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PULSATILE DRUG DELIVERY: A COMPREHENSIVE REVIEW

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ABSTRACT

Traditionally, drugs are released in an immediate or extended fashion. However, in recent years, pulsatile drug release systems are gaining growing interest. A pulsatile drug release, where the drug is released rapidly after a well defined lag-time, they deliver the drug at the right time, at the right site of action and in the right amount, which provides more benefit than conventional dosages. These systems are designed according to the circadian rhythm of the body, and the drug is released rapidly and completely as a pulse after a lag time. Pulsatile drug delivery systems (PDDS) can be classified into time controlled systems where the drug release is controlled primarily by the delivery system, stimuli induced PDDS in which release is controlled by the stimuli, such as the pH or enzymes present in the intestinal tract and externally regulated system where release is programmed by external stimuli like magnetism, ultrasound, and irradiation. Marketed technologies, such as Pulsin cap, Diffu caps, chronotherapeutic oral drug absorption system (CODAS), OROS and PULSYS, follow the above mechanism to render a sigmoidal drug release profile. Diseases wherein PDDS are promising include asthma, peptic ulcers, cardiovascular ailments, arthritis and attention deficit syndrome in children and hypercholesterolemia. Pulsatile drug delivery systems have the potential to bring new developments in the therapy of many diseases.

Keywords: Pulsatile drug delivery, Pulsin cap, Diffu caps, CODAS, OROS, PULSYS.

INTRODUCTION

Oral controlled drug delivery systems represent the most popular form of controlled drug delivery systems for the obvious advantages of oral route of drug administration. Such systems release the drug with constant or variable release rates. 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 [1]**.** However, there are certain conditions for which such a release pattern is not suitable. These conditions demand release of drug after a lag time. In other words, it is required that the drug should not be released at all during the initial phase of dosage form administration. Such a release pattern is known as pulsatile release [2]. There are many conditions that demand pulsatile release like,

- Many body functions that follow circadian rhythm. e.g: Secretion of hormones, acid secretion in stomach and gastric emptying.
- Chronopharmacotherapy of diseases which shows circadian rhythms intheir pathophysiology like bronchial asthma, myocardial infarction, angina pectoris,rheumatic disease, ulcer, and hypertension
- The lag time is essential for the drugs that undergo degradation in gastric acidic medium (e.g: peptide drugs) and irritate the gastric mucosa or induce nausea and vomiting.

The drugs that undergo first-pass metabolism resulting in reducedbioavailability, altered steady state levels of drug and metabolite, and potential fooddruginteractions require delayed release of the drug to the extent possible [3].

Pulsatile Drug Delivery Systems

A Pulsatile drug delivery system delivers drug in rapid and burst manner within a short time period instantaneously after a programmable lag phase [4]. Pulsatile Drug Delivery Systems (PDDS) are time-controlled drug delivery systems in which the drug is released over a definite pause time which is independent of environmental factors like pH, enzymes, gastrointestinal mobility, etc.

There are many circumstances where drug is needed to be released immediately (after bursting the delaying film coat) at specific site. These situations, therefore, force designing a delayed fast release systems. Drugs which have long *in- vivo*half lives showing an inherently prolonged duration of action,drugs with very

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short *in- vivo*half life which require a prohibitively large amount of active ingredients in dosage form, drugs which are required in large doses for beneficial effect and drugs which are required in very low dose. Additionally a delayed burst release can also be utilized for enhancing absorption, reducing side effects,increasing and decreasing dose [5, 6].

Fig 1. Pulsatile drug delivery

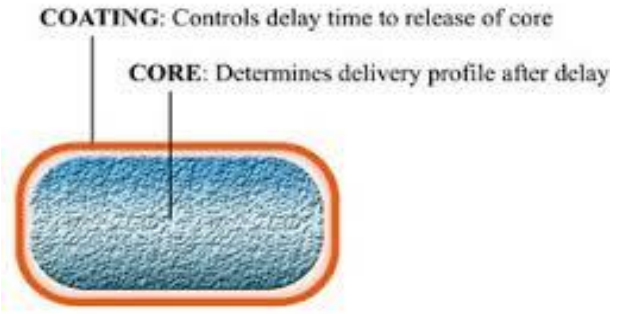
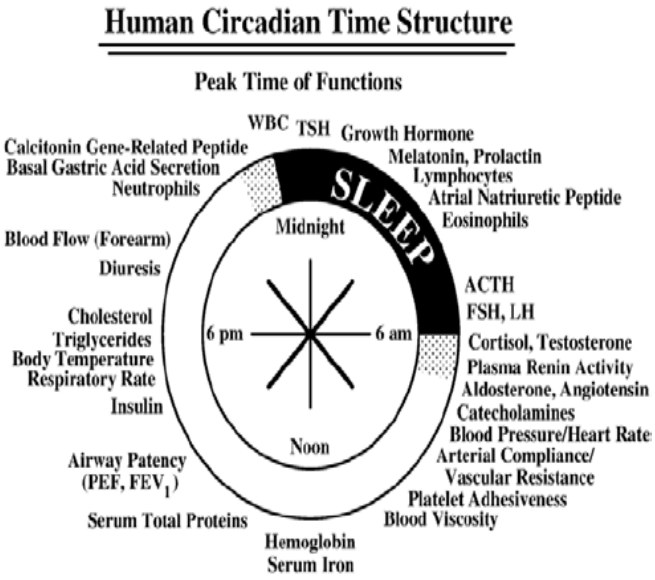


Fig 2. Human circadian time structure



Methodologies for Pulsatile drug delivery system

Methodologies for the PDDS can be broadly classified into four classes

I. Time controlled pulsatile release
   A. Single unit system
   B. Multi-particulate system
II. Stimuli induced
   A. Thermo-Responsive Pulsatile release
   B. Chemical stimuli induced pulsatile systems
III. External stimuli pulsatile release
   A. Electro responsive pulsatile release
   B. Magnetically induced pulsatile release
IV. Pulsatile release systems for vaccine and hormone products

Time Controlled Pulsatile Release System

These time-controlled systems can be classified as single unit (e.g., tablet or capsule) or multiple unit systems.

Single Unit Systems

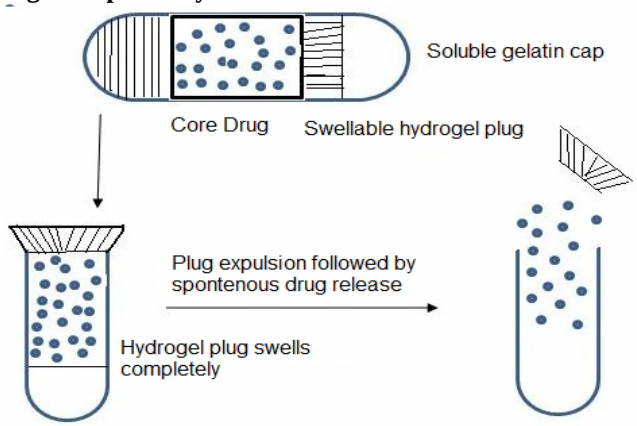
Delivery by Solubility Modulation

These systems contain a solubility modulator for pulsed delivery of variety of drugs. The system was especially developed for delivery of salbutamol sulphate. The compositions contain the drug (salbutamol sulphate) and a modulating agent, sodium chloride (NaCl).

Capsular system

In this system a water insoluble body containing the drug formulation, system is closed with a swellable hydrogel. Plugged (insoluble but permeable and swellable) at open end. Upon contact with, gastrointestinal fluid or dissolution medium the plug swells pushing itself out of the capsule after lag-time. Position and dimensions of plug, control lag-time. For rapid release ofwater insoluble drug effervescent or disintegrating agents are added.

Fig 3. Capsular system



Delivery by a Series of Stops

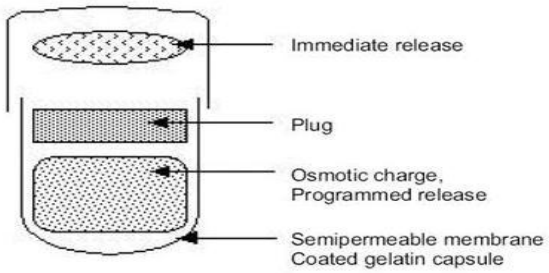
This system is described for implantable capsules. The capsule contains a drug and a water-absorptive osmotic engine that are placed in compartments separated by a movable partition. The pulsatile delivery is achieved by a series of stops along the inner wall of the capsule. These stops obstruct the movement of the partition but are overcome in succession as the osmotic pressure rises above a threshold level. The number of stops and thelongitudinal placements of the stops along the lengthof the capsule dictate the number and frequency of the pulses, and the configuration of the partition controls the pulse intensity.

Port systems

The Port System - consists of a gelatin capsule coated with a semi permeable membrane (e.g: cellulose acetate) housing an insoluble plug (e.g: lipidic) and an osmotically active agent along with the drug formulation. When it comes in contact with the aqueous medium, water

diffuses across the semi permeable membrane, resulting in increased inner pressure that ejects the plug after a – time lag.

Fig 4. Port system



Delivery by reservoir systems with erodible or soluble barrier 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. The time lag depends on the thickness of the coating layer [7].

The Time Clock system

Consists of a solid dosage form coated with lipid barriers containing carnauba wax and bees wax along with surfactants, This coat erodes or emulsifies in the aqueous environment in a time proportional to the thickness of the film, and the core is then available for dispersion.

Multiparticulate Systems

E.g: pellets, beads

These systems are reservoir type of devices with a coating, which either ruptures or changes its permeability. Drug is coated over sugar beads; these granules are then packaged in a capsule, or compressed with additional excipients to form a tablet. The active pharmaceutical ingredient may also be blended or granulated with polymers before coating to provide an additional level of control [8].

Mechanism of Drug Release from Multi-Particulates

The Multiparticulate's drug release mechanism can be occurring in the following ways:

Diffusion: Upon contact with aqueous fluid of the gastrointestinal tract (GIT), water gets diffused into the core of the particle. Drug dissolution get occurs and the drug solutions disperse across the release coat to the exterior.

Osmosis: Under the right circumstances when water is allowed to enter, an osmotic pressure can be created inside the interior of the particle. Due to this the drug is expelled out of the particle into the outside through the coating

Erosion: In some cases coatings can be designed to wear away gradually with time, thus delivering the drug contained within the particle.

Pulsatile System Based on Rupturable Coating

This is a multiparticulate system in which drug is coated on non-pareil sugar seeds followed by a swellable layer and an insoluble top layer [9].The swelling agents used include superdisintegrants like sodium carboxymethyl cellulose, sodium starch glycollate, L-hydroxypropyl cellulose, etc. Upon access of water, the swellable layer expands, resulting in rupture of film with subsequent rapid drug release.

Pulsatile Delivery by Change in Membrane Permeability

Several delivery systems based on ion exchange. It typically contains positively polarized quaternary ammonium group in the polymer side chain, which is always accompanied by negative hydrochloride counter-ions. The ammonium group being hydrophilic it facilitates the interaction of polymer with water, thereby changing its permeability and allowing water to permeate the active core in a controlled manner.

Sigmoidal Release System

This consists of pellet cores comprising drug and succinic acid coated with methacrylate copolymer USP/NF type B. The time lag is controlled by the rate of water influx through the polymer membrane. The water dissolves acid and the drug in the core. The acid solution in turn increases permeability of the hydrated polymer film [10].

Low density floating multiparticulate pulsatile systems

Conventional multiparticulate pulsatile release dosage forms mentioned above are having longer residence time in the gastrointestinal tract and due to highly variable nature of gastric emptying process may result in *in vivo* variability and bioavailability problems. In contrary, low density floating multiparticulate pulsatile dosage forms reside only in stomach 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 [11].

Stimuli Induced Pulsatile Release System

Several polymeric delivery systems undergo phase transitions and demonstrate marked swelling-deswelling changes in response to environmental changes including solvent composition, ionic strength, temperature, electric fields, and light. The mechanisms of drug release include ejection of the drug from the gel as the fluid phase synerges out, drug diffusion along a concentration gradient, electrophoresis of charged drugs towards an oppositely charged electrode and liberation of the entrapped drug as the gel or micelle complex erodes.

Chemical stimuli induced pulsatile systems

Glucose-responsive insulin release devices

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. Insulin by virtue of its action reduces blood glucose level and consequently gluconic acid level also gets decreased and system turns to the deswelling mode thereby decreasing the insulin release.

Inflammation-induced pulsatile release

During inflammation,hydroxyl radicals are produced from these inflammation-responsive cells. Degradation via hydroxyl radicals however, is usually dominant and rapid when Hyaluronic Acid gel is injected at inflammatory sites [12].

Temperature induced systems

Thermo-responsive hydrogel systems have been developed for pulsatile release. In these systems the polymer undergoes swelling or deswelling phase in response to the temperature which modulate drugrelease in swollen state [13].

pH sensitive drug delivery system

By selecting the pH dependent polymers drug release at specific location can be obtained. Examples of pH dependent polymers include cellulose acetate phthalate, polyacrylates, and sodium carboxymethylcellulose. These polymers are used as enteric coating materials so as to provide release of drug in the small intestine [14].

External Stimuli Pulsatile Release

This system was divided into three subparts and is discussed below.

Electro responsive pulsatile release

Electrically responsive delivery systems are prepared from polyelectrolytes (polymers which contain relatively high concentration of ionisable groups along the backbone chain) and are thus, pH-responsive as well as electro-responsive. Examples of naturally occurring polymers include hyaluronic acid, chondroitin sulphate, agarose, carbomer, xanthan gum and calcium alginate.

Micro electro mechanical systems (MEMS)

A micro fabricated device has the ability to store and release multiple chemical substances on demand by a mechanism devoid of moving its parts[(17)]. The microchip consists of an array of reservoirs that extend through an electrolyte-impermeable substrate. The prototype microchip is made of silicon and contains a number of drug reservoirs, each reservoir is sealed at one end by a thin gold membrane of material that serves as an anode in an electrochemical reaction and dissolves when an electric potential is applied to it in an electrolyte solution. When release is desired, an electric potential is applied between an anode membrane and a cathode, the gold membrane anode dissolves within 10-20 seconds and allows the drug in the reservoir to be released. This electric potential causes oxidation of the anode material to form a soluble complex with the electrolyte which then dissolves allowing release of the drug.

Pulsatile release systems for vaccine and hormone products

Vaccines are traditionally administered as an initial shot of an antigen followed by repeated booster shots to produce protective immunity. The frequency of the booster shots, and hence the exact immunisation- schedule is antigen dependent. Also, co-administration of vaccine adjuvant is often required to enhance the immune response to achieve protective immunity [15]. PDDS offer the possibility of single-shot vaccines if initial booster release of the antigen can be achieved from one system in which timing of booster release is controlled.

Recent Techniques of Oral Time Controlled Pulsatile Technology

Ipdas Technology

The Intestinal Protective Drug Absorption System is intended for use with GI irritant compounds. This is a high density, multi particulate tablet technology used for the manufacture of Naproxen. 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 subsequently pass into the duodenum and along the gastrointestinal tract in a controlled and gradual manner, independent of the feeding state.

Programmable Oral Drug Absorptionsystem

Programmable Oral Drug Absorption System (PRODAS) is presented as a number of mini tablets contained in hard gelatin capsule. It thus combines the benefits of tableting technology within a capsule. It is possible to incorporate many different mini tablets, each one formulated individually and programmed to release drug at different sites within the GIT. These combinations may include immediate release, delayed release and/or controlled release mini tablets. It is also possible to incorporate mini tablets of different sizes so that high drug loading is possible. Their size ranges usually from 1.5 – 4 mm in Diameter.

Fig 5. PRODAS

Eurands Pulsatile and Chrono Release System

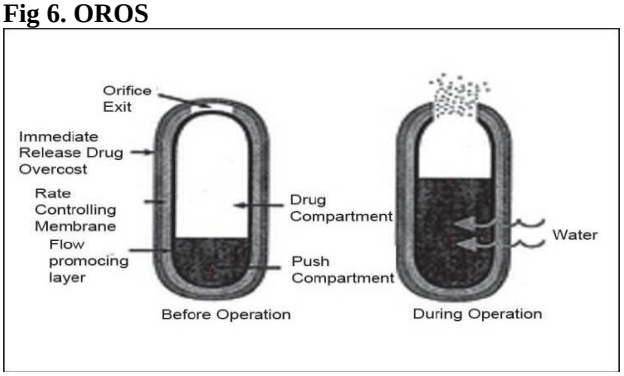
This system is capable of providing one or more rapid release pulses at predetermined times lag. They can help to optimize efficacy and/or minimize side-effects of a drug substance. For example, Eurand has created a circadian rhythm release (CRR) dosage form for a cardiovascular drug, Propranolol hydrochloride, with a four-hour delay in release after oral administration. When administered at bedtime, Propranolol is released after the initial delay such that maximum plasma level occurs in the early morning hours, when the patient is mostly at risk [16].

Orbexa Technology

This is a multi particulate system that enables high drug loading and provides a formulation choice for products that require granulation. After spheronization, the resultant beads can be coated with functional polymer membranes for additional release rate control and may be filled into capsules. This technology can be used for sensitive drugs such as proteins [17].

OROS Technology

Fig 6. OROS



This technology uses osmotic agents to provide preprogrammed, controlled drug delivery to the gastrointestinal tract This technology , especially the OROS® delayed push pull system, also known as controlled onset extended release (COER)was used to design covera-HS , a novel antihypertensive product. This enables delay, overnight release of verapamil to prevent surge in BP in morning.

INNOHERB

In this technology, pellets are coated inside of thecapsule. Desired active herbal compound converted into micro pellets or small beads. The coating of these carried out by semi permeable membrane to improve stability and mask taste/smell [18].

CONCLUSION

Although sustained and controlled drug delivery are not able to deliver drug according to circadian behaviour of diseases but pulsatile systems have importance in this regard. Due to their high efficiency and lack of undesirable adverse effects to the whole body, the stimuli-responsive feature of these systems is useful for treatment of patients. But major drawbacks arise from the biological variations among individuals. The basic parameters in the design of polymer based pulsatile systems are the biocompatibility and the toxicity of the polymers used. It can be concluded that Pulsatile drug delivery system provide a unique way of delivering drugs possessing chronopharmacological behaviour, extensive first pass metabolism, necessity of night time dosing, or absorption window in GIT. Pulsatile drug delivery system shall be promising in future.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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