ISSN: 2278-2648

International Journal of Research in Pharmacology & Pharmacotherapeutics (IJRPP)

IJRPP |Vol.15 | Issue 2 | Apr - Jun -2026

www.ijrpp.com

DOI : https://doi.org/10.61096/ijrpp.v15.iss2.2026.856-862

Review on Pulsatile Drug Delivery System

Mrs. Nagajyotsna*[1], K. Harish[2], S. Snehitha[3], T. Hymasrin[4], Dr. G.Tulja Rani

[1]Depatment of pharmaceutics, Malla Reddy Pharmacy College, Maisammaguda, Secunderabad, Medchal, Hyderabad, 500100.

[2,3,4]Student of Bachelor of Pharmacy, Malla Reddy Pharmacy College, Maisammaguda, Secunderabad, Medchal, Hyderabad, 500100.

Published by: 04.03.2026 Futuristic Publications

Abstract: The Pulsatile Drug Delivery System (PDDS) is a novel drug delivery approach designed to release drugs at specific time intervals, mimicking the body's natural biological rhythms. Unlike conventional controlled or sustained release systems, pulsatile delivery provides a rapid and complete release of the drug after a predetermined lag time. This system is particularly beneficial for the treatment of diseases that follow circadian rhythms, such as asthma, cardiovascular disorders, arthritis, diabetes, and peptic ulcer disease.

Pulsatile drug delivery systems are useful for drugs with short biological half-lives, extensive first-pass metabolism, or those that may cause tolerance when administered continuously. Various techniques, including time-controlled, stimulus-responsive (pH, temperature, enzyme, or glucose sensitive), and externally regulated systems, are employed to achieve pulsatile drug release. The use of specialized polymers and advanced formulation strategies enables precise control over drug release timing. Overall, pulsatile drug delivery systems improve therapeutic efficacy, reduce side effects, and enhance patient compliance by delivering drugs only when needed. This targeted and chrono therapeutic approach represents a promising advancement in pharmaceutical drug delivery technology.

Keywords: Biological half-lives, extensive first-pass metabolism, targeted and Chrono therapeutic approach.

Introduction

The Pulsatile Drug Delivery System (PDDS) is an advanced and specialized drug delivery approach designed to release therapeutic agents in a pre-programmed, time-controlled manner, rather than in a continuous or sustained fashion. In this system, the drug is released rapidly after a predetermined lag time, producing a pulse or burst of drug release. This pattern closely mimics the body's circadian rhythms, where physiological processes and disease symptoms vary with time.

Conventional drug delivery systems often maintain constant plasma drug concentrations, which may not be optimal for diseases that exhibit time-dependent patho-physiology. Pulsatile drug delivery overcomes these limitations by ensuring that the drug is released only when it is required, thereby enhancing therapeutic efficacy and minimizing side effects.

Concept and Rationale of PDDS

The fundamental concept of pulsatile drug delivery is based on the observation that many biological processes and diseases follow a circadian rhythm, typically repeating every 24 hours. Certain diseases show peak symptoms at specific times of the day or night.

For example:

- Asthma attacks are more frequent during early morning hours
- Blood pressure rises sharply in the early morning (morning surge)
- Rheumatoid arthritis symptoms worsen in the morning.
- Gastric acid secretion peaks at night

In such conditions, a drug administered conventionally may either be released too early or remain present in the body when it is not needed. PDDS ensures that the drug is released after a specific lag time, synchronized with disease activity.

Definition

A Pulsatile Drug Delivery System is defined as a dosage form that releases the drug rapidly and completely after a predetermined lag time, followed by little or no drug release during the lag phase.

Characteristics

- Presence of a lag phase with minimal or no drug release
- Rapid and complete drug release after the lag time
- Time-controlled or stimuli-responsive release mechanism
- Improved therapeutic effectiveness
- Reduced drug tolerance and side effects
- Enhanced patient compliance

Need for PDDS

Pulsatile delivery is required in the following situations:

- Drugs with short biological half-life
- Diseases exhibiting circadian rhythm
- Drugs causing tolerance (e.g., nitrates)
- Drugs requiring site-specific delivery (e.g., colon targeting)
- Drugs that are unstable in gastric environment
- Hormones and peptide drugs

Advantages of PDDS

- Improved therapeutic outcomes
- Reduced dosing frequency
- Decreased adverse effects
- Better synchronization with biological rhythms
- Lower risk of drug tolerance
- Enhanced bioavailability for certain drugs

Disadvantages of PDDS

- Formulation complexity
- High cost
- Dose dumping
- Variable release
- Limited drug load
- Stability problems
- Regulatory issues

Limitations of PDDS

- Complex formulation design
- Higher production cost
- Difficulty in predicting in vivo behavior
- Limited drug loading capacity
- Risk of dose dumping if system fails

Applications of Pulsatile Drug Delivery

PDDS is particularly useful in the treatment of:

- Asthma
- Hypertension
- Rheumatoid arthritis
- Diabetes mellitus
- Peptic ulcer disease
- Attention deficit disorders

Classification of Pulsatile Drug Delivery Systems

Pulsatile drug delivery systems are broadly classified into:

I. Time-Controlled Pulsatile Drug Delivery Systems
II. Stimuli-Induced Pulsatile Drug Delivery Systems
III. Externally Regulated Pulsatile Drug Delivery Systems

I. Time-Controlled Pulsatile Drug Delivery Systems

In these systems, drug release occurs after a specific lag time, independent of physiological conditions.

1. Single-Unit Pulsatile Systems

These consist of a single dosage form such as a tablet or capsule.

a) Capsule-Based Pulsatile Systems

i. Reputable Coating System

- Core contains drug + disintegrate
- Coated with water-insoluble but permeable polymers
- Water penetrates → pressure builds → coating ruptures

Polymers Used
- Ethyl cellulose
- Eudragit RL/RS

Examples
- Pulsincap system

Advantages
- Simple design
- Sharp drug release

Limitations
- Variability in coating thickness

ii. Erodible Coating System
- Drug core coated with hydrophilic polymers
- Coating erodes gradually → drug released after lag time

Polymers Used
- HPMC
- Polyvinyl alcohol (PVA)

Advantages
- Predictable lag time
- No rupture-related variability

Limitations
- Influenced by GI motility

b) Osmotic-Based Pulsatile Systems
- Drug core surrounded by semi-permeable membrane
- Water enters → osmotic pressure builds → plug expelled

Key Components
- Osmotic agents (NaCl, sugars)
- Swellable or erodible plug

Examples
- PORT system

Advantages
- pH-independent
- Reproducible release

Limitations
- Complex manufacturing
- High cost

2. Multiparticulate Pulsatile Systems

These systems contain multiple units like pellets or beads.

a) Reservoir-Type Multiparticulates
- Drug-loaded core
- Polymer coating controls lag time

Examples
- Chronotropic system

Advantages
- Reduced dose dumping
- Uniform GI distribution

Limitations
- Complex coating process

b) Matrix-Type Multiparticulates
- Drug dispersed within polymer matrix
- Polymer erosion leads to drug release

Advantages
- Simple preparation
- Good stability

Limitations
- Less precise lag time

II. Stimuli-Induced Pulsatile Drug Delivery Systems

Drug release is triggered by biological or environmental stimuli.

1. Internal Stimuli–Responsive Systems

a) pH-Sensitive Pulsatile Systems
- Utilize pH differences in GI tract
- Polymers dissolve at specific pH

Polymers Used
- Eudragit L, S
- Cellulose acetate phthalate

Applications
- Colon targeting
- Peptic ulcer therapy

b) Enzyme-Sensitive Systems

Polymers degraded by colonic bacteria

Polymers Used
- Pectin
- Chitosan
- Guar gum

Applications
- Ulcerative colitis
- Colon cancer

c) Glucose-Responsive Systems

Release drug in response to blood glucose levels

Mechanism

Glucose oxidase converts glucose → gluconic acid → pH change → insulin release

Applications
- Diabetes mellitus

d) Temperature-Sensitive Systems

- Polymers respond to temperature changes

Polymers Used

- Poly(N-isopropyl acrylamide)

Applications

- Fever-associated drug release

2. External Stimuli–Responsive Systems

a) Magnetic Field–Activated Systems

Magnetic beads respond to external magnetic field

Applications

- Targeted cancer therapy

b) Ultrasound-Triggered Systems

- Ultrasound increases membrane permeability

Advantages

- On-demand drug release

c) Electric Field–Responsive Systems

Drug release controlled by electric current

Applications

- Implantable devices

III. Externally Regulated Pulsatile Drug Delivery Systems

Drug release controlled by electronic or mechanical devices

Examples

- Infusion pumps
- Implantable microchips

Advantages

- High precision
- Patient-specific dosing

Limitations

- Expensive
- Surgical implantation required

Comparative Summary Table

Type	Trigger Mechanism	Examples	Advantages
Time-controlled	Lag time	Pulsincap	Simple
Osmotic	Osmotic pressure	PORT	PH
PH-sensitive	GI PH	Eudragit	Colon targeting
Enzyme- sensitive	Blood glucose	Insulin systems	Self regulated
External stimuli	Magnetic/ultrasound implants	Magnetic/ultrasound implants	Precise

Mechanism of Action of Pulsatile Drug Delivery System

A Pulsatile Drug Delivery System is designed to release the drug after a specific lag time followed by a rapid and complete drug release, rather than continuous release.

The mechanism aims to synchronize drug release with the body's circadian rhythm or disease progression.

General Mechanism of Action

The mechanism of action of pulsatile drug delivery involves three distinct phases:

1. Lag Phase (No Drug Release)

- After administration, the dosage form remains intact
- No drug is released during this period
- The system responds to time, physiological conditions, or stimuli

2. Triggering Phase

- Internal or external triggers activate the system
- Structural or physicochemical changes occur in polymers or membranes

3. Pulse Release Phase

- Sudden and rapid drug release.

Formulation of Pulsatile Drug Delivery System

Formulation of a pulsatile drug delivery system involves designing a dosage form that releases the drug after a predetermined lag time followed by a rapid and complete release, matching circadian rhythms or disease-specific requirements.

The formulation mainly focuses on:

- Lag time control
- Sharp pulse release
- Polymer selection
- System reproducibility

I. Selection of Drug for Pulsatile Delivery

Drugs suitable for pulsatile formulation should have:

- Short biological half-life
- Time-dependent therapeutic need
- Extensive first-pass metabolism

- Chronotherapeutic requirement

Examples

- Antihypertensives
- Salbutamol (asthma)
- NSAIDs (arthritis)
- Insulin

II. Selection of Excipients

1. Polymers (Key Component)

Purpose	Examples
Rupturable coating	Ethyl cellulose, Eudragit RL/RS
Erodible coating	HPMC,PVA
PH-sensitive coating	Eudragit L,S
Enzyme- degradable polymers	Pectin, Chitosan, Guar gum
Semi-permeable membrane	Cellulose acetate

2. Other Excipients

3. Swelling agents: Sodium starch glycolate, Croscarmellose sodium

- Osmotic agents: Sodium chloride, Mannitol
- Plasticizers: PEG 400, Triethyl citrate
- Fillers: Lactose, MCC
- Lubricants: Magnesium stearate

XII. Microbiological Evaluation (If Applicable)

- Required for enzyme-based systems
- Assesses polymer degradation by micro flora

Evaluation Tests of Pulsatile Drug Delivery System

Evaluation of pulsatile drug delivery systems is essential to ensure:

- Accurate lag time
- Sharp and rapid pulse release
- Reproducibility and stability
- Patient safety and therapeutic efficacy

Evaluation involves physicochemical, mechanical, in-vitro, in-vivo, and stability studies.

I. Pre-Formulation and Physicochemical Evaluation

1. Drug–Excipient Compatibility Studies Purpose

- To detect interactions between drug and polymers

Methods

- FTIR spectroscopy
- Differential Scanning Calorimetry (DSC)
- X-ray Diffraction (XRD)

2. Particle Size and Shape Analysis Methods

- Optical microscopy
- Laser diffraction
- Scanning Electron Microscopy (SEM)
- Significance
- Influences coating uniformity and release behavior

II. Physical Evaluation Tests

1. Weight Variation Test

- Ensures uniformity of dosage units
- Performed according to IP / USP limits

2. Thickness and Diameter

- Measured using vernier caliper or screw gauge
- Affects lag time and mechanical strength

3. Hardness / Crushing Strength

- Determines mechanical stability during handling
- Measured using Monsanto or Pfizer hardness tester

4. Friability Test

- Assesses resistance to abrasion
- Carried out using Roche friabilator
- Acceptable limit: < 1% weight loss

III. Coating Evaluation Tests

1. Coating Thickness Measurement

- Microscopic measurement
- SEM analysis
- Importance
- Directly influences lag time

2. Uniformity of Coating

- Visual inspection
- Weight gain method

IV. Swelling and Rupture Studies

1. Swelling Index

Procedure

- Dosage form immersed in dissolution medium
- Weight measured at regular intervals

Formula

Swelling Index=Wt−W0 W0×100\text{Swelling Index} = \frac{W_t -W_0}{W_0} \times 100 Swelling Index = W0Wt−W0×100

2. Rupture Time / Lag Time Determination

- Time taken for coating to rupture or erode
- Critical parameter for pulsatile release

V. In-Vitro Dissolution Studies

1. Dissolution Test

Apparatus

- USP Dissolution Apparatus I (Basket) or II (Paddle)
- Media
- pH 1.2 (simulated gastric fluid)
- pH 6.8 or 7.4 (intestinal fluid)
- Expected Result
- No drug release during lag time
- Sudden and complete drug release after lag phase

2. Lag Time Determination

- Time until 10% drug release
- Used to confirm pulsatile behaviour

1. Pulse Release Profile

2. Sharp drug release curve

- Minimal tailing

VI. pH-Dependent and Enzyme-Triggered Evaluation

1. pH Change Dissolution Study

- Sequential media of different pH values
- Confirms site-specific release

2. Enzymatic Degradation Study

- Use of colonic enzymes or rat cecal contents
- Evaluates enzyme-sensitive systems

VII. Osmotic and Pressure Studies

1. Water Uptake Study

- Measures osmotic fluid intake
- Correlates with pressure build-up

2. Plug Ejection Time

- Time taken for expulsion of osmotic plug

VIII. Mechanical Strength and Integrity Tests

1. Tensile Strength of Coating

Determines resistance to rupture

2. Stress Testing

- Simulates GI motility conditions

IX. In-Vivo Evaluation

1. Pharmacokinetic Studies

- Determines Cmax, Tmax, AUC
- Confirms pulsatile plasma drug levels

2. Gamma Scintigraphy

- Tracks dosage form movement in GI tract
- Determines site and time of drug release

3. Pharmacodynamic Studies

- Confirms therapeutic response at desired time

X. Stability Studies

1. Accelerated Stability Testing

- Conditions (ICH Guidelines)
- 40°C ± 2°C / 75% RH ± 5%

Parameters Evaluated

- Lag time
- Drug content
- Dissolution profile

XI. Evaluation of Multiparticulate Systems

1. Pellet Size Distribution

- Sieve analysis

2. Flow Properties

- Angle of repose
- Carr's index
- Hauser ratio

Summary Table: Evaluation Tests of PDDS

Evaluation Test	Purpose
Weight variation	Dose uniformity
Hardness & friability	Mechanical strength
Swelling index	Lag time prediction
Rupture time	Pulse accuracy
Dissolution study	Release pattern
Lag time determination	Pulsatile confirmation
In-vivo studies	Therapeutic validation
Stability testing	Shelf-life prediction

Conclusion

Pulsatile drug delivery systems represent an advanced and rational approach to drug administration by releasing medications in a predetermined, time-controlled manner that closely matches the circadian rhythm of diseases and the body's physiological needs. Unlike conventional sustained-release systems, PDDS provides drug release after a specific lag time or in distinct pulses, thereby improving therapeutic efficacy, reducing side effects, and minimizing drug tolerance.

These systems have shown significant potential in the management of chronotherapy-based disorders such as hypertension, bronchial asthma, rheumatoid arthritis, peptic ulcer disease, diabetes mellitus, and cancer. By delivering drugs at the most appropriate time, PDDS enhances patient outcomes and compliance.

However, challenges such as complex formulation design, high manufacturing cost, variability in drug release, and regulatory difficulties limit their widespread application. Continuous research in novel polymers, smart delivery systems, and improved manufacturing techniques is expected to overcome these limitations

References

1. Maroni A, Zema L, Del Curto MD, Loreti G, Gazzaniga A. *Oral pulsatile delivery: rationale and chronopharmaceutical formulations.* Int J Pharm. [classic review on PDDS strategies]
2. Patel VP, Soniwala MM. *Pulsatile drug delivery system for treatment of various inflammatory disorders: a review.* Int J Drug Dev Res. 2012; 4(3):67–87.
3. Habeeb F, Mohammed S. *A Review on Pulsatile Drug Delivery System.* Int J Pharm Res Technol. 2023.
4. Venkataswamy R, Nallaguntla L. *Review Article on Pulsatile Drug Delivery System.* Asian J Pharm Clin Res. 2021.
5. Mishra S, Mishra N. *Pulsatile Drug Delivery System – A Review.* Int J Recent Adv Multidiscip Topics. 2022.
6. Ravali V, Balaji P. *Pulsatile Drug Delivery Systems: A Comprehensive Review.* Int J Drug Delivery Technol. 2024.
7. *PULSATILE DRUG DELIVERY SYSTEM: A REVIEW.* Int Res J Pharm. 2012.
8. *Pulsatile Drug Delivery System: A Review.* IJPSR. 2023.
9. Yadav R, Jain D. *Pulsatile Drug Delivery System– A Systematic Review.* IJPSR. 2023.
10. Ingole B, Tiwari S. *Pulsatile Drug Delivery System and Recent Advances: A Review.* PharmaTutor. 2013.
11. Singh S, Koland M. *Formulation and evaluation of pulsatile drug delivery systems of Glipizide.* J Drug Delivery Ther. 2016.
12. Design and evaluation of pulsatile drug delivery system using tablet-in-tablet formulation. World J Pharm Sci. 2014.
13. Sadaphal KP et al. *Formulation and evaluation of pulsatile drug delivery system for chronobiological disorder: Asthma.* Int J Drug Delivery. 2025.
14. Bussemer T, Bodmeier R. *Pulsatile drug delivery systems.* Crit Rev Ther Drug Carrier Syst. [often cited review on pulsatile coating systems]
15. Conte U, Colombo P, Manna AL, Gazzaniga A. Tablet able to release drug according to circadian rhythm. Drug Dev Ind Pharm. 1989.
16. Ross AC, MacRae RJ, Walther M, Stevens HN. Chrono pharmaceutical drug delivery from a pulsatile capsule device based on programmable erosion. J Pharm Pharmacol. 2000.
17. Sharma R, Singh A, Kumar S. Pulsatile Drug Delivery System: A Review. lnt Res J pharm.2012; 3(7):1-5.
18. Kikuchi A, Okano T. Pulsatile drug release control using hydrogels. Adv Drug Deliv Rev. 2002; 54(1):53–77.
19. Alessandra M, Lucia Z, Matteo C, Maria ES. Oral pulsatile drug delivery systems. Expert Opin Drug Deliv. 2005; 2(5):863–871.
20. Albadri AA, Abdulbaqi MR, Almajidi YQ. Recent Trends in Chronopharmaceutics, Pulsatile Drug Delivery System. Al Mustansiriyah J Pharm Sci. (2025).