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Review Article

An updated review on pulsatile drug delivery system

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Abstract

Pulsatile Drug Delivery Systems are gaining a lot of interest as they deliver the drug at the right place, at the right time and in the right amount, thus providing spatial, temporal and smart delivery and increasing patient compliance. The use of pulsatile release of the drugs is desirable where constant drug release is not desired. PDDS can be classified into time controlled systems wherein the drug release is controlled primarily by the delivery system; stimuli induced PDDS in which release is controlled by the stimuli, like the pH or enzymes present in the intestinal tract or enzymes present in the drug delivery system and externally regulated system where release is programmed by external stimuli like magnetism, ultrasound, electrical effect and irradiation. The current article focuses on the diseases requiring PDDS, methodologies involved for the existing systems, current situation and future scope, recent advances in PDDS and PDDS product currently available in the market.

1. Introduction

Pulsatile systems are gaining a lot of interest as they deliver the drug at the right site of action at the right time and in the right amount, thus providing spatial and temporal delivery and increasing patient compliance. The release of the drug as a pulse after a lag time has to be designed in such a way that a complete and rapid drug release follows the lag time. These systems are designed according to the circadian rhythm of the body. The principle rationale for the use of pulsatile release is for the drugs where a constant drug release, i.e., a zero-order release is not desired. **[1, 2]**

1.1 Chronopharmacotherapy

Recent studies show that diseased have predictable cyclic rhythms and the timing of medication regimens can improve outcome in selected chronic conditions. “Chronopharmaceutics” consist of two words chronobiology and Pharmaceutics. Chronobiology is the study of biological rhythms and their mechanisms. There are three types of mechanical rhythms in our body, they are:-

Circadian, Ultradian, Infradian

1.1.1 Circadian: “Circa” means about and “dies” means day

1.1.2 Ultradian: Oscillation of shorter duration is termed as ultradian (more than one cycle per 24 h).

1.1.3 Infradian: Oscillations that is longer than 24 h (less than one cycle per day). **[3, 4]**

2. Necessities of pulsatile drug delivery system

2.1 First pass metabolism: Some drugs, such as beta blockers and salicylamide, undergo extensive first pass metabolism and require fast drug input to saturate metabolizing enzymes. Thus, a constant/sustained oral method of delivery would result in reduced oral bioavailability.

2.2 Biological tolerance: Drug plasma profiles are often accompanied by a decline in the pharmacotherapeutic effect of the drug, e.g., biological tolerance of transdermal nitroglycerin, salbutamol sulphate.

2.3 Special chrono pharmacological needs: Circadian rhythms in certain physiological functions are well established. It has been recognized that many symptoms and onset of disease occur during specific time periods of the 24 hour day, e.g., asthma and angina pectoris attacks are most frequently in the morning hours.

2.4 Local therapeutic need: For the treatment of local disorders such as inflammatory bowel disease, the delivery of compounds to the site of inflammation with no loss due to absorption in the small intestine is highly desirable to achieve the therapeutic effect.

2.5 Gastric irritation or drug instability in gastric fluid: Protection from gastric environment is essential for the drugs that undergo degradation in gastric acidic medium (e.g., peptide drugs), irritate the gastric mucosa (NSAIDS) or induce nausea and vomiting. **[5, 6]**

3. Advantages of pulsatile drug delivery system:

1. Extended daytime or night time activity
2. Reduced side effects
3. Reduced dosage frequency
4. Reduction in dose size
5. Improved patient compliance
6. Lower daily cost to patient due to fewer dosage units are required by the patient in therapy.
7. Drug adapts to suit circadian rhythms of body functions or diseases.
8. Drug targeting to specific site like colon.
9. Protection of mucosa from irritating drugs.
10. Drug loss by extensive first pass metabolism is prevented.
11. Patient comfort and compliance: Oral drug delivery is the most common. **[7]**

4. Limitations of pulsatile drug delivery system:

1. Multiple manufacturing steps in multiparticulate pulsatile drug delivery system.
2. Low drug load.
3. Incomplete release.
4. *In-vivo* variability in single unit pulsatile drug delivery system. **[8]**

5. Diseases requiring pulsatile drug delivery:

Thorough understanding of the disease physiology is required before designing the pulsatile drug delivery system. A disease where rhythmic circadian organization of the body plays an important role, pharmacokinetics and/or pharmacodynamics of the drugs is not constant within 24 h. Table1 enumerates various diseases showing such a chronological behavior. Asthma is one such disease where pulsatile drug delivery system can be useful. Circadian changes are seen in normal. **[9, 10]**

Table 1: Chronological behavior of diseases and drugs used

S. No.	Disease	Chronological behavior	Drugs used
1	Peptic ulcer	Acid secretion is high in the afternoon and at night	H_2 blockers
2	Asthma	Precipitation of attacks during night or at early morning hours	β_2 agonist, antihistaminic
3	Cardiovascular diseases	BP is at its lowest during the sleep cycle and rises steeply during the early morning awake	Nitroglycerin, Calcium channel
4	Arthritis	Pain in the morning and more pain at night	NSAIDs, Glucocorticoids
5	Diabetes mellitus	Increase in the blood sugar level after meal	Sulfonylurea, Insulin, Biguanide

6. Methodologies for PDDS:

From technological point of view pulsatile drug release system are further divided to single and multiple units system.

6.1 Single unit system:

6.1.1 Capsule Based: Amidon and Leesman described a drug delivery system for administering a drug in controlled pulse doses to an aqueous environment in the body of a living being. The formulation comprises of one or more, and preferably less than ten, individual drug-containing subunits in a unitary drug depot, such as a tablet or capsule. The individual subunits are designed to dissolve at different sites and/or times in the gastrointestinal tract to release pulse doses of drug into the portal system in an analogous manner to the rate of release from an immediate release dosage form administered according to an appropriate dosing schedule. The dissolution time of the individual subunits can be controlled by several methods including the provision of pH sensitive enteric coatings and permeability-controlled coatings. The drug delivery system has significant advantages for the oral administration of first-pass metabolized drugs which exhibit a non-linear relationship between input rate of the drug into the portal system and bioavailability.

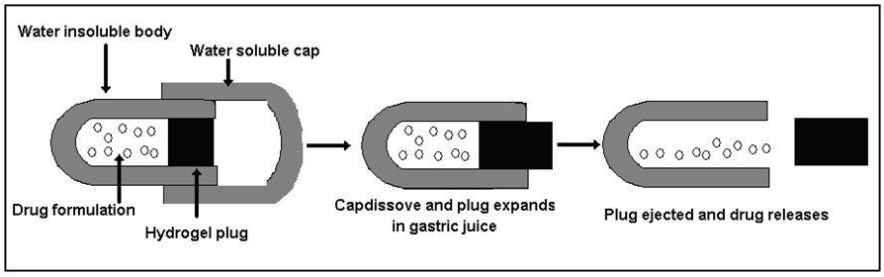

Fig. 1: Schematic diagram of capsular system

Percel and coworkers described a capsule capable of delivering therapeutic agents in the body in a time controlled or position-controlled pulsatile release fashion, composed of one or more populations of multicoated particulates (beads, pellets, granules, etc.). Each bead has been prepared by coating an inert particle such as a nonpareil seed (sugar sphere), with a drug and a polymeric binder or by preparing a drug containing particle by granulation and/or extrusion-spheronization, coating the active drug particle with a plasticized enteric coating, and coating plasticized enteric coated drug particle with a mixture of a water insoluble polymer and an enteric polymer. One of the membrane barriers is composed of an enteric polymer while the second membrane barrier is composed of a mixture of water insoluble polymer and an enteric polymer. The composition and the thickness of the polymeric membrane barriers determine the lag time and duration of drug release from each of the bead populations. Optionally, an organic acid containing intermediate membrane may be applied for further modifying the lag time and/or the duration of drug release. Jenkins described a Multiparticulate modified release composition in an erodable, diffusion controlled or osmotic form designed to release the active ingredients at about six to twelve hours so that the resulting plasma profile is substantially similar to the plasma profile produced by the administration of the two or more immediate release dosage forms given sequentially. The composition can be in the form of an erodable formulation in which the structural integrity of the particulates deteriorates within the body over time, in the form of a diffusion controlled formulation in which the particulates are dispersed in a liquid medium or in the form of an osmotic controlled formulation in which the release of the active ingredient from the composition is controlled by osmosis.

6.1.2 Osmotic based pump capsule: Osmotic delivery capsules ("osmotic pumps") function by virtue of walls which selectively pass water into the capsule reservoir. Absorption of water by the capsule through these walls is driven by a water-attracting agent in the capsule interior which creates osmotic pressure across the capsule wall. The water-attracting agent may be the beneficial agent itself whose controlled release is sought, but in most cases, it is a separate agent specifical1y selected for its ability to draw water, and this separate agent is being isolated from the beneficial agent at one end of the capsule. In either case, the structure of the capsule wall does not permit the capsule to expand, and as a result, the water uptake causes discharge of the beneficial agent through an orifice in the capsule at the same rate that water enters by osmosis.

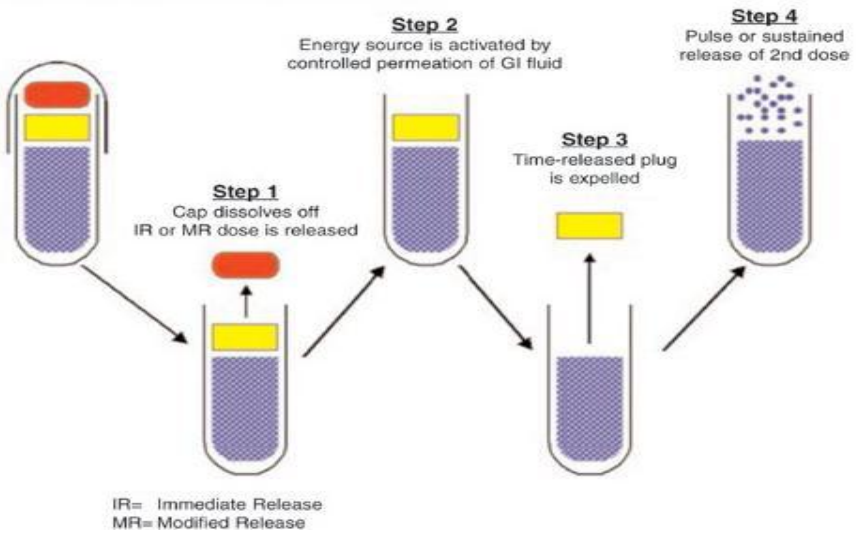

Fig. 2: Different type of osmotic pumps used for PDDS

Linkwitz and coworkers proposed a drug delivery capsule where drug delivery is driven by the osmotic infusion of moisture from a physiological environment. The capsule has a delivery orifice which opens intermittently to achieve a pulsatile delivery effect. The wall in which the orifice is formed is constructed of an elastic material (elastomer) which stretches under a pressure differential caused by the pressure rise inside the capsule as the osmotic infusion progresses. The orifice is so small that when the elastic wall is relaxed, the flow rate of drug through the orifice is substantially zero, but when the elastic wall is stretched due to the pressure differential across the wall exceeding a threshold, the orifice expands sufficiently to allow the release of the drug at a physiologically beneficial rate. The selection of the materials from which the device is constructed and the configuration of the device and its dimensions controls the length of time between pulses. **[11, 12, 13]**

6.1.3 Erodable Barrier System: Kim described a formulation of coated Donut Shaped Tablet (DST) and multi-layer DST so that immediate release or time-delayed release can be achieved. Both zero order or first order extended release kinetics are possible, depending on the excipients and types of drugs in the tablet formulation. The coating layer for time delay is made of high molecular weight water soluble polymers so that the dose dumping can be minimized even when the hydrated surface of the DST and MLDST peels off. Low molecular weight water soluble polymer coatings having a drug dispersed may be employed to provide a pulsatile release of a drug

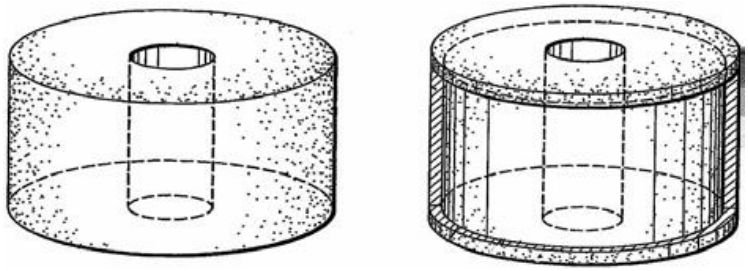

Fig. 3: a) Coated Donut Shaped Tablet (DST) and b) multi-layer DST MLDST's

So that immediate release or time-delayed release of a drug proposed by Kim. Kohn and coworkers uses the degradation products of one polymer to trigger the release of the active compound from another polymer. The delayed release of the active compound was achieved without using a barrier system that requires complex and sophisticated formulation techniques.

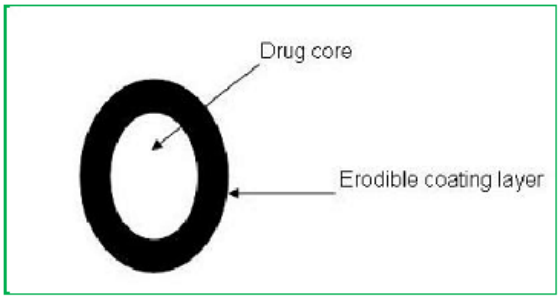

Fig. 4: Schematic diagram of delivery system of erodible coating layer.

The proposed formulation comprises the biologically active compound having a chemical structure with hydrogen bonding sites dispersed in a biocompatible, hydrolytically degrading polyarylates. In the case of peptide drugs, interactions between the peptide and the first polymer inhibit the release of the peptide. Bonding interactions between the polymer and the active compound are used to lock the active compound into the polymeric matrix. In order to control the time of peptide release from polyarylates, a second biocompatible polymer but less hydrophobic than polyarylates is also used. The second polymer can be degraded into acidic byproducts into the matrix. This is necessary because the hydrogen bonding interactions can be weakened under conditions of low pH, resulting in the release of the peptide. Degradation products lower the pH of the matrix, causing an interruption in the interactions and the subsequent release of the peptide. **[14-16]**

6.1.4 Rapturable Layers: A novel formulation for once daily administration (prior to sleeping) that provides an initial delay followed by controlled release of the drug. A method for preparing a time specific delayed, controlled release formulation of dosage is also provided which method includes coating a single pellet with at least one dosage layer, which is coated by at least one seal coat and at least one outer rate controlling layer of a water soluble polymer coat. The formulation affords excellent bioavailability while avoiding fluctuating blood levels. By that way, it is possible to maintain drug plasmatic concentrations in a desired, effective range in a circadian fashion while simplifying the administration of the drug to only once daily. **[17, 18]**

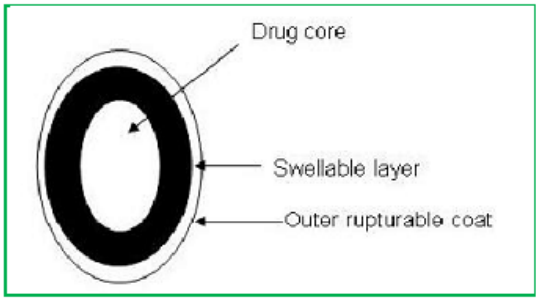

Fig. 5: Schematic diagram of delivery system with rupturable coating layer

6.2 Multiple units:

6.2.1 Systems Based on Change in Membrane Permeability: Numerous pharmaceutical forms with delayed release for oral administration are available. As already mentioned the release of the drug must be controlled according to therapeutically purpose and the pharmacological properties of the active ingredient. In consequence, it is not always desirable the blood levels to be constant. On the contrary, in order to avoid any habituation and in order to limit the side effects provoked by the active ingredient, it would be absolutely advantageous for the plasmatic rate to follow the metabolic rhythm and the specific needs of the patient during certain periods. For instance, in order to diminish the nocturnal symptoms or the symptoms upon awakening in the case of certain chronic diseases such as ischemic heart disease, asthma and arthritis, the drugs should be administered in such a way that the desired therapeutically plasmatic level is reached only at the desired moment, i.e. during sleep or at the moment of awakening Dosage form for Pulsatile release proposed by Chen containing a plurality of different pellets composed with a core and several coating layers. Chen described a dosage form for delivering drugs into the body in a series of sequential, pulsatile releasing events. The system can be used with drugs which cannot be released by diffusion through a porous coating, such as water insoluble drugs. A plurality of populations of pellets is provided within a unit dosage form such as a capsule or tablet. **[19,20]**

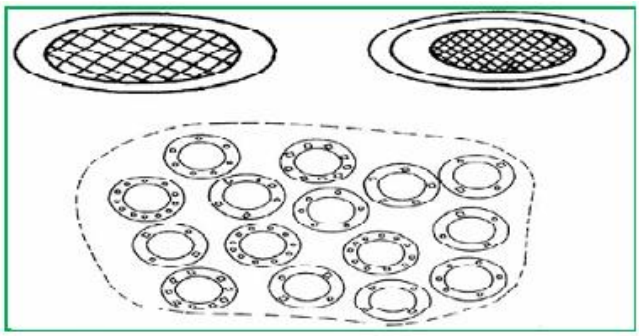

Fig. 6: Dosage form of pulsatile release proposed by chen containing a plurality of different pellets

Composed with a core and several coating layer Dosage form for pulsatile release proposed by Chen containing a plurality of different pellets composed with a core and several coating layers. The pellets are composed of a core containing the drug and a swelling agent which expands in volume when exposed to water. The core is enclosed within a membrane or coating which is permeable to water. The membrane is composed of a water insoluble and permeable film forming polymer, a water soluble film forming polymer and a permeability reducing agent. When the unit dose releases the pellets into the digestive tract, water diffuses through the coating and into the core. As water is taken up by the swelling agent, the core expands, exerting force on the coating until it bursts, releasing the drug. The permeability reducing agent reduces the rate at which water reaches the swelling agent, thereby delaying release time. The water soluble polymer dissolves, weakening the coating so that it bursts sooner. By varying the proportions of the three coating ingredients and/or coating thickness from one pellet population to another, the release timing of the pellets can be very effectively controlled. **[21, 22]**

Table 2: Marketed technologies of pulsatile system

Pulsincap® Scherer DDS, Ltd	A water impermeable capsule body with hydro gel plug. Plug length and insertion depth controls lag time. Patent No. US5631022
PULSYS ™ MiddleBrook Pharmaceuticals™	The typical PULSYS drug delivery format is a tablet containing multiple pellets with different release profiles
Diffucaps® Eurand	The active drug is layered onto a neutral core (such as cellulose spheres) and then one or more rate-controlling, functional membranes are applied. Patent No. US73877938
Orbexa® Eurand	This technology produces beads that are of controlled size and density using granulation, spheronization and extrusion techniques.
OROS® Push Pull™ Alza	A bilayer / trilayer tablet core consisting of one or more drug layers, surrounded by a semipermeable membrane with a drilled orifice.

7. Evaluation of pulsatile drug delivery system:

7. 1. Thickness and diameters: It is measured by using vernier calliper in mm.

7.2 Hardness: The hardness of tablet was measured by using monsanto hardness tester. The unit of hardness is kg/cm^2. **[23, 24]**

7.3 Friability: Friability of tablet was found to be USP friabilator. First of all tablet batch was weighed and placed in friabilator for 100 revolution in 4 minutes.

The % friability was calculated by

$F = (Wi-Wf)/ Wi\times100$

Where, Wi = initial weight

Wf = final weight. **[25, 26]**

7.4. Weight variation test: The USP weight variation test was done by weighing 20 tablets individually calculating average weight and comparing the individual weight to the average.

Table 3: Weight variation limit

S. No.	Average weight of tablet (mg)	Maximum difference
1	80mg or less	10 %
2	More than 80 mg but less than 250 mg	7.5%
3	250 mg or more	5%

7.5 Lag time and Drug release: The lag time and drug release studies was carried out in gastric and intestinal fluids at body tem. This test is performed in USP dissolution apparatus, in this test the tablet was placed in dissolution media and the sample was withdrawn at specific time interval and after that analyzed in UV spectroscopy. **[27-29]**

7.6 Rupture test: The Rupture test on coated tablets was carried out using USP paddle apparatus. Here all other Parameters were same as In-Vitro Dissolution Method. The time at which the outer coating layer starts to rupture is called as lag time. This was determined by Rupture test. **[30]**

7.7 Drug content: In this test accurately weight amount of powder was dissolved in water and filtered. After that the absorbance was measured at fixed wave length by UV spectrophotometer.

7.8 Water uptake study: The % water uptake of pulsatile release tablets was determined in medium filled container placed in a horizontal shaker (100 ml of 0.1 N Hcl, 37.5 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 follow:

%Water uptake= [(Wt-Wo/Wo)] 100 where, Wt- weight of tablet at time t and Wo - is weight of dry tablet.

7.9 Swelling index: The individual tablets were weighed accurately and kept in 50 ml of double distilled water. Then tablets were taken out properly after 60 min., then blotted with filter paper so as to remove the water present on the surface and weighed accurately. Percentage swelling index (SI) was calculated by using the formula

SI = (Wet weight – Dry weight / Dry weight) X 100. **[31]**

8. Conclusion

The literature review relating to this formulation strongly recommending constant need for new delivery systems that can provide increased therapeutic benefits to the patients. Pulsatile drug delivery is one such system that, by delivering a drug at right time, right place, and in right amounts, holds good promises of benefit to the patients suffering from chronic problems like arthritis, asthma, hypertension, etc. Extended release formulations and immediate release formulation are not efficient in treating the diseases especially diseases with chronological pathopysiology, for which, pulsatile drug delivery is beneficial. The drug is delivering in this system when its actual concentration is needed as per chronological need, so pulsatile release systems should be promising in the future.

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