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Pulsatile Drug Delivery System – A Review

Shilpi Mishra[1*], Nitin Mishra[2]
[1,2]*Assistant Professor, Department of Pharmacy, Shree Krishna College of Pharmacy, Sitapur, India*

***Abstract*: Pulsatile drug delivery systems are gaining popularity in modern pharmaceuticals as a means of developing medications for which standard continuous-release therapies are ineffective. In some circumstances, where maintaining a steady blood level of medications is undesirable, a pulsatile drug delivery device is recommended. After a lag time, they are built in such a way that complete and quick drug release is achieved. Site-specific pulsatile drug delivery devices release the medicine at a specified location inside the digestive tract. The delivery system, rather than the external environment, controls medication release in time-controlled release. Site-controlled release refers to medication release that is regulated by pH or enzymes found in the gastrointestinal system. This study looks at several pulsatile systems, such as capsular systems, osmotic systems, single and multiple systems based on soluble and erodible polymer coatings, and the existing PDDS on the market.**

***Keywords*: Pulsatile drug delivery systems, chronopharmacologic treatment, types of pulsatile drug delivery system.**

1. Introduction

After administration, timed-release formulations are designed to release a medicine at a certain period (the lag time). Orally given timed-release dosage forms have been extensively researched for application in chronopharmacologic treatment, site-specific drug administration, peptide drug absorption augmentation, and pharmacokinetic drug–drug interactions. However, as compared to immediate-release conventional dosage forms, timed-release dosage forms have a lower bioavailability. This effect is hypothesized to be caused by the drug's poor solubility and absorption in the lower GI tract. The ileum and colon are the most typically affected areas. There have been several timed-release technologies described. These include a rupturable coating that surrounds multiple pellets loaded with the drug, a compression-coated soluble barrier that erodes, surrounding a single unit-core tablet containing the drug, and a swellable hydrogel plug that dislodges when swollen, set into a water-insoluble capsule body filled with the drug. Compression-coated tablets are made up of an inner core that contains an active medicinal component and an outer coating that dissolves or disintegrates slowly to provide a drug release lag time. A time-release formulation might allow for faster medication release and higher plasma drug concentrations at the moment in the circadian cycle when clinical symptoms appear or worsen.

Advantages: Here are numerous advantages of the pulsatile drug delivery systems. Some of them are enlisted as below:

- These systems can be used for extended day time or night time activity.
- They reduce the dose frequency, dose size and cost, which ultimately reduces side effects, thereby improving patient compliance.
- Drug adapts to suit circadian rhythms of body functions or diseases.
- Drug targeting to a specific site, like the colon, can be achieved.
- They protect mucosa from irritating drugs.
- Drug loss by extensive first pass metabolism is prevented.
- They provide constant drug levels at the site of action and prevent the peak-valley fluctuations.

Disadvantages:

- Low drug loading capacity and incomplete release of drug.
- Multiple manufacturing steps.

2. Pulsatile Drug Delivery Methods

The pulsatile drug delivery system methodologies may be divided into four categories.

1) Time controlled pulsatile release system

Time-dependent dosage forms are designed to release their pharmacological load when a certain amount of time has passed. For maximum efficacy, a drug's activity should be coordinated with the appropriate place and timing. As a result, the development of a time-controlled release mechanism for patient treatment is sought. These systems are intended to deliver drugs in pulses controlled by device manufacture and, ideally, independent of environmental conditions.

2) Delivery systems containing erodible coating layer

Bulk-eroding system: Bulk erosion occurs when the rate of water intrusion exceeds the rate of deterioration. Degradation occurs throughout the polymer sample in this example and continues until a threshold molecular weight is achieved. Degradation products have shrunk to the point where they can be dissolved, and the structure has begun to become much more porous and moister.

3) Surface eroding system

The reservoir device is coated with a soluble or erodible layer that dissolves over time and releases the drug after a predetermined lag period, similar to a chronotropic system

*Corresponding author: shilpimisra53@gmail.com

where the drug is entrapped in the core layer with hydroxyl propyl methyl cellulose (HPMC) and an additional layer of enteric-coated film outside it.

4) Delivery system with rupturable coating layer

For the release of a medication, these methods rely on the breakdown of the coating layer. Effervescent excipients, swelling agents, or osmotic pressure can be used to provide the pressure required for coating rupture.It has been reported that an effervescent combination of citric acid and sodium bicarbonate was integrated in a tablet core covered with ethyl cellulose.

5) Capsule-shaped system provided with release controlling plug

In this system, in which the lag time is continued by a plug that gets pushed away by swelling or erosion, releasing the drug as a pulse from the insoluble capsule body.

6) Stimuli-induced pulsatile release system

Stimuli-based drug delivery systems distribute the medicine in response to biologically produced stimuli. The drug is released as a result of stimulation-induced changes in the gels or micelles, which may deswell, swell, or erode in response to the relevant stimuli. The medicine is released in these systems after being stimulated by any biological element, such as temperature or other chemical stimuli. They are further categorized as follows:

Thermoresponsive pulsatile release: Thermosensitive gels are hydrogels that exhibit reversible volume changes in response to temperature variations. Thermosensitive hydrogels have been examined as stimuli-responsive drug delivery vehicles. Hydrogels are networks of crosslinked biological, synthetic, or semi-synthetic polymers. These gels shrink at a transition temperature that is related to the linear polymer's lower critical solution temperature (LCST).

Chemical stimuli-induced pulsatile release: The most recent focus has been on the creation of stimuli-sensitive delivery systems. In the presence of any biological component, such as enzyme, pH, or any other chemical stimulation, these systems release therapeutic medicines. One notable use of this technology has been the creation of a system that can autonomously release insulin in response to high blood glucose levels.

7) Externally regulated pulsatile release system

Electro responsive pulsatile release: An electric field offers benefits as an external stimulus, such as the availability of equipment that provides precise control over the size of the current, duration of electric pulses, interval between pulses, and so on. Polyelectrolytes are used to make electrically responsive delivery systems, which are both pH and electro responsive. Electro responsive hydrogels usually deswell, swell, or erode when subjected to an electric field.

Ultrasonically stimulated: Ultrasound is primarily utilised to promote medication absorption across biological barriers such as the skin, lungs, intestinal wall, and blood vessels. Several studies have been published that describe the influence of ultrasonography on regulated medication delivery.

8) Magnetically induced pulsatile release

One of the earliest approaches studied to construct an externally controlled drug delivery system was the use of an oscillating magnetic to govern drug release from a polymer matrix. Magnetic carriers respond to magnetic fields via integrated minerals such as magnetite, iron, nickel, cobalt, and so on. Magnetic carriers for biomedical applications must be water-based, biocompatible, non-toxic, and non-immunogenic. The strategy's mechanistic approach is based on magnetic attraction, which slows the flow of oral medicines in the gastrointestinal system.

9) Marketed technologies of pulsatile drug delivery

Different marketed technologies has been developed for pulsatile drug delivery, Some of them are discussed below:

Pulsincap technology: This device is made up of a non-disintegrating half capsule body with an open end sealed with a hydrogel plug and covered by a water-soluble cap. To avoid the issue of variable gastric emptying, the entire unit is coated with an enteric polymer. When this capsule comes into touch with the dissolving fluid, it expands, and after a short delay, the plug pushes itself outside the capsule, releasing the medicine quickly.

DIFFUCAPS technology: The solubility and absorption of some medications are affected by pH variations throughout the GI tract. This pH sensitivity can be problematic, especially when formulating a prolonged or controlled release formula. Carvedilol and dipyridamole are medicines that are soluble in the acidic environment of the stomach but insoluble in the neutral/slightly alkaline environment of the intestine, where active drug absorption is optimal. Weak, basic medicinal molecules that are insoluble at pH levels higher than five are of special concern.

Three-dimensional printing: Three-dimensional printing (3DP) is a rapid prototyping (RP) technique or a unique solid freeform manufacturing process that has been utilised to the production of sophisticated pharmaceutical medication devices. Prototyping entails building precise layers with powder processing and liquid binding ingredients.

CODAS (chronotherapeutic oral drug absorption system): In certain cases, immediate release of drug is undesirable. A delay of drug action may be required for a variety of reasons. Chronotherapy is an example of when drug release may be programmed to occur after a prolonged interval following administration. Elan Drug Technology developed CODAS technology to achieve this prolonged interval.

OROS technology: OROS delivery systems were adopted for poorly water-soluble drugs. The push-pull system is comprised of a bilayer or trilayer tablet core consisting of one push layer and one or more drug layers. The drug layer contains the poorly soluble drugs, osmotic agents and a suspending agent. The push layer contains among other things, an osmotic agent and water swellable polymers. A semipermeable membrane surrounds the tablet core.

3. Conclusion

Rapid improvement and newer advances in the field of drug delivery have resulted in the formation of the pulsatile drug delivery system, which, on the one hand, is simple to construct while also providing considerable therapeutic benefits. These

systems deliver the medicine to the patient's body at the appropriate time, location, and dosage. Circadian disorders, in general, necessitate chronopharmacotherapy, which may be readily performed with a well-organized pulsatile drug delivery system. Rapid improvement and newer advances in the field of drug delivery have resulted in the formation of the pulsatile drug delivery system, which, on the one hand, is simple to construct while also providing considerable therapeutic benefits. These systems deliver the medicine to the patient's body at the appropriate time, location, and dosage. Circadian disorders, in general, necessitate chronopharmacotherapy, which may be readily performed with a well-organized pulsatile drug delivery system. The genesis of the terrible diseases can be connected to the release of certain medications through these systems, which would undoubtedly improve therapy. Although some milestones have been attained in this regard, there are still some undiscovered aspects of pulsatile drug delivery that can open up new vistas through improved engineering.

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