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Smart pulses, smarter medicine: A review of pulsatile delivery strategies

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Abstract
Pulsatile drug delivery systems (PDDS) represent an innovative approach in controlled drug release, designed to deliver medications at predetermined intervals or in a time-dependent manner. Unlike conventional drug delivery systems, which provide a continuous release, PDDS offer the advantage of releasing drugs in a "pulsatile" manner, closely mimicking the body's natural biological rhythms or therapeutic requirements. This system is particularly useful for drugs that require targeted delivery at specific times or for conditions where a drug's efficacy depends on the timing of its release, such as in circadian rhythm-based diseases, post-surgery care, or for the treatment of diseases like asthma, arthritis, and hypertension. The primary mechanisms employed in PDDS include osmotic pressure, swelling, and enzyme-sensitive materials. These systems are engineered to release phase followed by a 'g in an initial lag please phase. This paper explores the different types of pulsatile of releasing drugs in a "pulsatile" manner, closely mimicking the body's natural biological rhythms or therapeutic requirements. This system is particularly useful for drugs that require targeted delivery at specific times or for conditions where a drug's efficacy depends on the timing of its release, such as in circadian rhythm-based diseases, post-surgery care, or for the treatment of diseases like asthma, arthritis, and hypertension. The primary mechanisms employed in PDDS include osmotic pressure, swelling, and enzyme-sensitive materials. These systems are engineered to release a drug in an initial lag phase followed by a rapid release phase. This paper explores the different types of pulsatile delivery systems, such as time-controlled, stimuli-sensitive, and lag-phase delivery systems, along with their potential applications, benefits, challenges, and recent advancements in the field. By enhancing the temporal control of drug release, PDDS offer a promising solution to improve therapeutic outcomes, minimize side effects, and improve patient compliance.

Keywords: Pulsatile drug delivery, Time-controlled release, Chronotherapeutics, Controlled drug delivery, Delayed drug release, Site-specific delivery, Targeted drug delivery, Modified release systems

Introduction
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. [1]
The rapid and transient release of certain amount of 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.

Chronobiology
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 behavioural changes that follow a period of about 24 hrs. are circadian rhythms. [2]

1. Circadian Rhythms
2. Ultradian Rhythms
3. Infradian Rhythms

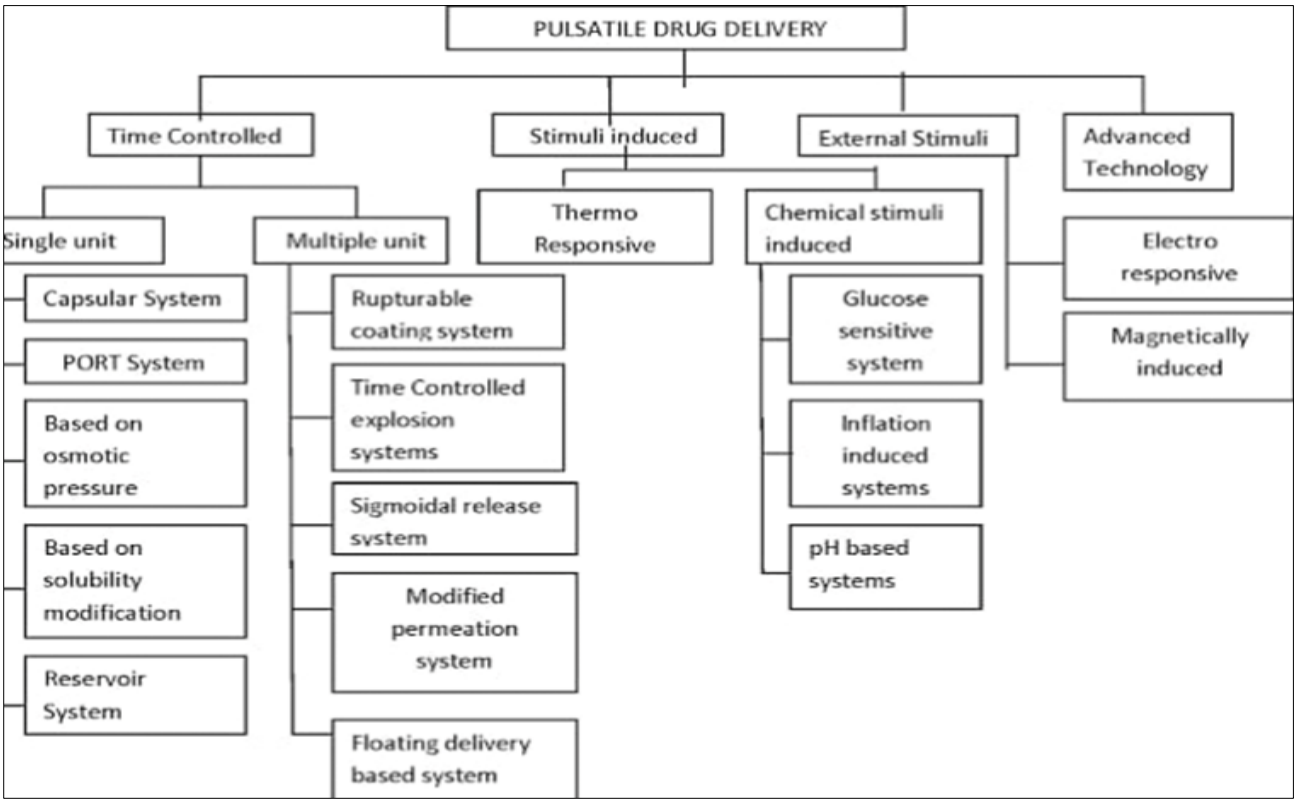
Advantages of PDDS
- Extended day and night presence of optimum drug concentration in body.
- Reduced side effects.

- Reduced dose frequency.
- Reduction of the drug used in dosage form.
- Improved patient compliance due to less dosing frequency.
- Drug targeting to colon and distinct place in git.
- Administration of gastric unstable drug is easier.
- Beneficial for the diseases which follows circadian rhythms.

Disadvantages of PDDS

- Low drug loading formulation.
- Multiple steps involved leads to variation in quality of dosage form.
- Incomplete release of the drug.
- Immediate withdrawal of the drug is not possible.
- Dose calculation for child and elder patient is difficult.
- In vivo variability may be seen in special cases. [3]

Classification



Methodologies used in PDDS

1. Time Controlled PDDS.

a. Single unit Systems.
b. Multi particulate Systems.

a. Single Unit System

1. Capsular systems
2. Tablet systems
3. Port systems
4. Osmotic pressure systems
5. Based on solubility modifications.
6. Reservoir system

b. Multi Particulate Systems.

i) Rupturable coating systems
ii) Time controlled explosion system
iii) Sigmoidal release systems
iv) Modified permeation systems
v) Floating delivery based systems

Single Unit System

1. Capsular System

- The fundamental method of capsular system consists of an insoluble capsule body housing a drug and a plug in it.
- The body is closed at the open end with a swell able hydrogel plug.
- The lag time is controlled by manipulating the dimension and position of plug
- Ex: swellable polymers (polymethacrylates), erodible compressed polymers (polyvinyl alcohols, hydroxyl propyl methyl cellulose), congealed melted polymers (glycerides) and enzymatically controlled polymers (pectin). [4]

2. Tablet System

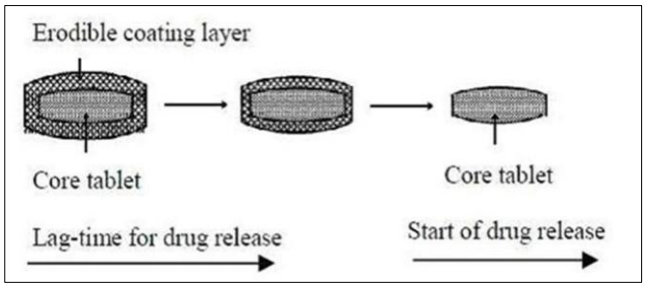
- In this type of drug delivery system, the lag time is controlled by the coating of erodible polymer on the core tablet containing the drug.
- The thickness of polymer used and type of polymer used decides the lag time of the tablet.
- Ex: Cellulose acetate phthalate (CAP), methyl cellulose phthalate etc. [4]

3. Port System

- Port system Consists of gelatin capsule coated with a semi permeable membrane.
- When it comes in contact with the GIT fluid the fluid penetrates the semi permeable membrane because of

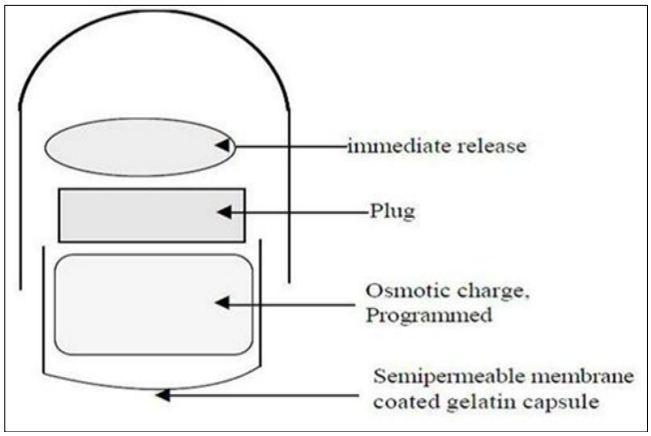
osmotic pressure exerted by osmotically active agents. [5]

- This forms a port to enter the liquid and drug is dissolved by this penetrated liquid.
- Ex: Cellulose acetate



4. Osmotic Pressure Based System

- This system is made up of immediate release and pulsatile released part.
- The immediate released part may contain powdered drug, tablet, capsule
- This immediate release part is subjected to achieve the immediate therapeutic concentration of drug in plasma.
- Osmotic delivery is given by single osmotic pump or by series of stops separated by movable partitions. [6]
- Ex: liposomes, niosomes etc.



5. Based on Solubility Modification

- The solubility of the capsule shell is modified by formalin. The capsule shells treated with formalin have reported time dependent insolubility of the 24hrs. [8]
- The capsule shells placed on wire mesh which is placed on some height on desiccators.
- In practical measure only 10 capsules are shrinked in group of 100 capsules.
- The drug incorporated may be tablet, pellets, niosomes, liposomes etc. [9]

6. Reservoir Systems

- Reservoir system consists of the drug reservoir.
- Drug is released from this depot which may or may not be the control released or pulsatile released. [10]
- This type of reservoir system is constructed of three parts:

a) Core tab containing 'api'.
b) Erodible outer layer.
c) External outer layer.

Multi Particulate Systems

1. Rupturable Coating System

- This system is based on the expansion of core which then rupture the coating to allow rapid release of the drug. [11]
- This system is mostly used in floating type of pulsatile drug delivery systems.
- Drug with effervescent material like sodium bicarbonate is used and gas trapped in the membrane which is made up of eudragit RL because Eudragit RL degrades at pH 5-6, so it will not degrade in stomach. [12]

2. Time Controlled Explosion System

- These system consists of osmotically active layer, core pellet or core tablet and third one outermost layer is enteric coated layer. [13]
- The core tablet is made up of 'api' and other excipients.
- The swelling layer consists of semi permeable membrane because of expulsion of membrane to degrade enteric coating and gives desired lag time. [13]

3. Sigmoidal Release System

- Sigmoidal release system is made up of core drug i.e. pellets or tablet compressed along with succinic acid. [14]
- The drug and succinic acid pellets are coated with the ammonium methacrylate polymers type-b.
- When water comes in contact with the system drug succinic acid gets dissolved. [14]
- Beside succinic acid other acids used are tartaric acid, acetic acid, glutaric acid, malic acid and citric acid

4. Modified Permeation System

- The pulsatile drug delivery system is made by change in membrane permeability.
- The change in membrane permeability acts similarly as the typical ion exchange resins.
- Eudragit RS contains positively charged quartnery ammonium group in polymer chain. [15].
- This ammonium group has interaction with the water. [15].

5. Floating Type Drug Delivery

- Floating type drug delivery along with pulsatile drug delivery system serving the both site specific and time specific drug delivery. [16]
- It increased GIT resident time of drug and give site specific targeting while PDDS gives lag time.
- This consists of buoyancy layer, coating layer which is insoluble and core material. [16]

Internal Stimuli Induced PDDS

Thermo Responsive System

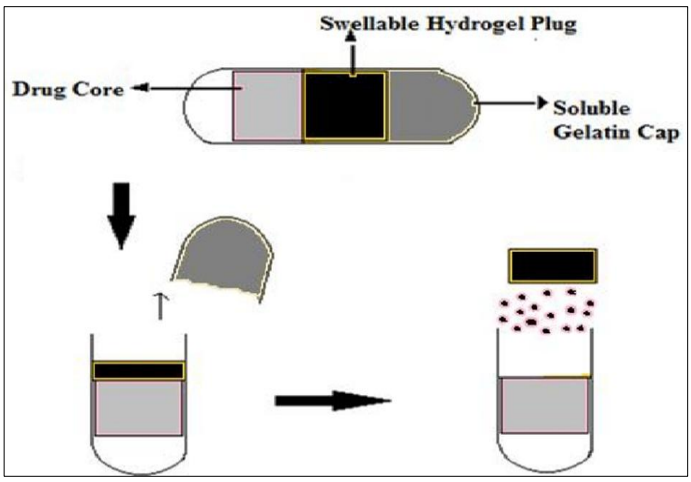
a) Thermo responsive hydrogel system
b) Thermo responsive polymeric micelli system

1. Thermo Responsive Hydrogel System

- This type employs hydrogels in which there is volume shift i.e. swell or deswell.
- These hydrogel shrink at temperature, known as LCST (lower critical solution temperature) of linear polymer. [17]

2. Thermo Responsive Polymeric Micelli System

- The thermo responsive micelle system is achieved by the tightly bound drug in micelles and release of drug in controlled manner which depends upon the temperature stimulus.
- The polymers used are poly(N-isopropyl acryl amide) i.e. [PNIPAM]-grafted polyphosphazene[PNIPAM-g-PPP]. [18]



Chemical Stimuli Induced

1. Glucose Sensitive System

- These types of systems are specially used in the case of Diabetes mellitus, when there is rise in the glucose concentration in the patient's blood and need insulin at that time. [18]
- This is a system which respond to blood glucose i.e. pH sensitive hydrogel containing glucose oxidase immobilized enzyme in it.
- When glucose concentration in blood increases glucose oxidase convert glucose to gluconic acid decreases the pH toward acidic. [19]
- Ex: Examples of polymer used are chitosan, polyol, N, N-dimethyl aminoethyl methacrylate.

2. Inflammation Induced System

- Physical or chemical stress and any injury results in release of inflammation mediators that produce hydroxyl radicals.
- The design of this type of drug delivery is based on the polymers. [20]
- Hyaluronic acid is mainly degraded either by hydroxyl radicals or hyaluronidase.
- But degradation by hydroxyl radical is very rapid when hyaluronic acid is injected at inflamed sites. [21]

3. pH Based System

- pH based PDDS is based on the pH sensitive polymers that are polyelectrolytes in nature. [22]
- These polyelectrolytes have acidic or basic group that either accept or donate protons when pH is changed.
- Various polymers are used in pH based PDDS. [23]
- Ex: cellulose acetate phthalate, sodium carboxy methyl cellulose and polyacrylates. [24]

External Stimuli Induced Systems

1. Electro Responsive

- The electro responsive delivery systems uses polymers which have very high ionizable group in parent chains.
- Because when electric stimulus there they get ionized and release drug. [25]
- Ionizing polymers act both as electro responsive and pH responsive polymer.
- Ex: Agarose, xanthan gum, chitosan, carbomer, calcium alginate etc.

2. Magnetically Induced

- The use of external magnetic field as stimulus in magnetically induced delivery has increased because of very less side effects on human body. [26]
- Oscillating magnetic field leads to the controlled release of the drug.
- Magnetic carriers receive magnetic response from incorporated material such as magnetite, iron, nickel, cobalt etc.
- When magnetic field is released rapidly. The slow release of drug can be adjusted by switching 'off' and 'on' the magnetic field.

Advanced Technology

Recent Advances in PDDS

1) Spheroidal oral drug absorption system (sodas).
2) Intestinal protective drug absorption system (ipdas).
3) Chronotherapeutic oral drug absorption system (codas).
4) Geoclock technology.
5) Pulse system technology.
6) Eurand's pulsatil and chrono release system. [27]

Reasons to Adopt PDDS

1) First pass metabolism.
2) Special chronopharmacological needs.
3) Local therapeutic needs.
4) Stability problems.
5) Absorption windows.
6) For potent drugs.
7) Inter and Intra subject variability. [28]

Diseases Requiring PDDS.

DISEASE	CHRONOLOGICAL BEHAVIOR	DRUGS USED
Peptic ulcer	Acid secretion is high in the afternoon and at night	Famotidine, Ranitidine, Cimetidine
Asthma	Precipitation of attacks during night or at early morning hour	Salbutamol, Formoterol ,Fexofenadine Azelastine, Diphenhydramine , Levocetirizine
Cardiovascular diseases	BP is at its lowest during the sleep cycle and rises steeply during the early morning awakening period	Nitro-glycerine, Nifedipine, Verapamil, Diltiazem Amlodipine Lisinopril, Enalapril, Fosinopril
Arthritis	Pain in the morning and more pain at night	NSAIDs, Methotrexate, Leflunomide, Ibuprofen
Diabetes mellitus Attention	Increase in the blood sugar level after meal Increase in DOPA level in afternoon deficit syndrome	Metformin, Glimepride,Insulin

Marketed Technologies of PDDS

Technology	Mechanism	Proprietory name and Dosage form	API	Diseases
OROS®	Osmatic mechanism	Covera-HS ®: XL Tablet	Verapamil HCL	Hypertension
Three	Externally regulated Dimensional system printing®	Theirform®	Dicloenac sodium	Inflammation
CODAS®	Multiparticular pH dependent system	Verelan® PM : XL release capsule	Verapamil HCL	Hypertension
DIFFUCAPS® system	Multiparticular Tablet	Innopran® : XL	Verapamil HCL Propranolol HCL	Hypertension
PULSINCAP®	Rupturable system	Pulsincap®	Dofetilid	Hypertension

Drawbacks of PDDS

- Lack of manufacturing reproducibility and efficacy.
- Large number of process variables.
- Multiple formulation steps.
- Higher cost of production.
- Need of advanced technology.
- Trained/skilled personal needed for manufacturing.

Characteristics of PDDS

- Differential scanning calorimetry
- Friability Test
- Hardness
- Density
- Bulk density
- Tap density
- Carr's Index
- Hausner's Ratio
- Angle of Repose [29].

Conclusion

There are various ways to formulate PDDS, but the design and choice of the effective method in developing of PDDS is dependent upon patients condition, drugs inherent properties, target site, lag time needed etc. [30]

Thus in real PDDS can take over traditional oral as well as the controlled and sustained release formulation for better efficacy.

But this era is developing era of PDDS and the diseases which are controlled by circadian rhythm can be effectively managed by PDDS in future.

Beside this various marketed formulation of PDDS are present in market and serving for effective disease management in recent years. [31].

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