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Pulsatile drug delivery: Advances, mechanisms and future perspectives

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Abstract
In recent years, pulsatile drug release systems (PDRS) have emerged as an advanced alternative to conventional drug delivery methods. Unlike continuous-release formulations, PDRS are designed to deliver drugs rapidly after a predetermined lag time, making them particularly advantageous for chronotherapy, targeted therapy, and drugs prone to degradation or side effects during sustained exposure.
PDRS can be broadly classified into single-pulse systems and multi-pulse systems. Typically, these formulations consist of a drug-containing core, an intermediate swelling layer, and an outer coating composed of an insoluble material combined with a semipermeable polymer. The lag time before drug release is influenced by several factors, including the permeability and mechanical strength of the outer coating as well as the swelling and rupture characteristics of the intermediate layer.

Keywords: Lag time, PRDS, chronotherapy, multipulse system

Introduction
Conventional oral formulations continue to dominate the global pharmaceutical market owing to their ease of administration, cost-effectiveness, and high patient compliance. Oral delivery remains the most widely accepted route for drug administration and therapeutic management. Within this domain, oral controlled-release systems have been developed to maintain drug concentrations within the therapeutic window for extended durations, thereby ensuring sustained therapeutic action and reducing dosing frequency.
To address these limitations, pulsatile drug delivery systems (PDDS) have attracted considerable attention. Unlike conventional controlled-release systems, PDDS are designed to release the entire drug load after a well-defined lag time. These systems provide site-specific and time-specific drug delivery, offering both spatial and chronological control. Such precision enhances therapeutic efficacy, minimizes side effects, and significantly improves patient compliance. Importantly, PDDS ensure rapid and complete drug release within a short duration immediately after the programmed lag phase, making them highly suitable for chronotherapy and other specialized therapeutic applications.

Advantages
1. Can be used extensively for day and night time action.
2. Low cost, side effects are low as dose frequency and dose size is less.
3. Adapts to body circadian rhythms.
4. Drug targeting is easy.
5. Defends the GI mucosa from irritating drugs.
6. First pass metabolism is lease.
7. Steady drug level is maintained in the blood plasma [7-10].

Disadvantages
1. Loading capacity of drug is less.

2. Release of drug is less.
3. Formulation steps are complex.
4. Reproducibility and efficacy is poor.
5. Skilled/trained persons needed for manufacturing.

Necessitate of pulsatile drug delivery systems

1. Circadian rhythm follows many body functions which fluctuates according to the time.
2. Acid secretion, cholesterol synthesis, gastric emptying and GI blood transfusion might change with circadian rhythm.
3. Chrono pharmacotherapy of illnesses which give an explanation for circadian rhythms of their path body structure.

Classification of PDDS

Pulsatile system are essentially time-controlled drug delivery system in which the system manages the lag time independent of environmental factors like enzyme, pH, GI motility etc. Pulsatile drug delivery systems can be generally categorized into four classes [15].

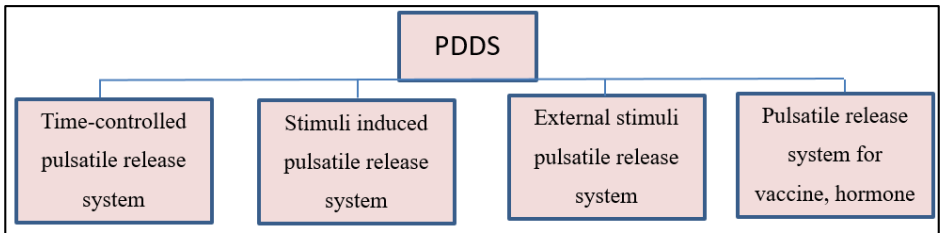

Fig 1: Classification of PDDS

1) Time-controlled pulsatile release system

These time-controlled systems can be classified as a single units (e.g., tablet or capsule) or multiple unit systems.

a) Single unit systems

Single-unit systems are mostly developed in capsule form. The insulate time is managed by way of a plug, which finds pushed away by erosion or swelling and the drug is launched as a Pulse from the insoluble pill frame. Polymers used for designing of the hydrogel plug are as following:

1. Swellable materials coated with but permeable polymer (polymethacrylates).
2. Erodible compressed polymer (polyvinyl alcohol, HPMC).
3. Congealed melted polymer (glyceryl mono oleate).
4. Enzymatically controlled erodible polymer (pectin) [16-17].

In certain pulsatile drug delivery designs, the drug reservoir is surrounded by a soluble or erodible barrier layer, which dissolves gradually upon contact with gastrointestinal fluids. This creates a predetermined insulation time (lag phase) before the drug is released. Such systems are often designed to align with the biological clock of the body, ensuring that drug release coincides with the optimal therapeutic window [20].

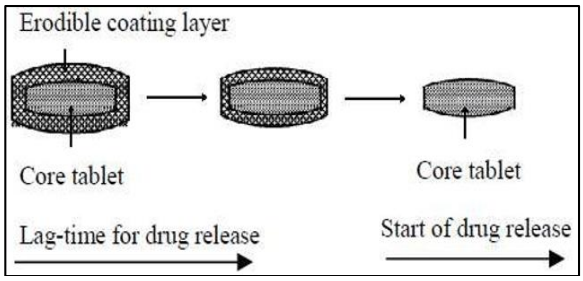

Fig 2: Schematic diagram of delivery system with erodible coating layers

In some pulsatile drug delivery systems, the core is coated with a rupturable membrane that enables time-controlled release. The rupture mechanism is triggered by the generation of internal pressure from effervescent agents, commonly a combination of sodium bicarbonate and citric acid. When the formulation comes into contact with gastrointestinal fluids, the reaction between these agents produces carbon dioxide gas, which accumulates inside the core and creates pressure against the polymeric coating [22-25].

Multiple unit pulsatile systems

The gastric emptying pattern plays a significant role in the performance of multi-particulate drug delivery systems, as these formulations are freely dispersed throughout the gastrointestinal tract (GIT) and are influenced by the transit time of food. Multi-particulate systems are generally classified into two types, depending on their design and mechanism of release.

2) Stimuli-induced pulsatile release system

This system releases the drug in answer to stimuli by the exterior surroundings [28].

a) Thermoresponsive pulsatile release

Hydrogels are excellent examples of thermo-sensitive drug delivery systems. These systems utilize crosslinked polymer networks that undergo a phase transition in response to temperature changes, leading to swelling or deswelling of the hydrogel and thereby regulating drug release [29].

b) Chemical stimuli-induced pulsatile release

Drug release from pulsatile systems can also be regulated by biological factors, such as pH, enzymatic activity, or other

chemical stimuli present within the body. A classic example of this concept is the automatic release of insulin in response to elevated blood glucose levels, which represents a model for glucose-responsive drug delivery [30-31].

3) Externally regulated pulsatile release system

a) Electro responsive pulsatile release

Well-studied example is the use of poly(2-acrylamide-2-methylpropane sulfonic acid-co-butyl methacrylate) hydrogels, which can swell or deswell in response to electrical signals or pH variations. Such hydrogels provide a versatile platform for designing on-demand, site-specific, and non-invasive drug delivery systems, particularly suitable for chronotherapy and personalized medicine [32-33].

b) Micro electro-mechanical systems

Devices developed using pulsatile drug delivery systems have the unique ability to store and release multiple drug moieties through controlled triggering mechanisms, thereby providing better control over drug release. One of the most notable advancements in this field is the development of microchip-based delivery systems. These microchips consist of an array of reservoirs fabricated from an impermeable substrate, each capable of storing a precise quantity of drug [35-36].

Recent Advances in the Pulsatile Drug Delivery System

Many diseases require pulsatile drug release for optimal management, including asthma, cancer, arthritis, peptic ulcers, cardiovascular disorders, and allergic conditions. To address such therapeutic needs, recent trends in drug delivery focus on the development of multiparticulate systems, which offer several advantages over single-unit dosage forms, such as improved bioavailability, reduced dose dumping, and better patient compliance.

The drug release pattern in these systems is influenced by multiple factors, including gastrointestinal pH, resident microflora, and programmed time-controlled mechanisms. To further enhance the therapeutic efficacy of oral delivery, a wide range of innovative technologies have been developed, such as pH-sensitive coatings, enzyme-triggered systems, osmotic pumps, and polymer-based carriers. These advancements are paving the way for more reliable and patient-friendly pulsatile drug delivery strategies.

a) Accubreak Technology

In these systems, the required dose can be divided into smaller units, such as mini-tablets or multiparticulate pellets, which are then incorporated into a controlled-release formulation. Upon administration, the drug remains protected within its coating until the predetermined lag time has elapsed. At that point, the outer membrane ruptures due to swelling, osmotic pressure, or enzymatic activity, leading to the rapid release of the drug [43].

b) TMDS Technology

In single tablet the release rate of multiple ingredients can be optimized.

c) Geoclock Technology

In this active drug is bounded by an outer layer which comprises a hydrophobic mixture and a inelastic material. E.g. LODOTRA - for rheumatoid arthritis.

d) Duredas Technology (Dual release drug absorption system)

In this there are two layers in which one layer is accountable for immediate release of second layer and sustained action is produced.

e) Innoherb

In this the herbal compound are converted into beads or pellets and coated within capsule. The coating is done by semi-permeable membrane which is also used to mask the bad taste.[44]

f) Orbexa technology

Granulation is done for loading of drugs. Polymers are used for coating and this technology can be imparted in proteins.

Conclusion

Oral drug delivery remains the most convenient, cost-effective, and widely accepted route of administration. The integration of chronopharmacology principles into drug delivery offers a promising approach, particularly for the management of chronic illnesses. While conventional controlled-release systems provide sustained therapeutic effects, they may not be suitable for diseases that follow biological rhythms, such as peptic ulcers, hypertension, osteoarthritis, and asthma, where chronotherapy is essential.

Pulsatile drug delivery systems (PDDS) address these challenges by ensuring the release of drugs at the right time and site, in alignment with the body's circadian rhythm. This not only improves therapeutic efficacy but also enhances patient compliance by delivering medication when it is most needed. With ongoing technological advancements and improved formulation strategies, many of the current limitations of PDDS can be overcome.

Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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