Review Article

CHRONOPHARMACOTHERAPY: A NIGHT TIME THERAPY

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ABSTRACT

Historically, extended release dosage forms were developed, which release the drug continuously over longer periods of time. Recently, however, delivery systems with a pulsatile-release pattern are receiving increasing interest for the development of drugs for which conventional continuous release systems are not ideal. This system is designed for chronopharmacotherapy which is based on circadian rhythm. A pulsatile-release profile is characterized by a time period of no release (lag time) followed by a rapid and complete drug release. 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 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. These systems are beneficial for the drugs having chronopharmacological behaviour where night time dosing is required.

Keywords: Pulsatile-release, chronopharmacotherapy, circadian rhythm, rupturable coating.

1. INTRODUCTION

Drug delivery systems may be basically deemed to be systems which are created to carry drugs to the living systems for overcoming a state of diseases and restore them to normal physiological state-the state of health.

The Drug Delivery Systems are divided mainly in 3 types:

a. Controlled drug delivery is the parent DDS of the remaining two systems, i.e. time dependent and pulsatile. Its characteristic is the release of the drug in a controlled fashion. It may depend on the time or the dose.

b. Time dependent drug delivery, as the name suggests, depends on the time/ the duration when a particular therapeutic action is most effectively desired. Its characteristic is that it depends on time.

c. Pulsatile drug delivery is basically related to the circadian rhythms of the body. Its characteristic is that the drug release occurs depending on the previously determined time interval, the artificial or natural stimuli etc. Pulsatile drug delivery systems are not similar to sustained released formulations. Pulsatile drug systems are much different than Sustained release drugs. This system is designed for chronopharmacotherapy which is based on circadian rhythm.

1.1 Chronopharmacotherapy

Recent studies have revealed that diseases have predictable cyclic rhythms and that the timing of medication regimens can improve outcome in selected chronic conditions. "Chronopharmaceutics"[2] 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:

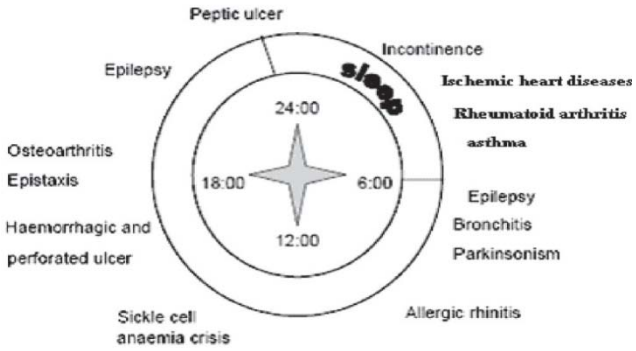
Circadian
This word comes from Latin word "circa" means about and "dies" means day.

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

Infradian
Oscillations those are longer than 24 h (less than one cycle per day).

Chronotherapy, a new approach for treating pathological conditions, is based on circadian rhythm.

Figure 1: Cycle of cardiac rhythum.



1.2 Need for Pulsatile System

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. The conditions that demand such release include:

- The drugs that undergo extensive first-pass metabolism (β blockers) and those that are characterized by idiosyncratic pharmacokinetics or pharmacodynamics resulting in reduced bioavailability, altered drug/metabolite ratios, altered steady state levels of drug and metabolite, and potential food-drug interactions require delayed release of the drug to the extent possible.

- Diseases like bronchial asthma, myocardial infarction, angina pectoris, rheumatic disease, ulcer, and hypertension display time dependence. Dethlefsan[3] and Repges reported sharp increase in asthmatic attacks during early morning hours. Such a condition demands considerations of diurnal progress of the disease rather than maintaining constant plasma drug level. A drug delivery system administered at bedtime, but releasing drug well after the time of administration (during morning hours), would be ideal in this case. Same is true for preventing heart attacks in the middle of the night and the morning stiffness typical of people suffering from arthritis.

- Many bodies functions that follow circadian rhythm, ie, their activity waxes and wanes with time. A number of hormones like rennin, aldosterone, and cortisol show daily fluctuations in their blood levels. Circadian effects are also observed in case of pH and acid secretion in stomach, gastric emptying, and gastro-intestinal blood transfusion.

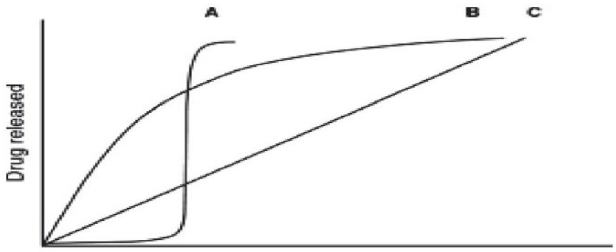
- Targeting a drug to distal organs of gastro-intestinal tract (GIT) like the colon requires that the drug release is prevented in the upper two-third portion of the GIT[4].

1.3 Design of Pulsatile drug delivery system

There is provided a novel drug delivery system which provides for intermittent drug delivery with readily adjustable intervals between drug delivery pulses. This is accomplished by providing a multilayer device in which layers of active drug are readily expandable or erodible when contacted with the environment in which the drug is to be administered. The drug layer is alternated with an inert layer and a multiplicity of such layers are contained within a tube impervious to such environment but provided with an opening into such environment. The multiplicity of such layers is driven along the length of such tube towards the opening. The interval between pulses is determined by the rate the layers are driven along the tube and the sizes of the layers. The duration of the pulse is determined by the rate of expansion or dispersion of the active layer into the environment, wherein the rate of expansion or dispersion is greater than the rate the layers are driven along the tube.

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. 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[5].

Figure 2: Drug release profiles



A) Pulsatile, (B) and (C) conventional extended release.

Circadian rhythm regulates many body functions in humans, viz., metabolism, physiology, behaviour, 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. The release of some 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.

The pulsatile effect, i.e., the release of drug as a "pulse" after a lag time has to be designed in such a way that a complete and rapid drug release should follow the lag time. Such systems are also called time-controlled as the drug released is independent of the environment.

2. CLASSIFICATION OF ORAL PULSATILE SYSTEMS

Pulsatile systems can be classified into:-

A. Single- unit systems.

B. Multiple-unit systems.

Single-unit systems are formulated either as capsule-based or osmosis-based systems. Single-unit systems are designed by coating the system either with eroding/soluble or rupturable coating. In multiple-unit systems, however, the pulsatile release is induced by changing membrane permeability or by coating with a rupturable membrane.

A) Single unit system

2.1. Single unit pulsatile systems

These are sub-classified as capsule-based systems, osmotic systems, delivery systems with soluble or erodible membranes, and delivery systems with rupturable coating.

- Swellable materials coated with insoluble but permeable polymer (polymethacrylates)

- Erodible compressed polymer (HPMC, polyvinyl alcohol, polyethylene oxide)
- Congealed melted polymer (glyceryl monooleate)
- Enzymatically controlled erodible polymer (pectin)

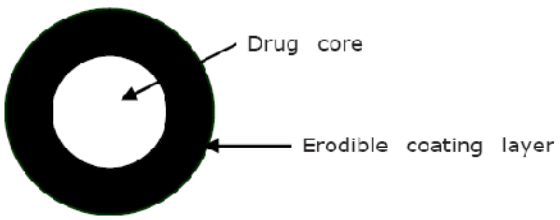
2.2. Capsule based systems

Single-unit systems are mostly developed in capsule form. The lag time is controlled by a plug, which gets pushed away by swelling or erosion, and the drug is released as a "Pulse" from the insoluble capsule body. Pulsincap® was developed by R. P. Scherer International Corporation, Michigan, US, and is one such system that comprises of a water-insoluble capsule enclosing the drug reservoir[6-8]. A swellable hydrogel plug was used to seal the drug contents into the capsule body. When this capsule came in contact with the dissolution fluid, it swelled; and after a lag time, the plug pushed itself outside the capsule and rapidly released the drug. Polymers used for designing of the hydro gel plug were various viscosity grades of hydroxyl propyl methyl cellulose, poly methyl methacrylates, poly vinyl acetate and poly ethylene oxide. As the swelling hydrogel polymer plug replaced the erodible tablet, the dependence of the dimensional accuracy between the plug and the capsule for the pulling mechanism of the plug from the capsule was also overcome. Ross et al. used low substituted hydroxypropylcellulose for the expulsion system for the release of propranolol over a time period of 2-10 h.

2.3. Drug delivery system with eroding or soluble barrier coating

These systems are based upon a drug reservoir surrounded with a soluble barrier layer that dissolves with time, and the drug releases at once after this lag time. Chronotropic® system consists of a core containing drug reservoir coated by a hydrophilic polymer HPMC[10-11]. An additional enteric-coated film is given outside this layer to overcome intra-subject variability in gastric emptying rates. The lag time and the onset of action are controlled by the thickness and the viscosity grade of HPMC. The time clock system is a delivery device based on solid dosage form that is coated by an aqueous dispersion. This coating is a hydrophobic-surfactant layer to which a water-soluble polymer is added to improve adhesion to the core. Once in contact with the dissolution fluid, the dispersion rehydrates and redisperses. The lag time could be controlled by varying the thickness of the film.

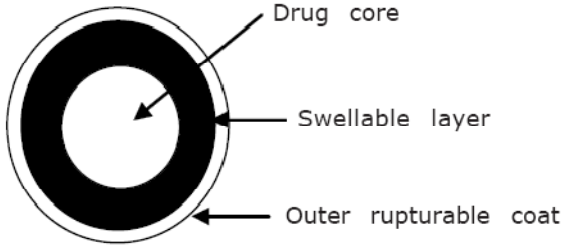
Figure 3: Diagram of Deliver system with erodible coating layer



2.4. Drug delivery system with rupturable layers/membranes

These systems are based upon a reservoir system coated with a rupturable membrane. The outer membrane ruptures due to the pressure developed by effervescent agents or swelling agents. Sungthongjeen et al. designed a pulsatile drug delivery system where the tablets of buflomedil HCl prepared by direct compression with varying amounts of spray-dried lactose and microcrystalline cellulose were coated with an inner swelling layer using croscarmellose sodium and an outer rupturable layer using ethyl cellulose[12]. It was observed that by increasing the amount of ethyl cellulose coating, the lag time could be prolonged. Ethyl cellulose, being water insoluble, retarded the water uptake. Similar results were obtained with croscarmellose sodium. Increasing the amount of microcrystalline cellulose decreased the lag time substantially.

Figure 4: Diagram of Deliver system with rutpurable coating system



2.5. Systems based on osmosis

The Port® system was developed by Therapeutic system research laboratory Ann Arbor, Michigan, USA, and consists of a capsule coated with a semipermeable membrane[9]. 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. Such a system was utilized to deliver methylphenidate used in the treatment of attention deficit hyperactivity disorder as the pulsatile port system. This system avoided second time dosing, which was beneficial for school children during daytime.

B) Multiple unit system

2.6. Multiple unit pulsatile systems

More reliable gastric emptying patterns are observed for multiparticulate formulations as compared to single-unit formulations[13], which suffer from 'all or none' concept. As the units of multiparticulate systems are distributed freely throughout the gastrointestinal tract, their transport is affected to a lesser extent than single-unit formulations by the transit time of food. Multiparticulate systems are further classified as systems based upon change in membrane permeability and systems based upon rupturable coating.

2.7. Pulsatile system based on change in membrane permeability

A Sigmoidal release system (SRS) is reported which is based upon the interaction of acrylic polymers with quaternary ammonium groups in the presence of different counter ions. SRS system consists of pellet cores having drug and succinic acid coated with ammonio-methacrylate copolymer USP/NF type (B). The water in the medium dissolves succinic acid. The drug inside and the acid solution increase the permeability of the polymer film. This system was used to design an acid-containing core[14]. The system was tested in beagle dogs. Good in vitro/in vivo correlation of lag time was observed.

2.8. Pulsatile systems with rupturable coating

Similar to single-unit system, the rupturing effect is achieved by coating the individual units with effervescent or swelling agents. Pulsatile drug delivery system comprising of a plurality of particles that are divided into several individual delivery units, each having its own distinct composition. Drug delivery was controlled by the rupture of the membrane. The timing of release was controlled by the thickness of coating and the amount of water-soluble polymer to achieve the pulsed release. The individual particles had the same composition of internal core, but the thickness of the external coating layer varied.

2.8.1. Pulsatile release by rupturing of membrane

In these multiparticulate system drug is coated on sugar seeds & then coated with insoluble & swellable top layer. The swelling agent includes superdisintegrents like carboxy methylcellulose, sodium starch glycollate, L-hydroxy propyl cellulose. Polymers like polyacrylic acid, polyethylene glycol etc. alternatively comprising of a mixture of tartaric acid & sodium bicarbonate that used as effervescent agent[15]. Water ingress to system causes the coating to swell, rupture & release of drug occurs. Release of drug is independent of pH or solubility of drug. Lag-time can be varied by varying thickness of coating or by changing amount of plasticizers in the outermost layer. If concentration of osmotic agent increases rapid release of drug after lag-time can be observed. In-vivo studies of time controlled explosion system with an in-vitro lag-time of three hours showed appearance of drug in blood after 3 hours, and maximum level after 5 hours

2.8.2 Rupturable coating with osmosis

These system contains core having drug (low bulk density solid or liquid lipid material) & disintegrant. Core is coated with cellulose acetate polymer. System is combination of swelling & osmotic effect, upon immersion in aqueous medium[16], water penetrates the core, displaces the lipid material, after depletion of lipid material internal pressure increases until a critical stress is reached, which causes rupture of coating.

Multiple unit systems show various advantages over single unit systems, which includes:

- Short gastric residence time
- Reproducible gastric residence time
- No risk of dose dumping
- Flexible to blend pellets with different composition or release pattern
- Lowest transit time variability
- Unique profiles
- Amenable to capsule & tablets
- Capable of pulsatile release

Disadvantages:

- Multiple manufacturing steps
- Low drug load
- Incomplete release

3. HOW THIS PULSATILE SYSTEM WORK

The operation of the pulsatile drug delivery device the constant driving force pushes the multiplicity of layers towards the opening at the opposite end of the layer compartment and the rate of dispersion or expansion of the medicament layer is greater than the constant driving force. As a medicament layer and its adjacent expansion/dispersion layer reach the opening, the physiological fluid causes the expansion or dispersion of the expansion layer which forces the medicament out of the opening. When the drug is fully expelled, the physiological fluid is then in contact only with the next inert spacer layer which does not erode and does not release any medicament into the physiological fluid. When the constant driving force has expelled the spacer layer, the next medicament layer and its adjacent expansion layer are then exposed to the physiological fluid and provide for a rapid pulse of medicament delivery.

The duration between pulses can be readily controlled by varying the rate of the constant driving force and the thickness of the spacer layers as well as the thickness of the expansion, drug or combined drug/expansion layers. The duration of the pulse can be readily controlled by varying the characteristics of the expansion layer, or combined drug/expansion layer, or by varying the size of the opening. A thicker spacer layer will certainly cause a longer duration between pulses of drug since it will take a longer period of time for the thicker spacer layer to completely traverse the opening. Also however, thicker layers of drug, or a thicker expansion layer will also cause a longer duration between pulses since after the active and expansion layers have dispersed into the environment, a void will be left between the opening and the next spacer layer.

The length of this void will have to be traversed by the next spacer layer, in addition to the length of the spacer layer itself, before the next drug pulse will begin.

In addition, the duration of the pulse itself can be varied by adjusting the dispersion characteristics of the drug layer to provide for a longer or shorter duration of the pulse. Thus, it is apparent that the physical dimensions of the various layers, the dissolution or dispersion characteristics of the expansion and drug layers, the physical characteristics of the container, and the rate characteristics of the driving force can be readily varied to provide for a pulsatile drug delivery device with rate characteristics to match any situation desired.

It should be further noted that the various layers need not be uniform in size. That is, the sizes of the expansion, drug or spacer layers can be adjusted to provide for a large initial dose followed by a series of smaller uniform doses; or the various layers could be planned to provide for a large initial dose followed by a series of doses of slowly decreasing or increasing size. The various doses could also be adjusted to correspond to seasonal needs of the animal administered the device or to provide for increasing doses to yield the correct constant dose rate for an animal which is increasing in size. The doses could also provide for a period of increased or decreased doses depending upon seasonal variations of parasite burdens or nutritional needs.

The various layers can be further modified to provide for pulses of drug administration where different materials are administered in each pulse or in selected pulses. Such arrangements can thus accomplish in a single device various treatment regimens which are now accomplished by the multiple administration of individual dosages, thus resulting in considerable cost and manpower savings by removing the need to assemble and individually dose the animals as well as avoiding the stress put to the animal during such procedures.

The pulsatile drug delivery system can find utility in those situations where the delivery device remains in the physiological fluid for extended periods of time and is not removed by normal bodily processes such as by alimentary function. Thus, the pulsatile device is ideally suited for use in veterinary medicine as an oral delivery device in ruminants and in human or veterinary medicine as an implanted device such as a subcutaneous implant.

When used in ruminant animals, the pulsatile delivery device is constantly bathed in the fermenting aqueous ruminal contents and can ideally be used to provide pulses of medicaments or other materials for a prolonged period of time. To prevent the regurgitation and expelling of the device, it is advisable to provide a densifying agent to maintain the device at the bottom of the rumen or to provide the device with variable geometry to prevent its expulsion.

4. PULSATILE DRUG DELIVERY DEVICE

The Time Clock® system (West Pharmaceutical Services Drug Delivery & Clinical Research Centre) consists of a solid dosage form coated with lipidic barriers containing carnuba wax and bees' wax along with surfactants, such as polyoxyethylene sorbitan monooleate.[17] 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. In a study with human volunteers, it was shown that the lag time was independent of gastric residence time, and the hydrophobic film redispersion did not appear to be influenced by the presence of intestinal enzymes or mechanical action of stomach or gastro-intestinal pH. The lag time increased with increasing coating thickness. Such systems are better suited for water-soluble drugs. The major advantage of this system is its ease of manufacturing without any need of special equipment. However, such lipid-based systems may have high *in-vivo* variability (eg, food effects). This invention is concerned with a device of compact size which is capable of providing for the pulsed delivery of a drug, medicament or nutrient where the interval between pulses of the drug can be prolonged and accurately regulated. This is accomplished by providing a tube containing a multiplicity of layers with an opening for the drug and a constant driving force to expel the drug from the tube, with the drug layers being expandable or dispersable when they are exposed to the environment at the opening in order to provide the pulse and with the duration between the pulses being provided by inert, non-erodable, layers, wherein the rate of expansion or dispersion of the drug layer is greater than the constant driving rate. Thus, it is an object of this invention to describe such devices. It is a further object to describe the particular materials which provide the device with its pulsatile characteristics.

The pulsatile drug delivery system can find utility in those situations where the delivery device remains in the physiological fluid for extended periods of time and is not removed by normal bodily processes such as by alimentary function[18]. Thus, the pulsatile device is ideally suited for use in veterinary medicine as an oral delivery device in ruminants and in human or veterinary medicine as an implanted device such as a subcutaneous implant.

These systems have a peculiar mechanism of delivering the drug rapidly and completely after a "lag time," i.e., a period of "no drug release." Though most delivery systems are designed for constant drug release over a prolonged 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 behaviour; drugs having specific absorption site in GIT (Gastro-Intestinal Tract), targeting to colon; and cases where night time dosing is required. When used as an implanted device, the pulsatile drug delivery system can be used in human and veterinary medicine for the prolonged pulsatile delivery of antiparasitic agents, antibiotics, growth promoting and growth permitting agents,

anticonvulsive agents, cardiovascular agents, corticosteroids, diuretics, hormones, enzymes, tranquilizers and the like. However, there was a potential problem of variable gastric residence time, which was overcome by enteric coating the system to allow its dissolution only in the higher pH region of small intestine.[19-20] Table.1 summaries the different available marketed technologies of pulsatile drug delivery system.

Table 1: Marketed technologies of pulsatile drug delivery

Technology	Mechanism	Proprietory name and dosage form	API	Disease
OROS®	Osmotic mechanism	Covera-HS®; XL tablet	Verapamil HCl	Hypertension
CODAS®	Multiparticular pH dependent system	Verelan® PM; XL release capsule	Verapamil HCl	Hypertension
DIFFUCAPS®	Multiparticulate system	Innopran®; XL tablets	Verapamil HCl, Propranolol HCl	Hypertension
Three dimen-sional printing®	Externally regulated system	TheirForm®	Diclofenac sodium	Inflammation
Pulsincap™	Rupturable system	Pulsincap™	Dofetilide	Hypertension

5. CONCLUSION

Pulsatile-release formulations have many advantages over immediate-release formulations. With these formulations, less-frequent drug administration is possible, and patient compliance can correspondingly be improved. In the field of drug delivery, increased attention has recently been focused on the potential of systems that are able to release drugs after a programmable lag phase commencing at administration time, i.e., in a pulsatile mode. During the last two decades, technologies to ensure time-controlled pulsatile release of bioactive compounds have been developed. Significant progress has been made towards achieving pulsatile drug delivery systems that can effectively treat diseases with non-constant dosing therapies, such as diabetes. However, there is much work that needs to be carefully demonstrated for the pulsatile delivery of bioactive compounds, especially hormones.

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.

It can be concluded that pulsatile drug delivery systems offer a solution for delivery of drugs exhibiting chronopharmacological behavior, extensive first-pass metabolism, necessity of night-time dosing, or absorption window in GIT. A variety of systems based on single or multiple units are developed for pulsatile release of drug. Most systems perform quite well *in vitro*; their performance *in vivo* has often not been tested. One major challenge will be to obtain a better understanding of the influence of the biological environment on the release performance of pulsatile delivery systems in order to develop simple systems based on approved excipients with a good *in vitro-in vivo* correlation.

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