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RESEARCH ARTICLE

Pros and cons of pulsatile drug delivery system

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Abstract:

Pulsatile drug delivery systems (PDDS) have diverted attention because of their variety of advantages over traditional drug delivery systems. It deliver the required drug at the right time, at the right site of action and in the desired amount, it provides more benefits than conventional dosages and increased patient compliance. These systems are fabricated as per the circadian rhythm of the body, and the drug is released rapidly and completely as a pulse after a lag time in the human body. These systems are suitable for the drug with chronopharmacological behavior, where night time dosing is required, and for drugs that show extensive first pass effect. This review covers methods and marketed technologies that have been developed to obtain pulsatile delivery. Diseases wherein PDDS are highly suitable include asthma, peptic ulcer, cardiovascular ailments, arthritis and attention deficit syndrome in children and hypercholesterolemia.

Keywords: Pulsatile, Drug delivery, Circardian rhythm, Chronobiology

Introduction

In healthy human being, various pathophysiological processes occur only at certain times of the day or at a specific interval of time. It has been observed that the exacerbation of disease also follows a circadian rhythmic pattern. With the knowledge of time at which the disease shows peak and trough phenomenon, dosage forms can be designed in a time-controlled manner so as to maximize the drug response and minimize its side effects[1-5].

Circadian rhythm regulates many body functions in humans, viz., metabolism, physiology, behavior, sleep patterns, hormone production, etc. It has been reported that more shocks and heart attacks occur during morning hours. The level of cortisol is higher in the morning hours, and its release is reported to decline gradually during the day. Blood pressure is also reported to be high in the morning till late afternoon, and then drops off during night. Patients suffering from osteoarthritis are reported to have less pain in the morning than night, while patients suffering from rheumatoid arthritis feel more pain in the morning hours.

To treat these conditions the release of drugs is preferred in pulses. A single dosage form provides an initial dose of drug followed by one release-free interval, after which second dose of drug is released, which is followed by additional release-free interval and pulse of drug release. Pulsatile drug delivery system offers some important advantages like extended daytime or night time activity, Reduced side effects, Reduced dosage frequency, Reduction in dose size, Improved patient compliance, Lower daily cost to patient due to fewer dosage units are required by the patient in therapy, Drug adapts to suit circadian rhythms of body functions or diseases, Drug targeting to specific site like colon, Protection of mucosa from irritating drugs, Drug loss is prevented by extensive first pass metabolism etc.

Thus, In recent years there is continuous interest in the development of Pulsatile drug delivery system which has number of advantages over conventional dosage forms for the treatment of some disease conditions like Hypertension, Angina Pectoris , Myocardial infarction, Asthma , ulcer , Rheumatoid arthritis, etc

Chronotherapeutics is a branch of pharmaceutics devoted to the design and evaluation of drug delivery systems that release a bioactive agent at a rhythm that ideally matches the biological requirement of a given disease therapy. Ideally, chronopharmaceutical drug delivery systems (ChrDDS) should embody time-controlled and site-specific drug delivery systems.

DISEASES THAT NEED PULSATILE DRUG DELIVERY:[6]

POLYMERS USED IN PULSATILE DRUG DELIVERY SYSTEM:
The system proposed by Langer and co-workers exploits the wide tailor ability of biodegradation of the polylactic-*co*-glycolic acid (PLGA) family of biocompatible polyesters. By varying the relative amounts of lactic acid and glycolic acid in the copolymer and also the molecular weight of the copolymer, one can controllably and widely vary the degradation rate of the material. To release bursts of drug at different times, several PLGA copolymers with different degradation rates were used as 'gatekeepers'. Each copolymer was designed to hold back a burst of drug until that particular membrane had degraded sufficiently to allow the drug to escape. Various grades of HPMC, Eudragit, CMC, HPC are also used as polymers for pulsatile drug delivery system.

CLASSIFICATION OF PULSATILE DRUG DELIVERY SYSTEMS:

I. Time controlled pulsatile drug delivery:

A) SINGLE UNIT PULSATILE SYSTEMS:

1) Capsule based systems: [7,8.]

a) Pulsincap:
It is one of the system in which water-insoluble capsule enclosing the drug reservoir. When this capsule comes in contact with the dissolution fluid, it swells and after a lag time the plug pushes itself outside the capsule and the drug is released rapidly from the dosage form.

2) Systems based on Osmosis:
a. Port system:[9-11.]
This system comprising capsule coated with a semi permeable membrane. Inside the capsule was an insoluble plug consisting of osmotically active agent and the drug Formulation. When this capsule came in contact with the dissolution fluid, the semipermeable membrane allowed the entry of water, which caused the pressure to develop and the insoluble plug expelled after a lag time

b. Expandable orifice.
As the osmosis proceeds, the pressure within the capsule rises, causing the wall to stretch. The orifice is small enough so that when the elastic wall relaxes, the flow of the drug through the orifice essentially stops, but when the elastic wall is distended beyond threshold value, the orifice expands sufficiently to allow drug release at a required rate. For example, elastomers, such as styrene-butadiene copolymer have been suggested.

c. Series of stops:[12.]
This system is for implantable capsules. The capsule contains a drug and water-absorptive osmotic engine that are placed in compartments separated by a movable slider that provides pulsatile release of drug. The number of stops and the longitudinal placements of the stops along the length of the capsule dictate the number and frequency of the pulses, and the configuration of the partition controls the pulse intensity.

d. Solubility modulation:[13.]
Solubility modulator of system provides pulsed delivery of variety of drugs. The system was especially developed for delivery of salbutamol sulphate that contained sodium chloride as modulating agent.

(3) Pulsatile system with erodible coatings:
Most of the pulsatile drug delivery systems are reservoir devices coated with a barrier layer. This barrier erodes or dissolves after a specific lag period, and the drug is subsequently released rapidly from reservoir core.

B) multiparticulate / multiple unit systems:
1) Pulsatile system with rupturable coating:[14,15]
These systems depend on disintegration of the coat for the release of drug. The pressure needed for the rupture of the coating is achieved by effervescent excipients, swelling agents, or osmotic pressure. An effervescent mixture of citric acid and sodium bicarbonate incorporated in a tablet core coated with ethyl cellulose produced carbon dioxide after penetration of water into the core resulting in pulsatile release of drug after rupture of the coat.

a) System based on time controlled explosion:
In this system drug is coated on non-pareil sugar seeds followed by a swellable layer and In this an insoluble top layer coating. The swelling agents used include Superdisintegrants like sodium carboxymethyl cellulose, sodium starch glycollate and Polymers like polyvinyl acetate, polyacrylic acid, polyethylene glycol etc. Upon ingress of water, the swellable layer expands, resulting in rupture of film with subsequent rapid drug release. This release is independent of environmental factors like pH and drug solubility.

2) Rupturable coating system based on osmosis :
This system is based on a combination of osmotic and swelling effects. The core contains drug, a low bulk density solid and/or liquid lipid material (e.g. mineral oil) and a disintegrant. The core is finally coated with cellulose acetate. Upon immersion in aqueous medium, water penetrates the core displacing lipid material. After the depletion of lipid material, internal pressure increases until a critical stress is reached, which results in rupture of coat.

3) System with Change in Membrane Permeability: [16, 17.]

The permeability and water uptake of acrylic polymers with quaternary ammonium groups can be influenced by the presence of differe1nt counter-ions in the medium. Eudragit is a polymer of choice for this purpose.

II. 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 into-

1) Temperature induced systems: [18]
Thermo-responsive hydrogel systems have been developed for pulsatile release. In these systems the polymer undergoes swelling or de-swelling phase in response to the temperature which modulate drug release in swollen state.

2) Chemical stimuli induced pulsatile systems:
a) Glucose-responsive insulin release system: [19, 20.]
In case of diabetes mellitus there is rhythmic increase in the levels of glucose in the body requiring injection of the insulin at proper time. Several systems have been developed which are able to respond to changes in glucose concentration. One such system includes pH sensitive hydrogel containing glucose oxidase immobilized in the hydrogel. When glucose concentration in the blood increases glucose oxidase converts glucose into gluconic acid which changes the pH of the system. This pH change induces swelling of the polymer which results in insulin release.

b) Inflammation induced system : [21.]
On receiving any physical or chemical stress, such as injury, fracture etc., inflammation take place at the injured sites. During inflammation, hydroxyl radicals are produced from these inflammation- responsive cells.

c) System based on intelligent gels responding to antibody concentration:
There are numerous kinds of bioactive compounds which exist in the body. Recently, novel gels were developed which responded to the change in concentration of bioactive compounds to alter their swelling/reselling characteristics. Special attention was given to antigen-antibody Complex formation as the cross-linking units in the gel, since such interactions are very specific.

d) pH sensitive drug delivery system:[18.]
Such type of pulsatile drug delivery system contains two components one is of immediate release type and other one is pulsed release which releases the drug in response to change in pH. In case of pH dependent system advantage has been taken of the fact that there exists different pH environment at different parts of the gastrointestinal tract. By selecting the pH dependent polymers drug release at specific location can be obtained.

III. EXTERNALLY REGULATED PULSATILE DRUG DELIVERY

For releasing the drug in a pulsatile manner, another way can be the externally regulated Systems in which drug release is programmed by external stimuli like magnetism, ultrasound, electrical effect and irradiation. Magnetically regulated system contains magnetic beads in the implant. On application of the magnetic field, drug release occurs because of magnetic beads.

ADVANTAGES OF PULSATILE DELIVERY: [22.]

1. Pulsatile drug delivery system has a less side effects.
2. It is feasible to maintain dosage frequency.
3. This technology reduces dose size.
4. Patient compliance increases due to low dose and minimum dosage frequency.
5. It also provide target specific action to colon.
6. Drug loss is avoided due to extensive First pass metabolism.

DRAWBACKS OF PULSATILE DELIVERY: [23.]
1. Manufacturing reproducibility and efficacy is less.
2. There are large number of process variables.
3. It requires multiple steps for formulation.
4. It needs advanced technology.

NECESSITY OF PULSATILE DRUG DELIVERY SYSTEMS:[24,25.]
1. Human body follows circadian rhythm(their functions depends on time)
2. Many of diseases like bronchial asthma, myocardial infarction, angina pectoris, peptic ulcer, and hypertension are time dependent.
3. Most of the drugs produces biological tolerance and hence there is demand for a system that will prevent their continuous presence at the site of action. E.g. Salbutamol sulphate.
4. It is useful in case of drugs that undergoes extensive first pass metabolism.

8.RECENT MARKETED TECHNIQUES OF PULSATILE TECHNOLOGY:

Currently, pharmaceutical companies have been focused on developing and commercializing PDDS that fulfill unmet medical needs in the treatment of various diseases. Recently developed patented technologies are SODAS® Technology, IPDAS® Technology, CODAS™ Technology, GEOCLOCK® Technology, PULSYS™ Technology, Eurand's pulsatile and Chrono Release System, Magnetic Nanocomposite Hydrogel.

a) Spheroidal Oral Drug Absorption System (SODAS):[26]

This is based on the production of controlled release beads and it is characterized by its inherent flexibility.This technique can provide a number of drug release profiles including immediate release of drug followed by sustained release to give rise to a fast onset of action and which is maintained for 24 hours.

b) Intestinal Protective Drug Absorption System (IPDAS):

This Technology is intended for gastrointestinal irritant compounds. The IPDAS® technology is composed of numerous high density controlled release beads, which are compressed into a tablet form. Once an IPDAS® tablet is ingested, it rapidly disintegrates and disperses beads containing a drug in the stomach, which is then pass into the duodenum and along the gastrointestinal tract in a controlled and gradual manner, independent of the feeding state. Release of active ingredient from the multiparticulates occurs through a process of diffusion either through the polymeric membrane and or the micro matrix of polymer/active ingredient formed in the extruded/spheronized multiparticulates.

c) Chronotherapeutic Oral Drug Absorption System (CODAS):[5]

This technology was designed to release its drug component after a prolonged period of time when administered. E.g. Verelan® PM, which was designed to release Verapamil approximately four to five hours after ingestion.The release-controlling polymer is used which is a combination of water-soluble and water-insoluble polymers. When fluid from the gastrointestinal tract contacts the polymer coat beads the water-soluble polymer slowly dissolves, and the drug diffuses through the resulting pores in the coating. The water-insoluble polymer continues to act as a barrier, maintaining the controlled-release of the drug.

d) GEOCLOCK® Technology :[27]

Geoclock® tablets have an active drug inside an outer tablet layer consisting of a mixture of hydrophobic wax and brittle material in order to obtain a pH-independent lag time prior to core drug delivery at a predetermined release rate. This dry coating approach is designed to allow the timed release of both slow release and fast release active cores by releasing the inner tablet first after which the surrounding outer shell gradually disintegrates.

e) PULSYS™ Technology:

This is an oral drug delivery technology that enables once daily pulsatile dosing. The PULSYS™ dosage form is a compressed tablet that contains pellets designed to release drug at different regions in the gastro-intestinal tract in a pulsatile manner.

f) EURANDs pulsatile and chrono release System:[28.]

This system is capable of providing one or more rapid release pulses at predetermined times lag. They can useful to optimize efficacy and/or minimize side-effects of a drug substance.

g) Magnetic Nanocomposite Hydrogel:[20]

Magnetic nanocomposite was synthesized by incorporation of super paramagnetic Ferric oxide particles in temperature sensitive poly (N-isopropylacrylamide) hydrogels. High frequency alternating magnetic field was applied to produce pulsatile drug release from nanocomposite hydrogel.

h) Futuristic Prospect of PDDS:[29]

The development of pulsatile-release products is very challenging since it requires the correct dose to reach the right site at the appropriate time. Multiparticulate PDDS offer more advantages when compared with the single-unit pulsatile systems since it has predictable, reproducible and short gastric empty time with no risk of dose dumping.

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 release. It should be pointed that these drug delivery systems are still in the early developmental stage and much research will have to be conducted for such systems become practical clinical alternatives.

2.DISEASES NEED PULSATILE DRUG DELIVERY:[6]

Disease	Chronological behavior	Drugs used
Peptic ulcer	Acid secretion is generally high at midnight or at afternoon.	H_2 blockers
Asthma	Precipitation of attack during night or at early morning.	β blockers, Antihistaminics.
CVS related diseases	BP is lowered durind sleep cycle and rises at morning.	ACE Inhibitors, calcium channel blockers.
Diabetes mellitus	Blood sugar level is increases after meal.	Sulphonylureas, Biguanides.
Hypercholesterolemia	Cholesterol synthesis is higher during night time.	HMG CoA reductase inhibitors
Arthritis	Pain in the morning and more pain at night	Glucocorticoids.

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