REVIEW ARTICLE

Pulsatile drug delivery system

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Pulsatile drug delivery system is the most interesting time- and site-specific system. This system is designed for chronopharmacotherapy which is based on circadian rhythm. 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. Pulsatile drug delivery system is defined as the rapid and transient release of certain amount of molecules within a short time period immediately after a predetermined off-release period, i.e., lag time. Various systems like capsular systems, osmotic systems, pulsatile system based on the use of soluble or erodible polymer coating, use of rupturable membranes and pulsatile system based on membrane permeability are summarized in this article. These systems are beneficial for the drugs having chronopharmacological behavior where night time dosing is required and for the drugs having high first-pass effect and having specific site of absorption in gastrointestinal tract.

Key words: *Capsular system, chronopharmacotherapy, erodible and rupturable system, osmotic system, pulsatile drug delivery system*

INTRODUCTION

Pulsatile systems are gaining a lot of interest as the drug is released completely after defined lag time. Pulsatile drug delivery system is time- and site-specific drug delivery system, thus providing special and temporal delivery and increasing patient compliance. Pulsatile drug delivery system is defined as the rapid and transient release of certain amount of molecules within a short time period immediately after a predetermined off-release period, i.e., lag time[1] [Figure 1].

Such a novel drug delivery has been attempted for the following:

i. Chronopharmacotherapy of diseases which shows circadian rhythms in their pathophysiology.
ii. Avoiding degradation in upper gastrointestinal tract, e.g., proteins and peptides.[2]
iii. For time-programmed administration of hormones and many drugs such as isosorbide dinitrate, respectively, to avoid suppression of hormones in the body that can be hampered by constant release of hormone from administered dosage form and development of resistance.
iv. For drugs which develop biological tolerance, for the drug with extensive first pass metabolism, for drug targeted to specific site in the intestinal tract, e.g., colon.

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.[3]

"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:

i. Circadian
ii. Ultradian
iii. Infradian

Circadian

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

Ultrdian

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

Infradian

Oscillations that are longer than 24 h (less than one cycle per day)

Diseases with established oscillatory rhythm in their pathogenesis

The diseases currently targeted for chronopharmaceutical formulations are those for which there are enough scientific background to justify chronopharmaceutical drug delivery system, compared to conventional drug administration approach. These include asthma, arthritis, duodenal ulcer, cancer, cardiovascular diseases (e.g., hypertension and acute myocardial infarction), hypercholesterolemia, and ulcer

Asthma

The circadian rhythm of asthma has been extensively

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studied. Airway resistance increases progressively at night in asthmatic patient.

Arthritis

There is circadian rhythm in the plasma concentration of C - reactive protein and interleukin-6 of patient with rheumatoid arthritis. Patients with osteoarthritis tend to have less pain in the morning and more at night. While patients with rheumatoid arthritis have pain that usually peaks in the morning and decreases throughout day.

Duodenal ulcer

Gastric acid secretion is highest during nights in peptic ulcer patients.

Cancer

The blood flow to tumors and tumor growth rate are up to threefold greater during each daily activity phase of the circadian cycle.

Cardiovascular diseases

Capillary resistance and vascular reactivity are higher in the morning and decreases latter in the day. Platelet agreeability is increased and fibrinolytic activity is decreased in the morning, leading to a state of relative hypercoagulability of the blood.

Hypercholesterolemia

Cholesterol synthesis is generally higher during the night time than during day light. The maximal production occurs early in the morning, i.e., 12 h after last meal. Studies with 3-hydroxy-3-methylglutaryl-Coenzyme A (HMG CoA) reductase inhibitors have suggested that evening dosing was more effective than morning dosing [Figure 2].

i. 1:00 am - Post surgical death
ii. 2:00 am - Peptic ulcer
iii. 3:00 am - Blood pressure
iv. 4:00 am - Asthma[4]

VARIOUS APPROACHES USED FOR PULSATILE DRUG DELIVERY SYSTEM

Pulsatile system based on capsule

Capsule-based system consists of pulsincap system, which consists of an insoluble capsule body and swellable and degradable plugs made of approved substances such as hydrophilic polymers or lipids.[5,6] The lag time is controlled by plug, which is pushed away by swelling or erosion and drug is released as a pulse from the insoluble capsule, i.e., Pulsincap®. A swellable hydrogel plug seals the drug contents into capsule body. When this capsule body came into contact with dissolution medium, the hydrogel plug swells, and after the lag time, the plug pushes itself outside the capsule and rapidly releases the drug. Various types of material used for formulation of swellable plug include hydroxyl propyl methyl cellulose (HPMC), polyvinyl acetate and polyethylene oxide. The length of plug decides the lag time. Krogel and Bodmeir prepared impermeable cylinder system for ibuprofen. The system consists of hollow, impermeable polypropylene cylinder in which the matrix tablet is inserted. There are three cases:

Case I: One drug containing tablet in the centre of hollow cylinder which restricted the exposed surface area to the two cylinder faces of the tablet.

Case II: Two drug-containing tablets within each opening of the cylinder which formed the air-filled space leading to a low-density floating device.

Case III: One drug-free tablet in one opening of the cylinder, the other orifice was closed with an impermeable ethyl cellulose tablet and the inside cylinder was filled with drug and filler. The drug-free HPMC matrix tablet forming the plug.[7]

The capsule has the capability of delivering therapeutic agents into the body in a time- or position-controlled pulsatile release fashion.[8] The dosage form comprises of a multitude of multicoated particulates. The time-controlled series of pulses occur several hours after oral administration, with or without immediate release. One of the coating membranes is

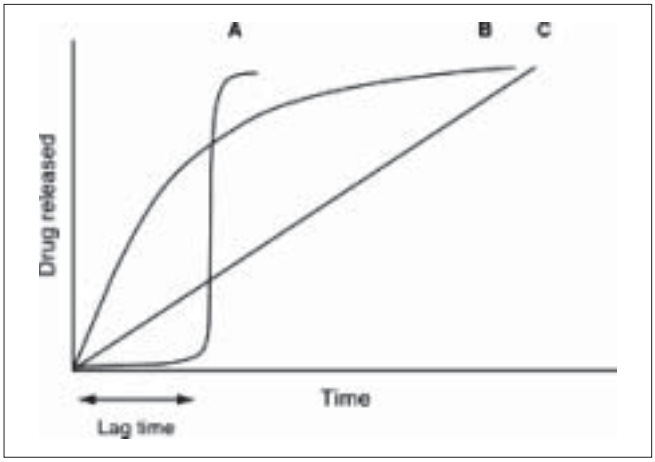

Figure 1: Drug release profiles: (A) pulsatile, (B) and (C) conventional extended release

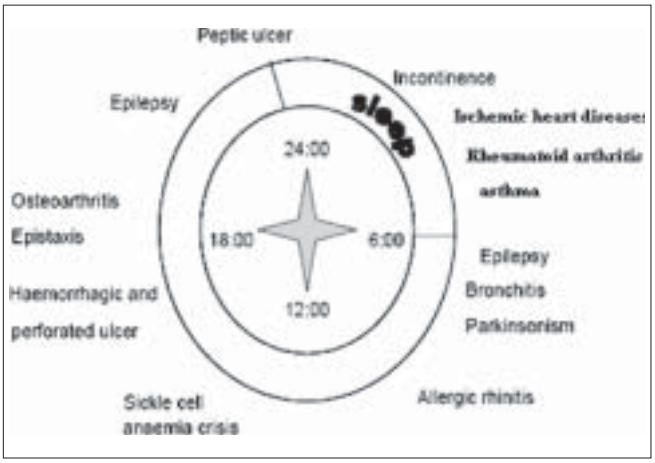

Figure 2: Cycle for circadian rhythm

composed of an enteric polymer and the second membrane barrier is composed of a mixture of water-insoluble polymer and an enteric polymer. The composition and thickness of the polymeric membranes determine the lag time and the duration of the drug release from each of the bead populations. In other preparations, an organic acid such as fumaric acid, citric acid, succinic acid, tartaric acid or malic acid, is included and a maleic acid-containing membrane may be provided between the first and second membrane layers to provide for the time-separated pulses. The acids in between the membranes may delay the dissolution of the enteric polymer in the inner layer, thereby increasing the lag time as well as decreasing the rate of release of the active ingredient from the coated microparticulates. The enteric coating membrane is generally incorporated in the innermost layer to have the drug released in the lower intestine.

Pulsatile system based on osmosis

Osmotic system consists of capsule coated with the semipermiable membrane. Inside the capsule was an insoluble plug, osmotically active agent and the drug formulation. When this capsule came in contact with the body fluid, the semipermeable membrane allowed the entry of water, which caused the pressure to develop and the insoluble plug expelled due to pressure after some lag time.

Osmotic capsule was developed which consists of hard gelatin capsule filled with acetaminophen, osmotic agent (sorbitol), a release promoter (sodium dodecyl sulfate) coated with semipermeable cellulose acetate membrane containing hydrophobic plasticizer (castor oil) and sealed with wax of white bees.[9] When placed in the sink water, it penetrates the membrane, dissolves the osmotic agent and increases the osmotic agent inside the capsule. The increased osmotic pressure enhances the water imbibition and consequently increases the hydrostatic pressure inside the capsule and when the latter pressure is high enough, then it expels out the plug and the drug release commences. The onset of drug imbibition, i.e., the lag time (t_L) depends on thickness of semipermeable membrane and plug thickness.

The delivery of agents from osmotic systems based on expandable orifice technology was developed.[10] The system is in the form of capsule from which the drug is delivered by the capsule's osmotic infusion of moisture from the body. The delivery orifice opens intermittently to achieve pulsatile delivery effect. The orifice forms in the capsule wall, which is constructed of an elastic material, preferably elastomer (e.g., styrene-butadiene copolymer), and stretches under a pressure differential caused by the pressure rise inside the capsule. The orifice is small enough that, when the elastic wall is relaxed, the flow rate of the drug through the orifice is substantially zero. However, when the elastic wall is stretched, because of the pressure differential across the wall exceeding a threshold, the orifice expands sufficiently to allow the release of the drug at a physiologically required rate.

A novel capsule made from ethyl cellulose for time-controlled release of drugs in the colon.[11] Initially, the capsule was prepared by using a gelatin capsule with ethyl cellulose. The thickness of ethyl cellulose capsule body was varied and the effect of the wall thickness on the release of the drug in the capsules was investigated. The ethyl cellulose capsules contained a large number of mechanically made micropores (400 μm) at the bottom. A swellable layer consisting of low-substituted hydroxy propyl cellulose (L-HPC) was located in the bottom of capsule body. Above the swellable layer was the drug reservoir which contained mixture of model drug, fluorescein and a bulking agent, such as lactose and starch. The capsule was then capped and sealed with a concentrated ethyl cellulose solution. After administration of the drug-containing capsule, water molecules penetrated the capsule through the micropores in the bottom of the capsule body. Hydration and swelling of the L-HPC induced an increase in the internal osmotic pressure, which resulted in the "explosion" of the capsule and a burst-like drug release was observed. The lag time of the drug release could be altered by altering the thickness of the capsule.

Systems with eroding, soluble or rupturable barrier coatings

These types of system generally comprise reservoir devices coated with a barrier layer. The barrier dissolves or erodes after a specified lag period, after which the drug is released rapidly from the reservoir core. In general, the lag time prior to drug release from a reservoir-type device can be controlled by the thickness of the coating layer, e.g., the chronotropic system which consists of a drug containing core layered with HPMC optionally coated with an outer enteric coating. The lag time prior to drug release is controlled by the thickness and the viscosity grade of HPMC layer.[12] The chronotropic system is an oral dosage form that is designed to achieve time-controlled delivery. This system has been developed keeping in view interaction between gastrointestinal fluids and the coating polymer, which causes time and site-controlled release. This reaction causes the liberation of the drugs by the mechanism of the swelling of the polymer, increasing the permeability and dissolution/erosion phenomena.

A release pattern with two pulses was obtained from three-layer tablet consisting of two drug-containing layers, separated by a drug-free gellable polymeric barrier layer.[13] The three-layer tablet was coated on three sides with an impermeable coating (ethyl cellulose) and the top side of the tablet remained uncoated. Upon contact with dissolution fluids, the initial dose incorporated into the top layer was released rapidly from the uncoated surface of the tablet. The second pulse was obtained from the bottom layer after the gelled barrier layer (HPMC) has been eroded and dissolved.

The Time Clock system was proposed for oral dosage form, which should enable fast and complete release of drug after a predetermined lag time.[14] A tablet containing the drug

molecule and bulking agents [lactose, polyvinyl-pyrolidone (PVP), corn starch and magnesium stearate] was prepared. This core was coated with a hydrophobic dispersion of carnauba wax, beeswax, poly (oxyethylene) sorbitan monooleate and HPMC in water. The lag time could be proportionally modulated by altering the thickness of the coating. *In vitro* results indicated rapid release after certain lag time for the Time Clock system with a hydrophobic coating. This approach may also be used to control the release onset time. Because the drug core is formulated with soluble ingredients, shell dissolution/disintegration becomes the key factor in controlling the lag time. Furthermore, drug release is independent of normal physiological conditions, such as pH, digestive state and anatomical position at the time of release.

Pulsatile release tablet was developed that can suppress release of the drug in the stomach and can release the drug rapidly after a predetermined time of about 3 h in the intestine.[15] The system consists of a core, swelling agent of cross-linked PVP and a coating film of ethyl cellulose/ Eudragit L. Eudragit L dissolves in an environment of pH above 6 and creates pores in the coating film. Penetration of water molecules from the surroundings through the pores into the core causes expansion of the swelling agent, bursting the film and releasing the drug with a single pulse. Manipulation of the thickness of coating film can control the lag time.

A pharmaceutical implant was developed for biologically active material, an excipient comprising at least one water-soluble material and above which polymer film coating adapted to rupture at predetermined period of time after implantation.[16] In one form, a bilayer film coating forms an impermeable barrier to the drug. An insoluble outer film controls the degree of access of physiological film to the inner film. A film coating comprising a mixture of ethyl cellulose and a copolymer of glycolic and lactic acids is used. As ethyl cellulose is an insoluble polymer, when the polylactic glycolic acid (PLGA) polymer in the film hydrolyses, the film becomes porous and allows release of the drug. The rate of hydrolysis of the PLGA depends on the ratio of the lactic acid to glycolic acid in the polymer.

Another pulsatile system was developed consisting of rupturable coating on drug present in heard gelatin capsule.[17] These capsules were first coated with a swelling layer and then with an insoluble but water-permeable coating. These coated capsules when immersed in the release media, the media penetrates the capsule which causes the swelling of the inner coating which ruptures the outer coating. However, by increasing the outer coating, the lag time could be prolonged.

Pulsatile system based on change in membrane permeability

A sigmoidal release type of pattern is obtained. Sigmoidal release system consists of pellet cores having drug and succinic acid coated with ammonio-methacrylate copolymer. 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.

Other types of pulsatile systems for multiparticulates oral administration are prepared.[18,19] The delivery system can be a capsule or tablet composed of a large number of pellets consisting of two or more particle populations. Each pellet has a core that contains the therapeutic drug and a water-soluble osmotic agent (e.g., NaCl). A water-permeable, water-insoluble polymer film encloses each core. A hydrophobic, water-insoluble agent that alters permeability (e.g., wax, fatty acids, or salts of fatty acids) is incorporated into the polymer film. The rate at which water passes from the film coating through the core differs for each pellet population in the dosage form. The osmotic agent dissolves in water, which causes the pellets to swell and thereby regulates the rate of diffusion of the drug from the dosage form.

Pulsatile system of multiparticulates for oral administration consists of a capsule or tablet composed of a large number of pellets consisting of two or more particle populations. Each pellet has a core that contains the therapeutic drug and a water-soluble osmotic agent (e.g., NaCl). A water permeable, water-insoluble polymer core encloses each core. A hydrophobic, water-insoluble polymer film encloses each core. A hydrophobic water-insoluble agent that alters the permeability (e.g., wax, fatty acid or salt of fatty acids) is incorporated into the polymer film. The rate at which water passes from the film coating to the core differs for each pellet population in dosage form. The osmotic agent dissolves in water, which causes the pellets to swell and thereby regulates the rate of diffusion of the drug from the dosage form.

CURRENT AND FUTURE DEVELOPMENT

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.

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