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PULSATILE DRUG DELIVERY SYSTEM: A REVIEW

B. Gangadhar, B. Sai Bhanu Sree *, PV Swamy, M. Aruna Devi
Shri Vishnu College of Pharmacy, Vishnupur, Bhimavaram, Andhra Pradesh, India

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*Corresponding author
E-mail: bhanuborusu17@gmail.com

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ABSTRACT

Pulsatile Drug Delivery Systems (PDDS) are gaining a lot of interest as the delivery of the drug will be at the right site and at the right time, and the amount of drug that is reaching the site of action will also be so accurate, and therefore it generally improves the patient compliance. These followed a sigmoidal drug release profile and were characterized by a time of no drug release followed by a rapid and complete drug release. This article focuses on the various types of methodologies involved for the existing system and different marketed technologies, including Pulsincap™, OROS, DIFFUCAPS, CODAS®, TIMERx®, and CONTIN®, which follow the above mechanism to render a sigmoidal drug release profile, diseases requiring pulsatile drug delivery system, need for PDDS and evaluation of PDDS.

Keywords: Pulsatile drug delivery system, sigmoidal drug release profile, patient compliance.

INTRODUCTION

Pulse medicine is an alternative to continuous medication for disease management. These medications or drug formulations are essential in diseases that follow a particular rhythm, for example, asthma attacks in the early mornings. In these delivery systems, the medication is released after a certain lag time, i.e., the introduction of API into systemic circulation will occur only after reaching lag time. This time delay of drug release can be achieved by employing various polymers in the coating, making formulations in matrices etc. [1,2]

The novelty in this drug delivery system attracts more attention because the drug delivery will be at the right site and at the right time, and the amount of drug that is reaching the site of action will also be so accurate, and therefore it generally improves patient compliance.[1,2] Pulsatile delivery system is more dependable and time specific according to the pathophysiological requirement of the disease. These systems are advantageous in conditions such as asthma, cardiovascular ailments, peptic ulcer, arthritis etc. These types of delivery systems are generally affected by blood pressure, enzymatic activity, and pH of the gastric region.[3-7]

Need for PDDS

Pre-systemic metabolism: Drugs such as propranolol, imipramine, and cimetidine are susceptible to the first-pass metabolic effect. The traditional oral delivery of such drugs generally decreases oral bioavailability. [45]

Drug Tolerance

Plasma profiles of drugs frequently go along with a reduction in the pharmacotherapeutic action of the drug. In the case of drugs like morphine or nitro-glycerine, the transdermal route may develop biological tolerance.

Importance of chrono-pharmacology

Particular physiological tasks are well coordinated with the body's circadian functionality, and it has been proved that various symptoms and occurrence of diseases happens during a specific time period in the entire day. In the case of angina or asthma, most of the attacks have been seen in the early mornings.[8]

Need in local therapeutic action

To treat certain local disorders, viz., irritable bowel syndrome and gastric irritation, delivery of drugs should be specific so that there should be no loss because of intestinal absorption or decomposition of drugs due to gastro enzymatic activity. In this case, PDDS-like delivery systems play a crucial role in achieving therapeutic action.[9,10]

Effect of gastro-intestinal enzymes

Drugs like NSAIDs, on continuous administration, produce irritation in the GI tract, and protein or peptide drugs undergo enzymatic degradation and lose therapeutic efficacy. Such drugs need unique formulations like enteric coating and can be formulated as pulsatile or effective drug delivery systems.[9,10]

Advantages

- Bioavailability increases due to a rise in absorption capabilities compared to traditional drug formulations.
- Site-specific therapeutic action for local ailments.
- Extended nocturnal or diurnal functionality.
- Reduction in frequency of dosage.
- Decreased side effects.
- Drug targeting to a specific site of action, such as the colon.
- There is no risk of dose missing or dose dumping.
- Improved patient compliance [11,12]

Limitations

- The cost of production is high
- Requires advanced and sophisticated technology.
- Variations in *In- Vivo* drug levels from single unit pulsatile dosage forms
- Requires trained and sound knowledge personnel. [13-15]

Diseases requiring pulsed drug delivery
In a disease where the rhythmic circadian organization of the body plays a vital role, the drugs' pharmacokinetics and/or pharmacodynamics are not constant within 24 hours[16,17].
(Table 1)

Drug release profiles from Pulsatile drug delivery system
Depending on the dosage form and delivery system, pulsatile drug delivery systems (Figure 1) can be classified as follows:

Time Controlled

Single Unit Systems
- Capsule based system
- Osmotic based system
- Solubility modulated system
- Erodible or soluble barrier layering
- Rupturable coat systems

Multiple Unit Systems
- Time-controlled rupturable coat system
- Permeability controlled osmotic based system
- Change in the extension of permeability

Stimuli Induced
- Inducing temperature
- Inducing chemical stimuli

Externally Regulated

Time-controlled pulsatile drug delivery: Single unit pulsatile systems: Capsule-based systems

Amidon and Leesman demonstrated the delivery of dosage forms into the aqueous environment of the body in a controlled pulse manner. These dosage forms were made into single units for better drug delivery. The whole drug formulation containing more than one, generally less than ten subunits, is preferred and formulated as a unitary depot, viz., tablet or capsule. Before the release of a drug, it should maintain a particular lag time so that the drug will be released as per pathological need. To achieve this, the lag time can be moderated with a plug, which will be pushed away by using swelling or rupture polymers. After such a phenomenon, the drug release from the formulation will follow a pulse pattern from the capsule body, which is insoluble. Generally, such a capsule comprises hydrogel along with gelatin. The hydrogel can be prepared using polymers like PVA, Pectin, Polyethylene oxide, and Glycerol monooleate.[21,22] The unitary subunits are designed uniquely to dissolve at various sites or times in the GIT to release the drug in a pulsed dosage manner as rate controlled or immediate release after lag time into the portal system. The dissolution rate can be controlled by employing various polymers like enteric coating or using such polymers in altered ratios. (Figure 2)

Osmotic Pump Capsule

'Port' System
In this port system, the capsule is coated by a semi-permeable layer. This port system is an insoluble plug with an osmotically active substance and drug formulation. Upon contacting dissolution fluid, the capsule system's semi-permeable layer allows fluid entry into the system. As a result, osmotic pressure will be developed, and the plug will be expelled after a lag time. (Figure 3)

Expandable orifice system
This system based on an expandable orifice, i.e., a drug which is in liquid form will be delivered by a capsular system depending on osmosis, where porous particles absorb the liquid drug and release the drug through an orifice made on the semi-permeable membrane of the capsule assisted by an osmotic layer that can be expanded after the dissolution of barrier layer along with the benefit of extended-release with increased bioavailability. Elastomers like styrene-butadiene copolymer can be employed in making elastic outer layers, and orifice can be made. Depending on the thickness and composition of the semi-permeable membrane, the lag time can be altered following pathophysiological needs. (Figure 4)

Delivery by series of stops
Systems like capsules of implantable type suit this type of delivery system. In this system, the capsule containing the drug and an osmotic system that can absorb water are placed in a compartment separated by a slider, which can be moved, providing pulsatile delivery. This system is best suited for delivering drugs like somatotropin, in which pulsatile release can be achieved by a series of stops in the capsule's embedded wall. This system was used to provide porcine somatotropin.

Delivery by solubility modulation
The name indicates that the drug's solubility is modulated so that pulsatile release can be achieved, depending on the osmotic pressure and solubility of the drug. This system is generally developed for salt-containing drugs, in which inorganic salt, solid organic acid, or organic salt can be used for modulating solubility. Different compositions of drugs with modulators can be considered to achieve a zero-order release profile to start the pulse release of the system.

Pulsatile System- Erodible Barrier Coatings
In this system, the drug's core is coated or layered with a barrier, i.e., a polymer having a dissolution rate retarding nature. Dissolution of the particular barrier will happen once it completes the lag time. The lag time can be modified by altering the thickness of the coating.

The Chronotropic System
Hydrophilic HPMC with swelling nature is coated on the core to achieve lag time.

"Time Clock" System
This system releases the drug from the core immediately following the rehydration of dosage form and can be affected by meal composition and quantity. (Figure 5)

Compressed Tablets
This compressed tablet system has an outer tablet that aids with the initial dose by immediately disintegrating in the gastric environment. The inner layer of the tablet is composed of gastric pH-resistant polymers, which resist the disintegration of the inner tablet in the stomach and subsequently aid in the intestinal release of the drug. Cellulose derivatives such as ethyl cellulose are used as a backing layer for tablets. This type of delivery system can well protect sensitive drugs like hygroscopic, light susceptible, and acid-labile medicines. One of the main drawbacks of this system is that it needs a high amount of coating polymers, and it is tedious and challenging to maintain the core in position while coating.

Multi-Layered Tablets
As the name multi-layered suggests that tablets are manufactured in different layers. All these layers are separated from one another with a barrier layer made of polymer. The layered tablet is coated on all sides with cellulose-derived polymer (ethyl cellulose), which act as a backing layer that leaves the top side uncoated. After administration, as the top layer is left uncoated, this layer provides an initial dose for the tablet, rapidly rupturing on contact

with the dissolution medium. The next pulsed release is obtained from the third layer, which is coated with HPMC. The gel-forming polymers such as methylcellulose, HPMC, polyvinyl alcohols and layering materials such as cellulose derivatives (ethyl cellulose, methylcellulose, cellulose acetate propionate), methacrylic polymers, acrylic acid, and poly alcohols are used for the second drug layer. (Figure 6)

Rupturable Coating
Dual layering is employed in this system. Drug core coated with swellable layer and rupturable layer, after administration in contact with dissolution media, the swellable layer expands, resulting in film rupture. This gives rapid drug release. This type of system can be affected by pH and solubility.

Multiple Unit System
To avoid the risk of dose dumping and improve the system's flexibility, multiple-unit systems are more advantageous than single-unit systems. [24,25]

Time Controlled
In these multiple systems, the drug is layered on sugar seeds and then coated with a swellable polymer and a top layer is coated with an insoluble polymer layer. In contact with dissolution media, the swellable layer expands and ruptures the top insoluble layer. This results in the release of the drug from the formulation. Initial lag time can be altered by changing the composition and thickness of coating polymers.

Permeability Controlled
The core of this system is generally composed of low-density material (mineral oil) and disintegrants. It also holds drugs, and the entire core is coated with a polymer such as cellulose acetate. Osmotic agents employed in this formulation are dissolved in the medium, the pellets will be swelled, and the swelling regulates the diffusion rate.

Modifying membrane permeability
In this system, alteration of the porous nature of the membrane is employed. The system's core, consisting of drug and succinic acid pellets, is layered with the ammonio-methacrylate copolymer. After performing dissolution studies, it is proved that the drug in the pellet core is released after the dissolving of succinic acid.

Stimuli Induced Pulsatile Drug Delivery
There are two types:
1. Temperature-induced
2. Chemical stimuli-induced

Temperature-Induced
The release of the drug depends on stimulating biological factors such as temperature and other chemical stimuli. Drug carrier systems which are thermo-responsive (hydrogels made of poly-N-isopropyl acrylamide) will be of greater use for this type of delivery.

Chemical Stimuli-Induced
Delivery of drugs depending on various types of chemical stimuli such as inflammation-induced, ultrasound-induced, electric stimuli-induced, pH-sensitive delivery, light-induced, and magnetic-induced delivery systems are some examples of this type of system.

Externally regulated
This drug release pattern is programmed depending on externally induced stimuli such as ultrasound and electrically induced irradiation. Delivery systems of magnetic induced are composed of magnetic beads embedded in the formulation; drug release will take place on applying a magnetic field and due to the presence of magnetic beads.

Evaluation

Thickness and Diameter: Vernier callipers are used to measure thickness and diameter. [26]
Hardness: Monsanto hardness tester is used to determine the hardness of the tablet,[27,28] and expressed as kg/ cm^2.
Friability: Roche Friabilator is used to determine the friability of tablets. All batches were placed the in friabilator for 100 revolutions in 4 minutes.[29,30]

Percentage friability is calculated by:

$$F = (W_{initial}-W_{final})/ W_{initial}\times 100$$

Weight Variation Test: This test is performed by accurately weighing20 tablets individually, calculating average weight and comparing the individual weight to the average. Weight variation limits as per Indian Pharmacopoeia are tabulated in Table 2.

Lag Time and Drug Release: The drug release studies and lag time was carried out in gastric and intestinal fluids at body temperature. This test was carried out using the USP dissolution apparatus; in this test, the tablet was placed in dissolution media, and the sample was taken out at a specific time interval and then analysed by UV spectroscopy. [31,32]

Rupture Test: Using the USP paddle apparatus, a rupture test on coated tablets was performed. The time the external coating layer starts ready to rupture is called lag time. The Rupture test determined this. [33]

Drug Content: Weighed accurately the required amount of powder dissolved in distilled water, and it is filtered. After that, the absorbance is measured at the fixed wavelength using a UV spectrophotometer.

Water Uptake Study: The percentage water uptake of pulsatile release tablets was determined in a medium-filled container placed in a horizontal shaker (100 ml of 0.1 N HCl, 37.5 ^{0}C, 74 rpm n=3) at predetermined time points. The tablets were removed from the dissolution medium. They were then carefully blotted with the tissue paper to remove surface water, then weighed and then placed back in the medium up to the time when the coating of the tablet ruptured. The % water uptake update was calculated as follows:

$$\%\text{Water uptake} = [(W_t - W_o/W_o)] \times 100$$

Where; W_t= weight of tablet at a time 't',
W_o =weight of the dry tablet.

Swelling Index: Weighed accurately the individual tablet and it was kept in 50 ml of double distilled water. Then tablets were taken out after 60 min, and then they were smudged with filter paper to remove the water present on the surface and weighed accurately.[34]

The percentage swelling index (SI) was calculated by using the formula:

SI = (Wet weight – Dry weight / Dry weight) x 100.

Polymers used in Pulsatile Systems

Polymer plays a most important role in a pulsatile drug delivery system. The following are examples of the most widely used polymers:

1) Ethylcellulose
2) Microcrystalline cellulose
3) Methocel E50
4) Delonix regia gum (DRG) and HPMC K4M
5) Hydroxypropyl methylcellulose acetate succinate (HPMCAS)
6) Calcium silicate
7) Sodium alginate [41-43]

Table 1: Diseases Requiring Pulsatile Drug Delivery:[14,16-18]

Class	Disease	Chronological behaviour	Drugs used
Gastro-Intestinal	Peptic ulcer	Acid secretion is higher in the afternoon and at night	H2 blocker
Respiratory	Asthma	Pain at night or early morning	B2 Agonist, Antihistamines
Hyperglycaemia	Diabetes mellitus	Blood sugar level after meal is increased	Sulfonylurea, Insulin, Biguanide
Cardiovascular	Hypertension	BP is lowest during the sleep, rises in the early morning	Nitroglycerin, calcium channel blocker, ACE inhibitors.
Inflammation	RA	Pain in the morning and more pain at night	NSAID, Glucocorticoids

Table 2: Evaluation of weight variation [26]

Average Weight of Tablets	Maximum Difference
80 mg or less	10%
More than 80 mg but less than 250 mg	7.5%
250 mg or more	5%

Table 3: Marketed Technologies of Pulsatile Systems [35-40]

Technology	Technology Mechanism	Proprietary Name and Dosage form	API	Disease
Pulsincap™	Rupturable system	Pulsincap™	Dofetilide	Hypertension
OROS	Osmotic mechanism	Covera-H5; XL tablet	Verapamil HCl	Hypertension
DIFFUCAPS	Multiparticulate system	Innopran; XL tablets	Verapamil HCl, propranolol HCl	Hypertension
3D printing	Externally regulated system	Their Form	Diclofenac sodium	Inflammation
CODAS®	Extended-release capsule	Verelan® PM	Verapamil HCl	Hypertension
TIMERx®	Erodible/ soluble barrier coating ER Tablets	OPANA®	Oxymorphone	Pain management
CONTIN®	Extended-release tablet	Uniphyl®	Theophylline	Asthma
Physico-chemical modification of API	Tablet	Zocor®	Simvastatin	Hypercholesterolemia

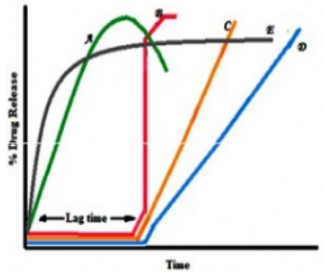

Figure 1: Drug Release Profiles from Pulsatile Drug Delivery System.[19,20,44]

Where A: Conventional release profile; B: Burst release of drug a after a lag time; C: Delayed-release profile after a lag time; D: Constant release profile in the prolonged period after lag time; E: Extended-release profile without lag time

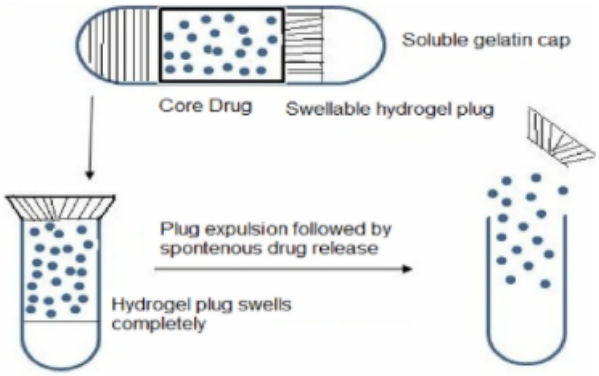

Figure 2: Single unit capsule-based system[23]

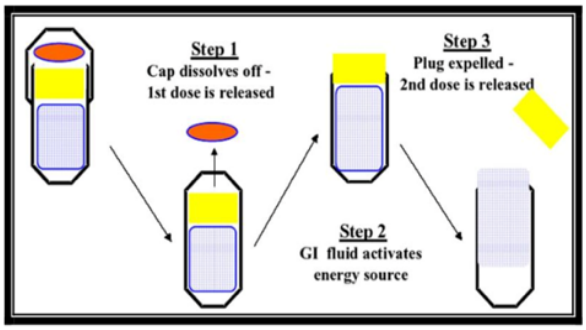

Figure 3: Port system[23]

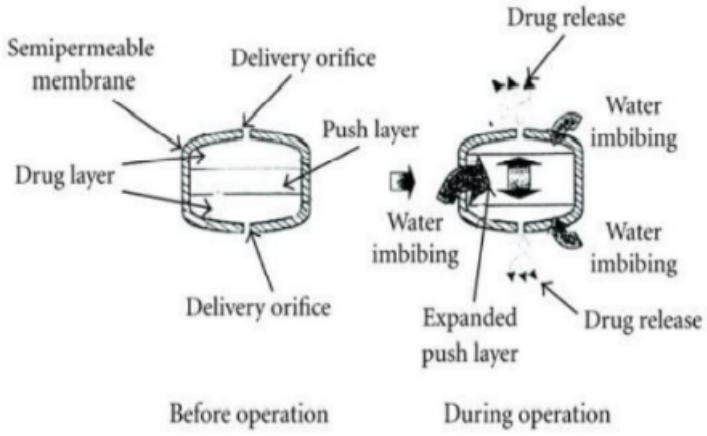

Figure 4: Expandable orifice system[16,17]

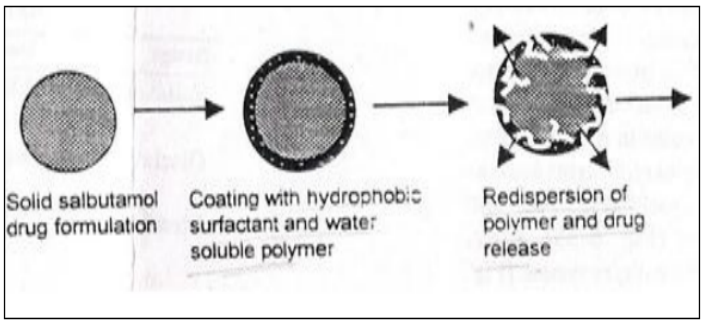

Figure 5: Time clock system [16,17]

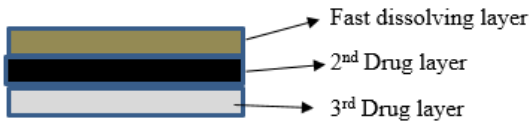

Figure 6: Multi-layer tablet system [11, 20]

CONCLUSION

Pulsatile systems are gaining popularity because they deliver drugs at the precise site of action at the right time and amount, offering spatial and temporal delivery and boosting patient compliance. Patients with asthma, high blood pressure, diabetes, and other illnesses benefit from this pulsatile drug delivery system. Extended and immediate-release formulations are ineffective in treating disorders, particularly those having chronological pathophysiology, for which pulsatile medication administration is advantageous.

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