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A REVIEW ON PULSATILE DELIVERY SYSTEM

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Abstract:

Pulsatile Drug Delivery systems (PDDS) are basically time-controlled drug delivery systems in which the system controls the lag time independent of environmental factors like pH, enzymes, gastro-intestinal motility, etc. Traditionally, drugs are released in an immediate or extended fashion. However, in recent years, pulsatile drug release systems are gaining growing interest. These systems are designed according to the circadian rhythm of the body. According to Latin literature Circa means Day and Dian means night. A pulsatile drug release, where the drug is released rapidly after a well defined lag-time, could be advantageous for many drugs or therapies. Diseases wherein PDDS are promising include asthma, peptic ulcer, cardiovascular diseases, arthritis, attention deficit syndrome in children, and hypercholesterolemia. This drug delivery system is programmed drug delivery system in harmonization with body clock. The pulse has to be designed in such a way that a complete and rapid dug release is achieved after the lag time. Therefore Pulsatile drug delivery is one such systems that, by delivering drug at the right time, right place and in right amounts, holds good promises of benefit to the patients suffering from chronic problems like arthritis, asthma, hypertension.

Keywords: Time controlling, Lag time, Pulsatile drug release, circadian rhythm

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INTRODUCTION

Drug delivery refers to approaches, formulations, technologies, and **systems** for transporting a pharmaceutical compound in the body as needed to safely achieve its desired therapeutic effect [1].

Drug delivery is of two types:

1. **Conventional**
    - Oral/Enteral
    - Buccal
    - Rectal
    - Parenteral
2. **Modified**
    - Delayed Release
    - Sustained Drug Delivery
    - Extended Release
    - Site specific targeting
    - Pulsatile [1]

1.1. PULSATILE DRUG DELIVERY SYSTEM

Pulsatile drug delivery is defined as the rapid and transient release of certain amount of active molecules within a short time period immediately after a predetermined off-released period, i.e., lag time, or these systems have a peculiar mechanism of delivering the drug rapidly and completely after a lag time, i.e., a period of no drug release. Such a release pattern is known as pulsatile release [2].

Pulsatile drug delivery systems (PDDS) have attracted attraction because of their multiple benefits over conventional dosage forms. They deliver the drug at the **right time, at the right site of action and in the right amount**, which provides more benefit than conventional dosages and increased patient compliance. These systems

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are designed according to the circadian rhythm of the body, and the drug is released rapidly and completely as a pulse after a lag time. These products follow the sigmoid release profile characterized by a time period. These systems are beneficial for drugs with chronopharmacological behavior, where nocturnal dosing is required, and for drugs that show the first-pass effect [2].

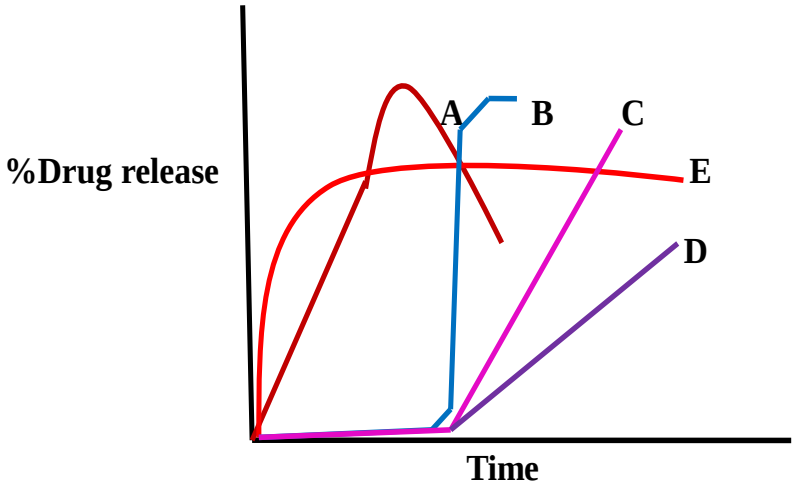

Fig 1.1 Drug release profiles from pulsatile drug delivery system.

Where, **A:** Conventional release profile, **B**: Burst release of drug as a 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.

Chrono-therapeutics refers to a therapy in which *In vivo* availability of drug is timed to match rhythms of disease or disorders in order to optimize therapeutic responses and minimize side effects, which makes it a profound and purposeful delivery of medications in unequal amounts over time (during the 24 h). Chronotherapeutics takes into account rhythm determinants of the human circadian time structure to determine the drug-delivery pattern, dose, and administration time to optimize desired and/or minimize adverse effects. **Circadian rhythms** are self-sustaining, endogenous oscillations that occur with a periodicity of about 24 h and regulate many body functions like-metabolism, sleep pattern, hormone production etc. Several

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physiological processes in humans vary in a rhythmic manner, in synchrony with the internal biological clock [3].

Fig 1.2: Human Circadian Time Structure; shows approximate peak time of the circadian (24-hour) rhythms in persons adhering to a normal routine of day-night cycle (6-7 a. m. to 10-11 p. m.)

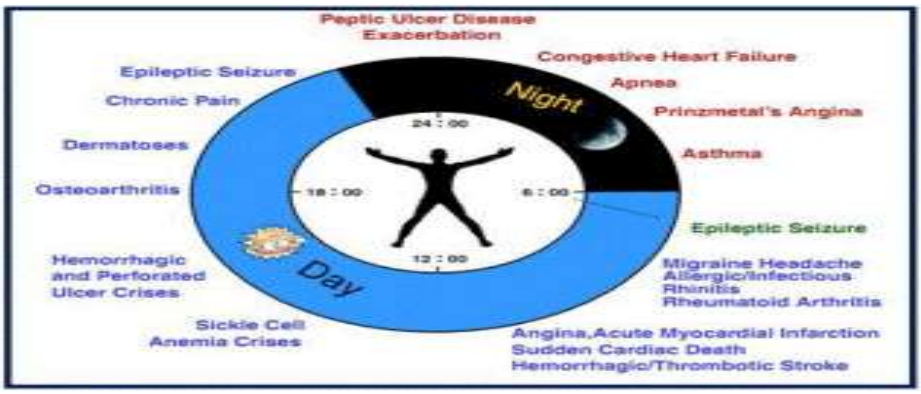

Fig 1.3: A 24 h clock diagram of the peak time of selected human circadian rhythms with reference to day-night cycle.

1.2. Advantages

- Predictable, reproducible, and short gastric residence time.
- Less inter-and intra-subject variability.
- Improves bioavailability.
- Reduced adverse effects and improved tolerability.
- Limited risk of local irritation.
- No risk of dose dumping.

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- Flexibility in design.
- Ease of combining pellets with different compositions or release patterns
- Improves stability.
- Improves patient comfort and compliance.
- Achieves a unique release pattern [3].

1.3. Disadvantages

- Low drug loading.
- Proportionally higher need for excipients.
- Lack of manufacturing reproducibility and efficacy.
- Large number of process variables.
- Multiple formulation steps.
- Higher cost of production.
- Need of advanced technology.
- Trained/skilled personnel were needed for manufacturing [3].

Table 1.1: Diseases that require pulsatile drug delivery [2].

Diseases	Chronological behavior	Drugs used
Peptic ulcer	Acid secretion is high in the afternoon and at night.	H_2 blockers [4]
Cancer	The blood flow to tumors is 3-fold greater during each daily activity phase of the circadian cycle than during the daily rest phase.	Vinca alkaloids, Taxanes [5]
Duodenal ulcer	Gastric acid secretion is highest at night while gastric and small bowel motility and gastric emptying are all slower at	Proton pump inhibitors [6]

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	night.	
Neurological disorders	The central pathophysiology of epilepsy and the behavioral classification of convulsive events.	MAO-B inhibitor [7]
Hypercholesterolemia	Cholesterol synthesis is generally higher during night than day time.	HMG CoA reductase Inhibitors [8]
Diabetes mellitus	Increase in the blood sugar level after meal.	Sulfonylurea, Insulin [9]
Arthritis	Level of pain increases at night.	NSAIDs [10], Glucocorticoids [11]
Cardiovascular diseases	BP is at its lowest during the sleep cycle and rises steeply during the early morning.	Nitroglycerin, calcium channel blocker, ACE inhibitors [12]
Asthma	Precipitation of attacks during night or at early morning.	B_2 agonist, Antihistamines [13]
Attention deficit syndrome	Increase in DOPA level in afternoon.	Methylphenidate [2]

1.4. Cardiovascular disease (**CVD**) is a class of diseases that involve the heart or blood vessels. Cardiovascular disease includes coronary artery diseases (CAD) such as angina and myocardial infarction (commonly known as a heart attack). Other CVDs include stroke, heart failure, hypertensive heart disease, rheumatic heart disease, etc. These diseases are mainly caused by high blood pressure, smoking, diabetes, lack of exercise, obesity, high blood cholesterol, poor

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diet, and excessive alcohol consumption, among others. CVD is leading cause (45.1%) of deaths.

Angina pectoris is the medical term for chest pain or discomfort due to coronary heart disease. It occurs when the heart muscle doesn't get as much blood as it needs. This usually happens because one or more of the heart's arteries is narrowed or blocked, also called **ischemia**. Angina usually causes uncomfortable pressure, fullness, squeezing or pain in the center of the chest. It may also feel the discomfort in neck, jaw, shoulder, back or arm.

1.5 METHODS OF DEVELOPMENT OF PULSATILE DRUG DELIVERY SYSTEM

1. Time Controlled system

a. Capsule Shaped Pulsatile Drug Delivery System/ Pulsincap System

b. Pulsatile System Based on Osmosis/ port system.

c. Pulsatile Delivery by Solubilisation or Erosion of layer

d. Pulsatile Delivery by Rupture of Membrane

2. Internally stimuli induced system

a. Temperature–induced pulsatile release

b. Chemical stimuli induced pulsatile release

3. Externally Regulated System

a. Magnetic induces release

b. Ultrasound induces release

c. Electric field induces release

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d. Light induces release [14]

1. Time controlled system

a. Capsule Shaped Pulsatile Drug Delivery System/ Pulsincap System

This system is comprised of a water insoluble capsule enclosing the drug reservoir. A swellable hydrogel plug was used to seal the drug contents into the capsule body. When the capsule comes in contact with dissolution fluid, the plug gets swells, and after a lag time, the plug pushes itself outside the capsule and rapidly releases the drug. Here the plug decides lag time which is inserted in to the body. A hydrostatic pressure is generated inside the capsule [2].

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., hydroxypropylmethyl cellulose, polyvinyl alcohol, Polyethylene oxide)
- Congealed melted polymers (e.g., saturated polyglycolated glycerides, glyceryl monooleate)
- Enzymatically controlled erodible polymer (e.g., pectin)

The lag time can be controlled by manipulating the dimension and the position of the plug [15].

Examples of polymers used as plug:

1. In PDDS of meloxicam, pulsincap technique was used. HPMC was used as a plug and the drug release was by erosion of plug [32].
2. In PDDS of Doefitilide, pulsincap technique was used. Cellulose Acetate Phthalate (CAP) was used as a plug and the drug release was by diffusion mechanism [46].

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3. In PDDS of Indomethacin Microsponges, pulsincap technique was used. Gelatin half enteric coated with 10% CAP, 10% HPMCP, 10% Eudragit L-100 was used as a plug and the drug release was by diffusion mechanism [16].
4. In PDDS of Diltiazem Microspheres, pulsincap technique was used. Sodium alginate, guar gum and xanthum gum were used as a plug and the drug release was by burst of the plug [34].
5. In PDDS of Tramadol Hcl, pulsincap technique was used. SSG (5%) and HPMC K_4 M (40%) coated with Eudragit S-100 was used as a plug and the drug release was by diffusion mechanism [40].
6. In PDDS of Nateglinide Microcrystals, pulsincap technique was used. HPMC (100%) were used as a plug and the drug release was by erosion of plug [39].
7. In PDDS of Lovastatin Microspheres, pulsincap technique was used. Karaya gum (50%) was used as a plug and the drug release was by diffusion mechanism [33].
8. In PDDS of Theophylline Pellets, pulsincap technique was used. Xanthum gum (300mg) and Karaya gum (300mg) were used as a plug and the drug release was by erosion of the plug [42].
9. In PDDS of Propranolol Hcl Floating Capsules, pulsincap technique was used. Polyethylene Oxide WSR 303 was used and the drug release was by erosion [35].
10. In PDDS of Metoprolol Succinate, pulsincap technique was used. Gum Kondagogu grade III (70%) was used as a plug and the drug release was by diffusion mechanism [57].

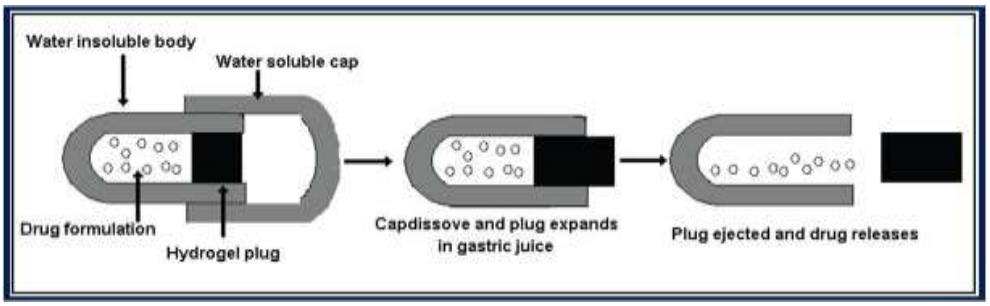

Fig 1.4: Design of Pulsincap system

b. Pulsatile System Based on Osmosis/ port system

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In this System, a capsule coated with semi permeable membrane is employed. There is an insoluble plug consisting of osmotically active agent and the drug formulation inside the capsule. This system divides the capsule interior into two compartments- one for the beneficial agent and the other for the osmotically active agent. Water diffuses across the semi permeable membrane when this cap comes into contact with GI fluids and it results in increased pressure inside that ejects the plug after a predetermined lag time. Thickness of the coating decides the lag time. E.g. Ritalin (methylphenidate) used in the treatment of attention deficit hyper active disorder (ADHD) in children [14].

c. Pulsatile Delivery by Solubilisation or Erosion of layer

In such systems the drug release is controlled by the dissolution or erosion of the outer coat which is applied on the core containing drug. The release of the active ingredient can be controlled by thickness and viscosity of the outer coat. The Time Clock system consists of a solid dosage form coated with lipid barriers containing carnauba wax and bees wax along with surfactants. Chronotropic system consists of a core containing drug reservoir coated by a hydrophilic polymer HPMC. System is composed of a drug-containing core and swells able polymeric coating of HPMC which slow the interaction with aqueous fluids [14].

d. Pulsatile Delivery by Rupture of Membrane

These systems consist of an outer release controlling water insoluble but permeable coating subject to mechanically induced rupture phenomenon. The rupturing effect is achieved by coating the individual units with effervescent or swelling agents. Water permeation and mechanical resistance of the outer membrane are major factors affecting the lag time. The lag time can be varied by varying coating thickness or adding high amounts of lipophilic plasticizer in the outermost layer [14].

2. Internally stimuli induced system

a. Temperature–induced pulsatile release

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Temperature is the most widely applied triggering signal for a variety of triggered or pulsatile drug delivery systems. The body temperature often deviates from the physiological temperature (37^0 C) in the presence of pathogens or pyrogens. This deviation from normal range acts as a stimulus that triggers the release of therapeutic agents from several temperature-responsive drug delivery systems [14].

Thermo responsive hydro gel systems

In thermo-responsive hydro gel systems, hydro gels undergo reversible volume changes in response to changes in temperature. These gels shrink at a transition temperature that is referred to the lower critical solution temperature (LCST) of the linear polymer. As it undergo volume change, this property can be utilized to obtain a squeezing hydro gel device by positioning hydro gel within a rigid capsule. The reversible volume change of temperature-sensitive hydro gels accomplish on off release. e.g. PIPAAm cross-linked gels [14].

b. Chemical stimuli induced pulsatile release

1. Glucose-responsive insulin release devices

These devices have been developed to respond with changes in glucose concentration in the blood. The hydro gels showed a glucose-responsive, sol–gel phase transition dependent upon the external glucose concentration. These devices also have pH sensitive hydro gel containing glucose oxidase immobilized in the hydro gel. When glucose concentration in the blood increases glucose oxidase converts glucose into gluconic acid which changes the pH of the system. This swelling of the polymer induced by this pH change 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. Examples of the pH sensitive polymers include N, N- dimethylaminoethyl methacrylate, chitosan, polyol etc [14].

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2. pH sensitive drug delivery system

This system contains two components- one is of immediate release type and second is pulsed release which releases the drug in response to change in pH. As different pH environment exist at different parts of the gastrointestinal tract so this advantage is utilised by pH dependent system. By selecting the appropriate pH dependent polymers, desired drug release can be achieved at specific location. Examples of pH dependent polymers are cellulose acetate phthalate, polyacrylates, and sodium carboxymethylcellulose. These polymers are used as enteric coating materials so as to provide release of drug in the small intestine [14].

3. Inflammation-induced pulsatile release

Any physical or chemical stress such as injury, fracture etc cause inflammation at the injured sites. The inflamed responsive cells produce hydroxyl radicals. Yui and co-workers focused on the inflammatory induced hydroxyl radicals and designed drug delivery systems. 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 [14].

4. Drug release from intelligent gels responding to antibody concentration

In the human body numerous kinds of bioactive compounds are exist. The change in concentration of these bioactive compounds can be detected by recently developed novel gels to alter their swelling/deswelling characteristics. Antigenantibody complex formation is of great importance as the cross-linking units in the gel due to such specific interaction. Reversible gel swelling/deswelling and drug permeation changes occurs by the utilization of the difference in association constants between polymerized antibodies and naturally derived antibodies towards specific antigens [14].

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3. Externally Regulated System

a. Magnetic induces release

Magnetically regulated system contains magnetic beads in the implant. Magnetic steel beads were engrafted in an ethylene and vinyl acetate (EVAc) copolymer matrix that was loaded with bovine serum albumin as a model drug. The beads oscillate within the matrix on exposure to the magnetic field, alternatively creating compressive and tensile forces. This in turn acts as a pump to push more amount of the active solute out of the matrix [14].

b. Ultrasound induces release

Ultrasound is used as an enhancer for the improvement of drug permeation through a biological barrier, such as skin, lungs, intestinal controlled drug delivery e.g. Miyazaki et al. used ultrasound to achieve up to a 27-fold increase in the release of 5-fluorouracil from an ethylene and vinyl acetate matrix. As degradation of biodegradable matrix was enhanced by ultrasonic exposure, the rate of drug release also increased. Increasing the strength of the ultrasound resulted in a proportional increase in the amount of 5- fluorouracil released [14].

c. Electric field induces release

As these devices use polyelectrolyte thus are pH responsive as well as electro responsive. Polyelectrolyte contains polymers with comparatively high concentration of ionisable groups along the backbone chain. For chronotherapy, several technologies are required such as microelectronics and micromachining and potential etc. These technologies also include iontophoresis and infusion pumps. Under the influence of electric field, electro-responsive hydro gels generally bend, depending on the shape of the gel which lies parallel to the electrodes whereas de-swelling occurs when the hydro gel lies perpendicular to the electrodes [14].

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d. Light induces release

In this system drug delivery is regulated by the interaction between light and material and can be achieved by combining a material that absorbs light at a desired wavelength and a material that uses energy from the absorbed light to regulate drug delivery [14].

Table 1.2: Marketed technologies of pulsatile drug delivery [3]

Technology	Mechanism	API	Disease	Proprietary name
CODAS®	Multiparticular pH dependent	Verapamil Hcl	Hypertension	Verelan® P M
CONTIN®	Extended release tablet	Theophylline	Asthma	Uniphyl®
CEFORM®	Extended release tablet	Diltiazem HCl	Hypertension	Cardiazem®
Diffucaps®	Multiparticulate	Verapamil HCl, Propranolol HCl	Hypertension	Innopran®
Geoclock™	Chronotherapy focused precoated	Prednisone	Rheumatoid arthritis	Lodotra
Geomatrix™	Multilayered tablet	Verapamil	Calcium channel blocker	
OROS®	Osmotic	Methylphenidate	Anti-psychotic	Concerta®
Port®	Osmotic	Food Nutrition	Supplement of diet	
Pulsincap®	Rupturable system	Metronidazole	Antihelminthic	
Pulsincap®	Rupturable	Dofetilide	Hypertension	

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	system			
PULSYS ™	Multiple pellets with different release profiles	Amoxicillin	Antibiotic	Moxtag™
Three dimensional printing®	Externally regulated system	Diclofenac sodium.	Inflammation	Theirform®
TIMERx®	Erodible/soluble barrier coating ER tablets	Oxymorphone	Pain management	OPANA®
OROS®	Tablet	Paliperidone	Schizophrenia	Invega™
PROCARDIA XL®	Sustained release	Nifedipine	Hypertension	Procardia XL
Physico-chemical modification of API	tablet	Famotidine	Ulcer	Pepcid®
Physico-chemical modification of API	Tablet	Simvastatin	Hypercholesterolemia	Zocor®

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Conclusion:-

Oral drug delivery is the largest, oldest, and most preferred route of drug delivery. Universally sustained and controlled-release products provide a desired therapeutic effect, but fall for diseases following biological rhythms. Circadian disorders such as asthma, osteoarthritis, RA, cholesterol synthesis, etc., require chronopharmacotherapy. Pulsatile drug delivery can effectively crack this problem as it is modulated according to body's circadian clock giving release of drug after a specified lag time. During the last two decades, technologies to ensure time controlled pulsatile release of bioactive compounds have been developed. A significant progress has been made toward achieving pulsatile drug delivery system that can effectively treat diseases with nonconstant dosing therapies. Various pulsatile technologies are researched and brought in the market, which surely assure a bright and promising future.

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