used.

**b) Osmotic based rupturable coating system:** It is based on osmotic and swelling effects. A drug is present in the core with a low bulk density solid and/ liquid lipid material (eg, mineral oil) and a disintegrant was prepared. cellulose acetate was coated on the core. By liquifying in aqueous medium the water enters to the core and it displaces in lipid material. After the depletion of lipid material, internal pressure increases until a critical stress is reached, and as a results rupture of coating takes place.

**c) Pulsatile delivery by change in membrane permeability:** Different counter-ions are present in the sample the permeability and water uptake of acrylic polymers with quaternary ammonium groups influence 48many delivery systems based on this ion exchange and they are developed. Eudragit RS 30D is a choice. This property is essentially to achieve a precisely defined lag time.

**B. Stimuli-induced pulsatile release[17-19]**

**1. Temperature-induced pulsatile release-**Thermoresponsive hydrogels are enquired as a drug delivery carrier for stimuli responsiveness.

**2. Chemical stimuli-induced pulsatile release**

**a) Glucose-responsive insulin release devices**-There are different devices which are developed to respond glucose concentration changes. Oxidation was involved. By using Ishihara et al. two possible types of gel membrane systems to regulate insulin permeability.

**b) Inflammation-induced pulsatile release**-In stresses like physical and chemical like injuries and brokens etc. At injury site inflammation occurs. The inflammation responsive phagocytic sites, macrophages and the polymorphonuclear cells plays important role in healing of injury. During inflammation, hydroxyl radicals are produced from the inflammation-responsive cells.

**c) Drug release from intelligent gels responding to antibody concentration-** It has many types of bioactive compounds that exist in the body. Now a days novel gels were developed which responded to change in concentration of bioactive compounds to alter their swelling/deswelling characteristics. Miyata and co-workers are concentrated for introduction of stimuli-responsive cross-linking structures into hydrogels.

**d) Electric stimuli-responsive pulsatile release-** The evaluations, such as microelectronics and micromachining, and the need for chronotherapy, have currently used for the development of electronically assisted drug delivery technologies. It includes iontophoresis, infusion pumps, and sonophoresis.

**e) pH sensitive type:** It is of two sigments - Quick discharge & Beat discharge It discharges the drug based on the response to change in the pH.

**III. EXTERNAL REGULATED[20,21]:** It is of three types

1. Electro responsive to drug release
2. Stimulation by ultrasonic method
3. Stimulation by the magnetically induced method.

The release of drug can be externally regulated by using ultrasound, magnetic, and radiation stimuli. In magnetic system the magnetic beads are placed in the implant, so by applying of the magnetic field it releases the drug. In ultrasonic the drug is released with the help of waves. In irradiation system the drug release by the radiation.

**RECENT ADVANCES IN THE PULSATILE DRUG DELIVERY[21]**

PDDS gains importance in various diseases.

- ❖ It has no risk of dose dumping.
- ❖ It improves efficacy.

- It is safe.
- It targets the drug at specific site.
- It includes different techniques like OROS, CODAS, CEFORM etc.

**PRESENT CONDITIONS AND FUTURE GOALS**: In recent days PDDS attains higher position. The primary lead is, the drug releases when it is essential or needed only. The growth of development will be high. It has higher bioavailability. Patient compliance is good. Its main goal is to achieve higher popularity with a high range of benefits.

**Table 02: Technologies Are Involved In Pdds.**

| S.No | Technology | Description |
|---|---|---|
| 1. | DIFFUCAPS[22] | It consists of a capsule with a single or more drug particles and it includes beads, pellets and granules. It is a orally disintegrating tablet or rapidly disintegrating tablet. It enhances the drug solubility. It reduces gastric mucosal irritation also food effect. Its mechanism involves multi particulate system. |
| 2. | Orbexa® technology[23] | This technology involve granulation, spheronization and extrusion technique. The beads are used to controlled size and density which are perfect for formulation and controls the release of drug with the use of above techniques. It results in beads and they are coated with functional polymer membrane. |
| 3. | IPDAS®[24] | The intestinal protective drug absorption system is an oral system. NSAID's like drugs are also used in this technique. This approach is applicable to gastro intestinal irritancy. It also involves multiparticulate system. |
| 4. | Geoclock®technology[25] | It is a press coated tablet and oral drug delivery technology which allows the time release of active ingredient from the tablet. It is independent to PH and food. It can also use for multi pulse delivery. It is easily manufactured. |
| 5. | Controlled-onset-extended – release (COER-24) technology[25] | It is used to control blood pressure and angina pectoris is Covera -HS tablet and the active ingredient is verapamil hydrochloride. It is one of the unique tablets which is made up of COER-24TM technology which is used to minimize cycle period fluctuations in heart rate and hyper tension. |
| 6. | Diffutab[26] | It contains fusing mixtures [waxes and a hydrophilic polymer]. It is used to control drug release. |
| 7. | CODAS[27] | Chronotherapeutic oral drug absorption system is a multiunit system for bed time dose. The main advantages include, it is independent of food and also PH for release of the drug. |
| 8. | Covera-HS[27] | It is one of the approved preparations which is used to control high blood pressure and angina disease is Covera-HS. This Covera-HS is made up of COER-24TM technology which minimize regular cycle period fluctuations in heart rate and hypertension. |
| 9. | Minitabs[28] | It is a small size(mm) tube shaped (2×2) which is covered with film layer to control the drug discharge rate. Minitabs are in gel nature |
| 10. | OROS[28] | This system delivers the drug reproducibly based on the time or site |

| | | |
|---|---|---|
| | | specific model in the GIT. The mechanism involve osmosis. Tablet is present in the form of reservoir and it is enclosed by the semipermeable membrane with a laser drilled orifice used to deliver the drug. The bilayer and tri layer tablet contain osmotic agent and drug, when it dissolves with Gastro intestinal fluid, the osmotic agent generate some pressure and it pushes the drug and it releases the drug through an orifice. |

## CONCLUSION

We conclude that the pulsatile drug delivery system play a very key role in the treatment of many chronological diseases like Asthma, Hypertension, Rheumatoid Arthritis etc. It delivers the drug at right time, right dose, right place. It is a good approach. It increases patient compliance. It shows maximum bioavailability. It is safe. It is more beneficial than the conventional dosage form. This system is based according to the circadian rhythms. There is no loss of drug. It has good efficacy. It has high flexibility. So, it is more important in the field of pharmaceutical technology.

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