Review Article

AN APPROACH ON PULSATILE DRUG DELIVERY SYSTEM

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ABSTRACT

Pulsatile drug delivery systems (PDDS) are gaining importance as these systems deliver the drug at specific time as per the pathophysiological need of the disease, resulting in improved patient therapeutic efficacy and compliance. A Pulsatile drug release, where the drug is released rapidly after a well defined lag-time.. A pulse has to be designed in such a way that a complete and rapid drug release is achieved after the lag time so as to match body's circadian rhythms with the release of drug which increases the efficacy and safety of drugs by proportioning their peak plasma concentrations during the 24 hours in synchrony with biological rhythm. Various techniques are available for the pulsatile delivery like pH dependent systems, time dependent systems, etc. Pulsatile release systems can be classified in multiple-pulse and single-pulse systems. These systems are beneficial for drugs having high first-pass effect; drugs administered for diseases that follow chronopharmacological behavior, drugs having specific absorption site in GIT, targeting to colon, and cases where night time dosing is required. Therefore Pulsatile drug delivery is one such systems that, by delivering drug at the right time, right place and in right amounts, holds good promises of benefit to the patients suffering from chronic problems like arthritis, asthma, hypertension.

Keywords: pulsatile drug delivery system, circadian rhythms, lag- time, plasma concentrations, chronopharmacology.

INTRODUCTION

The emphasis of pharmaceutical research is turned towards the development of more efficacious drug systems with already existing molecule rather going for new drug discovery because of the inherent delivery hurdles posed in drug discovery and development process. Pulsatile drug delivery systems are gaining a lot of interest and attention these days. These systems have a peculiar mechanism of delivering the drug rapidly and completely after a lag time, i.e no drug release. Though most delivery systems are designed for constant drug release oveprolonged period of time, pulsatile delivery systems are characterized by a programmed drug release, as constant blood levels of a drug may not always be desirable .Pulsatile systems are designed in a manner that the drug is available at the site of action at the right time in the right amount. These systems are beneficial for drugs having high first-pass effect; drugs administered for diseases that follow chronopharmacological behavior, drugs having specific absorption site in GIT, targeting. The oral controlled release system shows a typical pattern of drug release in which the drug concentration is maintained in the therapeutic window for a prolonged period of time (sustained release), thereby ensuring sustained therapeutic action.

Advantages

1. Predictable, reproducible and short gastric residence time.
2. Less inter- and intra-subject variability.
3. Improve bioavailability.
4. No risk of dose dumping.
5. Flexibility in design.
6. Improve stability.

Drawbacks

1. Manufacturing reproducibility and efficacy.
2. Large number of process variables.
3. Multiple formulation steps.
4. Higher cost of production.
5. Need of advanced technology.

DISEASES REQUIRING PULSATILE DELIVERY

Recent studies have revealed that diseases have predictable cyclic rhythms and that the timing of medication regimens can improve outcome in selected chronic conditions. The list of diseases which are required pulsatile release given in table 1.

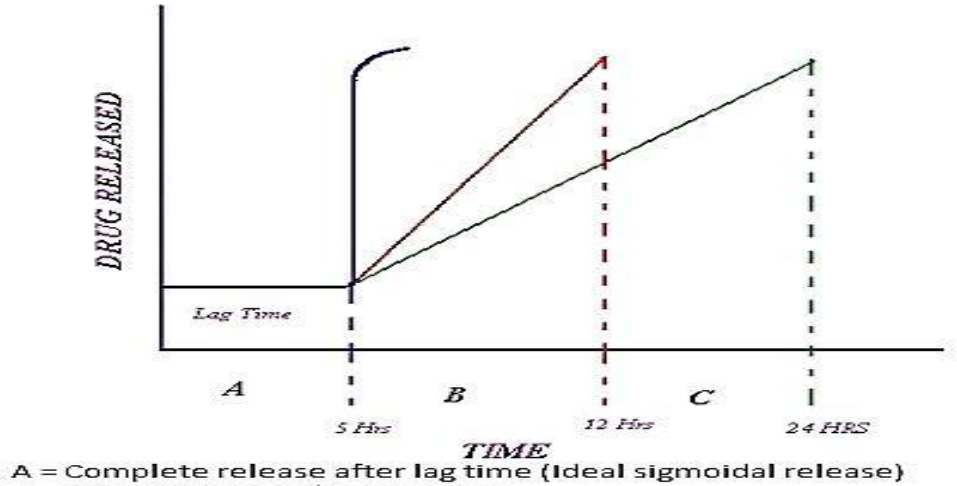


Table 1: Drugs used in pulsatile delivery system

Chronological behavior	Drugs used	Diseases
Pain in the morning and more pain at night.	NSAIDS and glucocorticoids.	Arthritis.
Precipitation of attacks during night or at early morning.	β_2 agonist, Antihistamines	Asthma.
BP is at its lowest during the sleep cycle and rises steeply during the early morning.	Nitroglycerin, ACE inhibitors, Calcium channel blockers.	Cardiovascular diseases.
Acid secretion is high in the afternoon and at night	H_2 blockers.	Peptic ulcer.
Increase in the blood sugar level after meal.	Sulfonylurea, Insulin.	Diabetes mellitus.
Cholesterol synthesis is generally higher during night than day time.	HMG CoA reductase Inhibitors.	Hypercholesterolemia.
Increase in DOPA level in afternoon.	Methylphenidate.	Attention deficit syndrome.

METHODS FOR PULSATILE DRUG DELIVERY

Methodologies for the pulsatile drug delivery system can be broadly classified into four classes;

A. Time controlled.
B. Stimuli induced.
C. Externally regulated.
D. Multi particulate.

A. Time controlled pulsatile release system: In time controlled drug delivery systems pulsatile release is obtained after a specific time interval in order to mimic the circadian rhythm. Such type of pulsatile drug delivery system contains two components

1. Immediate release type
2. Pulsed release type.

a. Delivery systems with rupturable coating layer: Most pulsatile delivery systems are reservoir devices coated with a rupturable polymeric layer. Upon medium ingress, drug is released from the core after rupturing of the surrounding polymer layer, due to pressure buildup within the system. The pressure necessary to rupture the coating can be achieved with swelling agents, gas producing effervescent excipients or increased osmotic pressure. Water permeation and mechanical resistance of the outer membrane are major factors affecting the lag time[5].

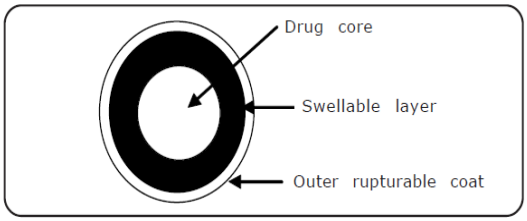


Diagram of drug delivery with rupturable coating layer

b. Delivery system with erodible coating layers

In such systems, the core containing drug is coated with the soluble or erodible polymer as outer coat and drug release is controlled by the

dissolution or erosion of the outer coat. Time dependent release of the drug can be obtained by optimizing the thickness of the outer coat.

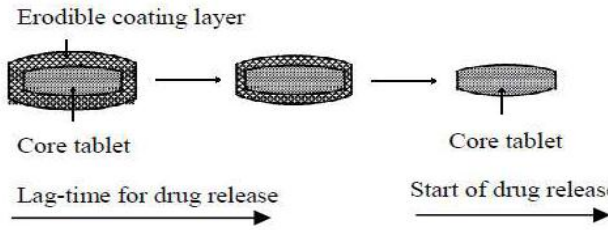


Diagram of drug delivery with erodible coating layer

c. Capsule shaped system provided with release controlling plug : This dosage form consists of an insoluble capsule body containing a drug and swellable and degradable plugs made of approved substances such as hydrophilic polymers or lipids and release controlling plug between immediate release compartment and pulsed release compartment. On contact with aqueous fluids, the cap rapidly dissolves thereby releasing the immediate release component followed by pulsed release component.

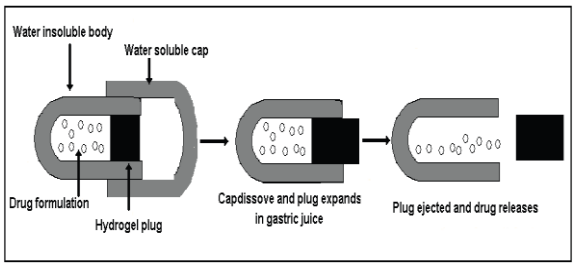


Diagram of release of drug from capsule

d. Pulsatile system based on Osmosis

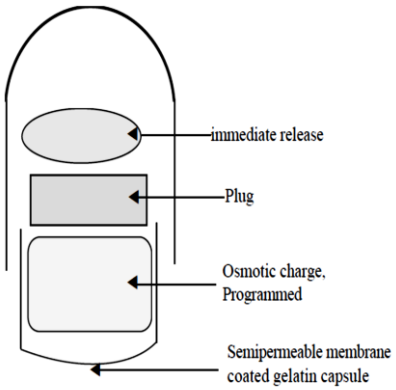


Diagram of osmosis system

Osmotic system consists of capsule coated with the semipermeable membrane. Inside the capsule there is an insoluble plug consisting of osmotically active agent and the drug formulation.

B. Stimuli induced pulsatile systems: In these systems there is release of the drug after stimulation by any biological factor like temperature, or any other chemical stimuli. These systems are further classified in to temperature induced systems and chemical stimuli induced system, on the basis of stimulus.

a. Temperature induced systems: Temperature is the most widely utilized triggering signal for a variety of triggered or pulsatile drug delivery systems. The use of temperature as a signal has been justified by the fact that the body temperature often deviates from the physiological temperature (37˚C) in the presence of pathogens or pyrogens. This deviation sometimes can be a useful stimulus that activates the release of therapeutic agents from various temperature-responsive drug delivery systems for disease accompanying fever. Thermal stimuli-regulated pulsed drug release is established through the design of drug delivery device such as hydrogels and micelles.

1. Thermo-responsive hydrogel systems
2. Thermo-responsive polymeric micelle systems

b. Chemical stimuli induced pulsatile systems: In these systems, there is release of the drug after stimulation by any biological factor like enzyme, pH or any other chemical stimuli. In these systems, the polymer undergoes swelling or Deswelling phase in response to chemical reaction with membrane, alteration of pH and Inflammation induce, release of drug from polymer by swelling the polymer.

I. Glucose-responsive insulin release devices
II. pH sensitive drug delivery system
III. Inflammation-induced pulsatile release

C. Externally regulated pulsatile release system: This system is not self-operated, but instead requires externally generated environmental changes to initiate drug delivery. These can include magnetic fields, ultrasound, electricfield, light, and mechanical force.

a. Magnetic induces release: Magnetic carriers receive their magnetic response to a magnetic field from incorporated materials such

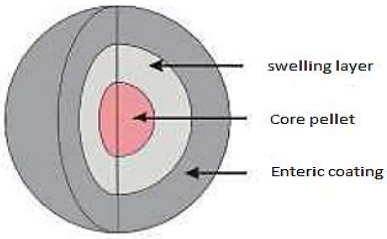
as magnetite, iron, nickel, cobalt etc. An intelligent magnetic hydrogel (ferrogel) was fabricated by mixing poly vinyl alcohol (PVA) hydrogels and Fe_3O_4 magnetic particles through freezing-thawing Cycles. Although the external direct current magnetic field was applied to the ferrogel, the drug get accumulated around the ferrogel, but the accumulated drug spurt to the environment instantly when the magnetic fields instantly switched "off". Furthermore, rapid slow drug release can be tunable while the magnetic field was switched from "off" to "on" mode. The drug release behavior from the ferrogel is strongly dominated by the particle size of Fe_3O_4 under a given magnetic field.

b. Ultrasound induces release: Ultrasound is mostly used as an enhancer for the improvement of drug permeation through biological barriers, such as skin. The interactions of ultrasound with biological tissues are divided into two broad categories: thermal and non-thermal effects. Thermal effects are associated with the absorption of acoustic energy by the fluids or tissues. Non-thermal bio-effects are generally associated with oscillating or cavitating bubbles, but also include non-cavitations' effects such as radiation pressure, radiation torque, and acoustic streaming.

c. Electric field induces release: As an external stimulus have advantages such as the availability of equipment, which allows precise control with regards to the magnitude of current, duration of electric pulses, interval between pulses etc. Electrically polyelectrolyte's (polymers which contain relatively high concentration of ionisable groups along the backbone chain) and are thus, pH-responsive as well as electro-responsive. Under the influence of electric field, electro-responsive hydrogels generally deswell or bend, depending on the shape of the gel lies parallel to the electrodes whereas deswelling occurs when the hydrogel lies perpendicular to the electrodes

d. Light induces release: Light-sensitive hydrogels have potential applications in developing optical switches, display units, and ophthalmic drug delivery devices. The interaction between light and material can be used to modulate drug delivery. When hydrogel absorb the light and convert it to heat, raising the temperature of composite hydrogel above its LCST, hydrogel collapses and result in an increased rate of release of soluble drug held within the matrix**.**

D. Multi particulate pulsatile drug delivery system: The purpose of designing multiparticulate dosage form is to develop a reliable formulation that has all the advantages of a single unit formulation and yet devoid of the danger of alteration in drug release profile and formulation behavior due to unit to unit variation. The release of drug from micro particles depends on a variety of factors including the carrier used to form the multiparticles and the amount of drug contained in them. The expected drug-release mechanism and corresponding target bimodal plasma concentration profile of the above designed multiparticulate pulsatile system.



Hypothetical design of a multiparticulate pulsatile system

a. Reservoir systems with rupturable polymeric coatings: Most multiparticulate systems are reservoir devices coated with a rupturable polymeric layer. Upon water ingress, drug is released from the core after rupturing of the surrounding polymer layer, due to pressure buildup within the system. The pressure necessary to rupture the coating can be achieved with swelling agents, gas producing effervescent excipients or increased osmotic pressure. Water permeation and mechanical resistance of the outer membrane are major factors affecting the lag time.

b. Reservoir systems with soluble or eroding polymer coatings: Another class of reservoir-type multiparticulate pulsatile systems is based on soluble/erodible layers in place of rupturable coatings. The barrier dissolves or erodes after a specific lag time followed by burst release of drug from the reservoir core. In general, for this kind of systems, the lag time prior to drug release can be controlled by the thickness of the coating layer. However, since from these systems release mechanism is dissolution, a higher ratio of drug solubility relative to the

dosing amount is essential for rapid release of drug after the lag period.

c. Floating multiparticulate pulsatile systems

Multiparticulate pulsatile release dosage forms mentioned above are having longer residence time in the GIT and due to highly variable nature of gastric emptying process, may resulted in *In-vitro – In*-vivo relationship was poor and bioavailability problems. In contrary, floating multiparticulate pulsatile dosage forms reside in stomach only and not affected by variability of pH, local environment or gastric emptying rate. These dosage forms are also specifically advantageous for drugs either absorbed from the stomach or requiring local delivery in stomach. Overall, these considerations led to the development of multiparticulate pulsatile release dosage forms possessing gastric retention capabilities.

CONCLUSION

Circadian rhythm of the body is an important concept for understanding the optimum need of drug in the body. There is a 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 drug at the 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. Thus designing of proper pulsatile drug delivery will enhances the patient compliance, optimum drug delivery to the target site and minimizes the undesired effects. The approaches in this article represent attempts conducted over the past decade to achieve pulsatile.

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