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Overview on Chronopharmaceutical Drug Delivery System

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ABSTRACT

Chronotherapeutics is the discipline concerned with the delivery of drugs according to inherent activities of a disease over a certain period of time. Chronotherapy can particularly benefit patients suffering from allergic rhinitis, rheumatoid arthritis and related disorders, asthma, cancer, cardiovascular diseases, and peptic ulcer disease. The biological systems require different amounts of drug at expected times within the circadian cycle. Many therapeutic agents are most effective when made available at constant rates, near the absorption sites or at the correct time of administration. Hence there exists a need for the development of such delivery system that matches the circadian rhythm. With the Chronotherapeutic drug delivery system this requirement can be fulfilled. As these systems deliver the right dose at right time at a specific site, they are gaining importance in the field of pharmaceutical technology. Hence a desired effect at the required time can be achieved by selecting a pulsatile system based on the pathological behavior. And also there will be a reduction in undesirable side effects due to the therapeutic action of the drug delivery system at the time of flare up of the disease symptoms. This review gives a comprehensive emphasis on circadian behavior of certain diseases, various approaches for the chronotherapeutic drug delivery systems and the existing technologies. Pulsatile drug delivery system can be classified as time controlled pulsatile release, stimuli induced and external stimuli pulsatile release systems etc. Still, a significant progress in achieving chronopharmaceutical drug delivery systems for the treatment of diseases in a pulsatile manner.

Keywords: Chronological behaviour, circadian rhythm, Chronotherapeutic drug delivery system, pulsatile release, chronopharmaceutical technologies.

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INTRODUCTION

The biological clock within our body regulates our various physiological body functions for E.g. Similarly circadian rhythms control the pathophysiology of certain diseases. These diseases exhibit their symptoms at a peak level during a particular time period within a day. For instance, Particular rhythms in the onset and extent of symptoms are observed in diseases such as bronchial asthma, ulcer, rheumatoid disease[1], hypertension and hyper cholesterolemia etc as given in the Figure 1. Due to the presence of 24hr rhythms in the processes that makeup the pathophysiology of diseases, there is a need to provide the medication at that particular time period where there is a flare-up in disease symptoms. This can be achieved by developing a novel chronopharmaceutical drug delivery system.[5] List of diseases and their chronological behaviour with reasons was tabulated in table 1.[1,2,3,4]

Table 1: List of diseases and their chronological behaviour with reasons

S. No	Disease	Chronological Behaviour / Flare-up time*	Reason	Drugs used in the treatment
1	Asthma	Airway resistance increases progressively at night *4.00AM	Release of adrenaline and nor adrenaline	Oral corticosteroids, Theophylline
2	Hypercholesterolemia	Cholesterol synthesis is higher during night time than day light	Activity of rate limiting enzyme HMG CoA is higher in the night time	HMG CoA reductase inhibitors
3	Rheumatoid arthritis	Pain peaks in the early morning compared to day time *7.00AM	Increased concentration of C reactive protein and interleukin-6 in blood	NSAIDS like ketoprofen, flubiprofen
4	Diabetes mellitus	Blood sugar level higher in the day time	Insulin synthesis and storage is less during the day	Sulfonyl urea, insulin
5	Duodenal ulcer	Ulcer exacerbation during night time *12.00AM	Gastric acid secretion is highest at midnight	Proton pump inhibitors
6	Myocardial infraction	Myocardial insufficiency at early morning *4.00AM	Release of catecholamine,cortisol and increased platelet aggregation	β-blockers, calcium channel blockers, ACE inhibitors

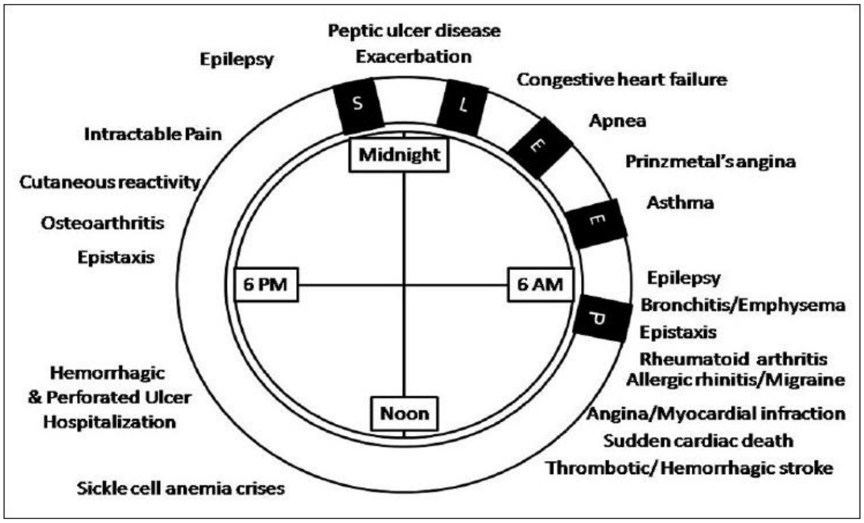

Figure 1: Schematic diagram of diseases showing circadian rhythm [1]

Concept of chronopharmaceutical drug delivery system

In case of treating diseases exhibiting chronological behaviour, it is not required to have the drug at therapeutic concentrations in the body throughout the day, so, it is better to use a chronopharmaceutical drug delivery system rather than using a controlled drug delivery system. This delivery system releases the drug at once as a pulse after a time lag where there is a complete and rapid drug release. Due to this drug is available at therapeutic concentrations at the right time to meet biological rhythm determined needs. In turn, desired effects are optimized and adverse effects are minimized.[5] Chronopharmaceutical drug delivery systems are promising this type of release, where the drug is released suddenly after a well-defined lag time or time gap according to the circadian rhythm of disease states. Drug is not released from the device within this lag time. Drug release pattern of different drug delivery systems are depicted in Figure 2.

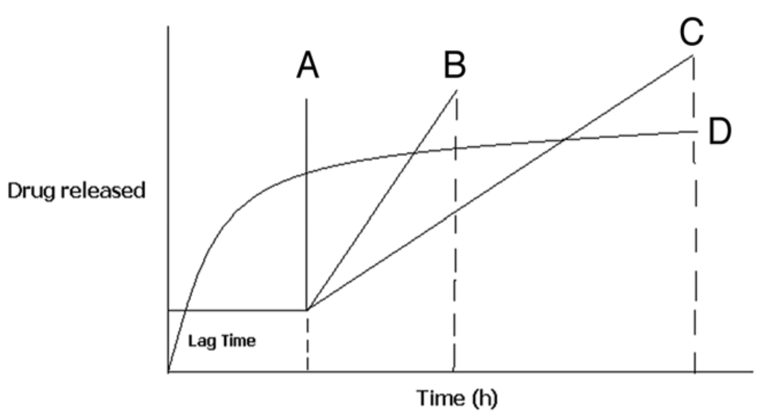

Figure 2: Schematic representation of different drug delivery systems, with (A) Sigmoidal release after lag time, (B) delayed release after lag time, (C) sustained release after lag time and (D) extended release without lag time.

Various Approaches to Develop Chronopharmaceutical Drug Delivery Systems

Several methodologies have been developed and applied to design chronopharmaceutical drug delivery system to obtain pulsatile drug release. These methodologies can be broadly classified into five major categories. They are

I. Time controlled pulsatile release systems

II. Stimuli induced pulsatile release systems

III. Externally regulated pulsatile release systems

IV. Pulsatile release systems for vaccine and hormone products

Time controlled pulsatile release systems [2]

A burst release of drug within a short time period of time immediately after a predetermined off release period. The drug release is independent of the environment (gastrointestinal transit time or motility, pH, enzymes and food intake. Different methods can be applied to design this type of systems. They are

Capsular system with a swellable plug

Capsular system based osmosis

Capsular system based on expandable orifice

Osmotic capsule having micropores

Delivery by a series of stops

Delivery by solubility modulation

Pulsatile system with erodible or soluble barrier coatings

Pulsatile system based on rupturable coating

Time controlled expulsion system

Pulsatile system based on changed membrane permeability

Sigmoidal release system

Time controlled, low density floating pulsatile system

Capsular system with a swellable plug

A general design of such systems consists of an insoluble capsule body containing a drug and a plug. The plug is removed after a predetermined time lag due to swelling, erosion, or dissolution. The plug material consists of insoluble but permeable and swellable polymers E.g: polymethacrylates, erodible compressed polymers (E.g: hydroxypropylmethyl cellulose, polyvinyl alcohol, polyethylene oxide) etc. When the capsule body comes in contact of gastrointestinal fluids, the plug swells and pushes itself outside the capsule after a lag time, followed by a rapid drug release.

E.g: PULSINCAP SYSTEM as depicted in figure 3[6]

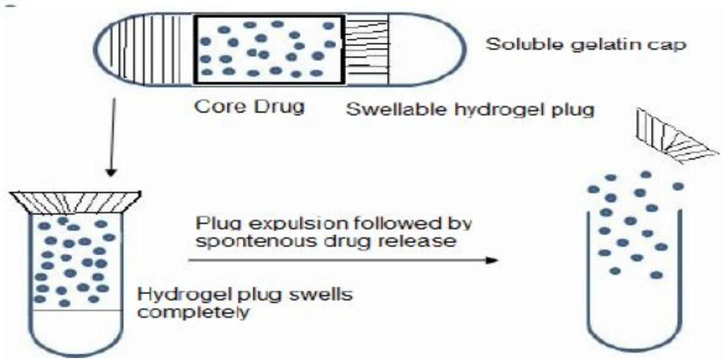

Figure 3: Diagrammatic representation for pulsincap

Capsular system based osmosis

This system consists of a capsule enclosed in a semi permeable membrane. The capsule contains an insoluble plug and an osmotically active agent along with a drug. When it comes in contact with the body fluids, water diffuses across the semi permeable membrane. Due to this pressure increases and thus the plug is ejected after a time lag. The thickness of semi permeable membrane determines the time lag. An osmotically driven capsular system was developed to deliver drug in liquid form. Here, liquid drug is absorbed into highly porous particles, which release the drug through an orifice of a semi permeable capsule supported by an expanding osmotic layer after the barrier layer is dissolved.[6]

E.g: PORT SYSTEM as depicted in Figure 4.

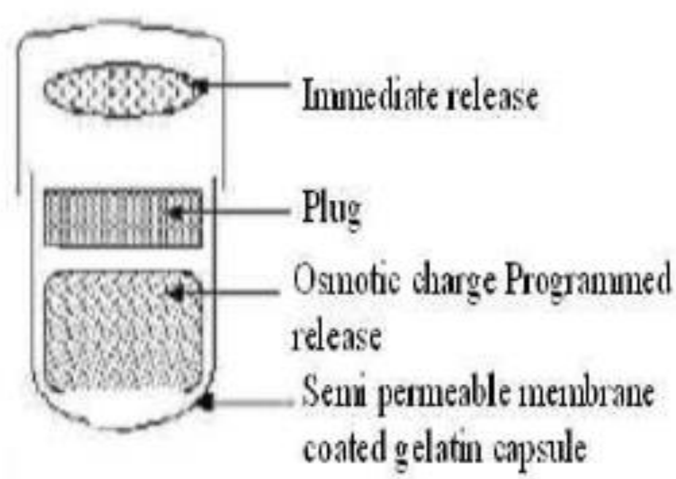

Figure 4: Diagrammatic representation for Port Systems

Capsular system based on expandable orifice

Drugs can be delivered as liquid formulations by using this system. It contains a liquid drug layer, an osmotic engine, push layer and a semi permeable membrane coating. When the system is in contact with the aqueous environment, water permeates across the rate controlling membrane and activates the osmotic layer. The expansion of the osmotic layer results in the development of hydrostatic pressure inside the system, which results in the delivery of the liquid formulation from the delivery orifice. In this system, liquid drug is absorbed into highly porous particles, which release the drug through an orifice of a semi permeable capsule supported by an expanding osmotic layer after the barrier is dissolved.[2]

E.g: LIQUID OROS SOFT CAP

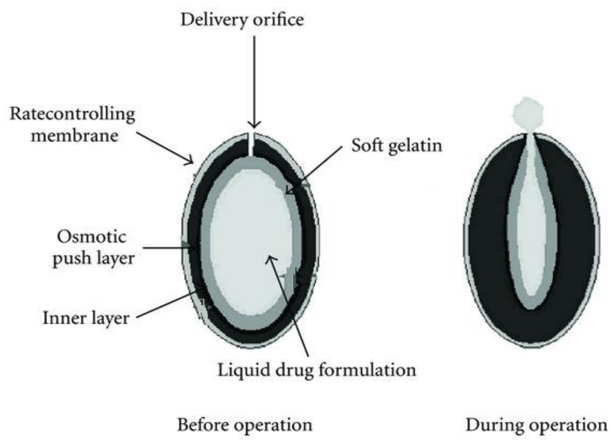

Figure 5: L-OROS system before and during operation [7]

Osmotic capsule containing micropores

The ethyl cellulose capsules contained a large number of mechanically made micropores (400 μm) at the bottom. A swellable layer like lowsubstituted hydroxy propyl cellulose (L-HPC) is present in the bottom of capsule body. Above this a drug reservoir which contained mixture of model drug, fluorescein and a bulking agent, such as lactose and starch is present. The capsule is capped and sealed with a concentrated ethyl cellulose solution. After administration of the drug containing capsule, water molecules penetrate the capsule through the micropores in the bottom of the capsule body. Hydration and swelling of the L-HPC induces an increase in the internal osmotic pressure, which resulted in the "explosion" of the capsule and a burst-like drug release was observed.[8]

Delivery by a series of stops

This system consists of a capsule containing a drug and a water absorptive osmotic engine separated by a movable partition. Pulsatile delivery is achieved by a series of stop along the inner wall of the capsule.[9]

Delivery by solubility modulation

These systems contain a drug and a solubility modulator like sodium chloride. The modulating agent can be a solid organic acid, inorganic salt, or organic salt. When body fluids diffuse into the tablet through the semi permeable film coat, interact with osmotic core contents. Internal pressure develops, which results in the pumping of dissolved drug out through the laser drilled hole.[10]

Pulsatile system with erodible or soluble barrier coatings

These systems consist of a drug reservoir which is coated with a soluble or erodible barrier. Single unit and multi particulate systems can be developed. In Single unit systems, drug containing core is coated by hydrophilic swellable hydroxypropyl methyl cellulose. In Multi particulate systems, drug containing core is primarily coated by hydroxyl propyl methyl cellulose. Outermost erodible layer consisted of ethyl cellulose, hydroxyl propyl methyl cellulose phthalate and a plasticizer diethyl phthalate. Barrier layer erodes in the aqueous environment and the drug is released rapidly. Eg. Time Clock® system, Chronotropic® system.[11]

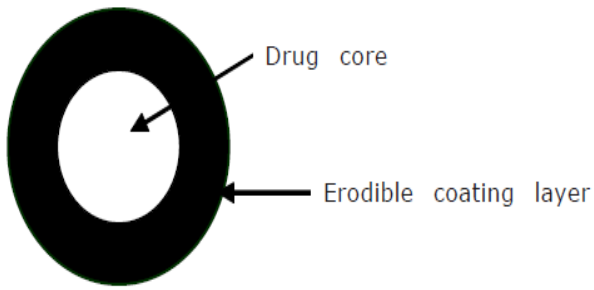

Figure 6: Schematic diagram of Delivery systems with erodible coating layers[12]

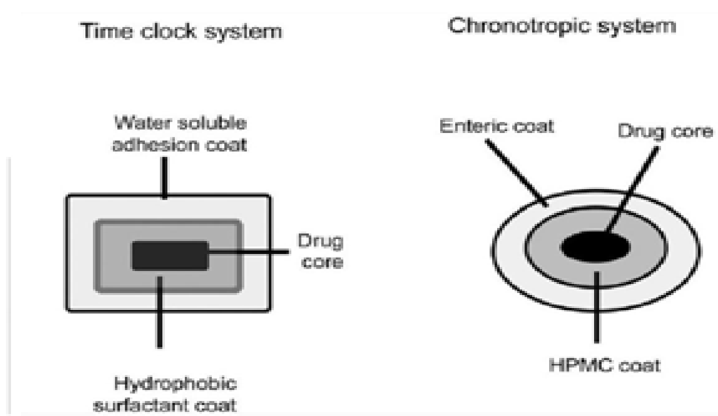

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Figure 7: Time clock and Chronotropic systems[13]

Pulsatile system based on rupturable coating

This system consists of a reservoir system coated with a rupturable membrane. Single unit systems consist of a core, a swelling agent and a coating film of ethyl cellulose. Core contains the drug and a disintegrant. In Multi particulate systems, drug is coated on nonpareil seeds followed by a swellable layer and an insoluble layer. Swelling agents include low substituted hydroxyl propyl cellulose, sodium carboxy methyl cellulose etc. When water enters into the system, the swellable layer expands resulting in rupture of film with a rapid drug release. The effervescent excipients, swelling agents provide the pressure necessary for the rupture of the coating.[13]

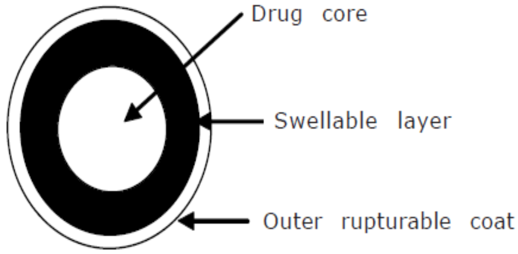

Figure 8: Schematic diagram of Deliver systems with rutpurable coating layer[12]

Time controlled expulsion system

This system is based on a combination of osmotic and swelling effects. The core contains the drug, a low bulk density solid and/or liquid lipid material (e.g., mineral oil) and a disintegrant. The core is further coated with cellulose acetate. When water penetrates the core displaces the lipid material. After the depletion of lipid material, internal pressure increases which results in rupture of the coating material[14]. The swelling agents used include superdisintegrants like sodium carboxymethyl cellulose, L hydroxypropyl cellulose. Polymers like polyvinyl acetate, polyacrylic acid, polyethylene glycol, etc.[15]

Pulsatile system based on changed membrane permeability

This system consists of pellet cores having drug and succinic acid coated with amino-methylacrylate copolymer.The water in the medium dissolves succinic acid. The drug inside and the acid solution increase the permeability of the polymer film. Actually permeability and water uptake of acrylic polymers with quaternary ammonium groups can be controlled by the presence of different counter-ions in the medium. The release profile of systems depend strongly on physicochemical properties of the drug and its interaction with membrane.[16]

Sigmoidal release system

Multiple unit preparations contain an osmotically active organic acid like succinic acid which has been coated with insoluble polymer like ammonio-methacrylate copolymer USP/NF type B to achieve different lag-times. The time lag is controlled by the rate of water influx through the polymer membrane. Presence of acid increases the permeation and hence causes the drug delivery.[17, 18]

Time controlled, low density floating pulsatile system

This type of drug delivery systems consists of a drug-containing effervescent core and a polymeric coating. Preliminary studies identified important core and coating properties for the two systems.

The mechanical properties (puncture strength and elongation) of acrylic (Eudragit® RS, RL or NE) and cellulosic (cellulose acetate, ethyl cellulose) polymers, which primarily determined the type of delivery system.[19] Further, combined floating and pulsatile principles were achieved using a specific technology, in which low density microporous polypropylene, Accurel MP 1000, were used as a multiparticulate carrier for ibuprofen. This drug delivery system showed distinct behaviour from other approaches in chronotherapy with desired low drug release in acidic medium.[20]

Stimuli induced pulsatile release systems

Such systems are novel drug delivery approaches meant for targeted drug delivery at specific site due to induction of certain physiochemical stimuli at target site. Release of certain enzymes, hormones, antibodies, pH of the site, temperature of the site, presence of certain cells, and concentration of bio molecules (glucose, neurotransmitters, inflammatory mediators) act as stimuli to trigger the release of drug from these types of drug delivery systems.

Temperature-induced pulsatile release

Chemical stimuli induced Pulsatile systems

Temperature-induced pulsatile release

Temperature is the most widely applied triggering signal for a variety of triggered or pulsatile drug delivery systems. Various polymer properties, including the thermally reversible coil/globule transition of polymer molecules, swelling change of networks, glass transition and crystalline melting are utilized in developing temperature induced triggered drug delivery systems.[21]

Thermo responsive hydro gel systems

Swelling and deswelling kinetics of thermo sensitive hydrogels can exhibit reversible swelling changes with temperature changes. Swelling rates from a deswollen state to swollen state are usually faster than the opposite deswelling process from swollen state to deswollen state. Changes in the deswelling process show an initial rapid shrinking followed by a slow deswelling. This can be explained as an initial immediate shrinking of the outermost layer of the gel in contact with the stimulating solution, which restricts further bulk water outflow from the interior of the gel. The quick response of the gel surface to temperature changes may be utilized as an on-off switch for drug release.[22]

Thermo responsive polymeric micelle systems

In this type, the gel system tightly stores targeted drug in the micelles and rapidly releases controlled amount of the drug by switching on-off of external stimuli such as temperature or infrared laser beam. Jianxiang Zhang *et al*., synthesized thermally responsive amphiphilic poly

(N-isopropylacryl-amide) (PNIPAm)- grafted-poly-phosphazene (PNIPAm-g- PPP) by stepwise cosubstitution of chlorine atoms on polymer backbones with amino-terminated NIPA oligomers and ethyl glycinate (GlyEt).[23] Block copolymers were prepared by development of end functionalized PIPAAm with hydrophobic polymers, such as poly (butyl methacrylate) (PBMA), polystyrene (PST) etc. In aqueous solution, block copolymers formed micellar structure (with core shell structure) below PIPAAm's transition temperature.[21]

Pulsatile systems based on chemical stimuli

Inflammation-induced pulsatile systems

During inflammation, hydroxyl radicals are produced from these inflammation-responsive cells and the presence of which can induce a dominant and rapid degradation when Hyaluronic Acid gel is injected at inflammatory sites. Thus, it is possible to treat patients with inflammatory diseases like rheumatoid arthritis; using anti-inflammatory drug incorporated HA gels as new implantable drug delivery systems.[24]

pH Sensitive Drug Delivery System

A pulsatile drug release of the drug occurs in response to change in pH. Based on the required site of action, pH dependent polymer can be selected. By this drug release can be obtained at the site of action. Examples of pH dependent polymers include cellulose acetate phthalate, polyacrylates, sodium carboxy methyl cellulose.[25]

Glucose-responsive insulin release devices

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 there is a rise in the glucose concentration in the blood glucose oxidase converts glucose into gluconic acid which causes a change in the pH. This pH change induces swelling of the polymer which results in insulin release.[26]

Drug release from intelligent gels responding to antibody concentration

Novel gels which respond to the change in concentration of bioactive compounds to alter their swelling/deswelling characteristics are used in this approach. Antigen-antibody complex formation as the cross-linking units in the gel gained special attention, since such interaction is very specific. Reversible gel swelling/deswelling and drug permeation changes occurs by the utilization of the difference in association constants between polymerized antibodies and naturally derived antibodies towards specific antigens.[21, 27]

Externally regulated pulsatile release systems

In this type of drug delivery systems, externally generated environmental changes initiate the drug delivery. The following are the types of externally regulated pulsatile release systems

Electric stimuli-responsive pulsatile release

Micro Electro Mechanical Systems (MEMS)

Magnetic stimuli-induced pulsatile release

Ultra sound induced pulsatile release

Light induced pulsatile release

Mechanical force induced pulsatile release

Electric stimuli-responsive pulsatile release

It is prepared from polyelectrolytes. These polyelectrolytes contain high amount ionisable groups along with backbone chain. So, it is both pH and electroresponsive. Under the influence of electric field, electro responsive hydrogels generally deswell, swell or erode. Initiation of erosion of the polymer and release of drug from the polymer matrix occurs due to change in local pH caused by presence or absence of electric field. Kwon et al. have studied release of insulin from polymers controlled electric.In response to small electric current local pH is raised because of production of hydroxyl ions at the cathode. It disrupts the hydrogen bonds in solid state of the polymers and liquefies the polymers.[16]

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.[35, 36]. The digital capabilities of MEMS may allow greater temporal control over drug release compared to traditional polymer-based systems. 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. The reservoirs are filled with any combination of drug or drug mixtures in any form (i.e. solid, liquid or gel). 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 electrolytes which then dissolves allowing release of the drug. Complex release patterns can be achieved from the microchips. Microchip has the ability to control both release time and release rate.[14]

Magnetic stimuli-induced pulsatile release

Magnetic carriers receive their magnetic response to a magnetic field from incorporated materials such as magnetite, iron, nickel, cobalt etc. This approach uses an oscillating magnetic field to regulate the rates of drug delivery from a polymer matrix. Magnetic steel beads can be embedded in a polymer matrix with model drug. During exposure to the magnetic field, the beads oscillate within the matrix; Magnetic-sensitive behavior of intelligent ferrogels for controlled release of drug was studied by Tingyu Liu, et al. An intelligent magnetic hydrogel was fabricated by mixing poly vinyl alcohol 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 got 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_4under a given magnetic field. Tingyu Liu, et al developed the magnetic hydrogels which was successfully fabricated by chemically crosslinking of gelatin hydrogels and Fe_3O_4 nanoparticles through genipin as cross-linking agentalternatively creating compressive and tensile forces. This in turn acts as a pump to push an increased amount of the drug molecule out the matrix.[16, 28]

Ultra sound induced pulsatile release

Pulsed drug delivery can be achieved by the on–off application of ultrasound. During polymer degradation incorporated drug molecules are released by repeated ultrasonic exposure. Ultrasound is predominately used as an enhancer for the improvement of drug permeation through biological barriers, such as skin, lungs, intestinal wall and blood vessels. Incorporated drug molecules were released during polymer degradation, by repeated ultrasonic exposure. As degradation of biodegradable matrix was increased by ultrasonic exposure, the rate of drug release also increased.[16] Miyazaki and co-workers employed ultrasound to achieve up to a 27-fold increase in the release of 5-fluorouracil from an ethylene and vinyl acetate matrix. Enhancing the strength of the ultrasound resulted in a relative increase in the amount of 5- fluorouracil released. Enhancement in the rate of p-nitroaniline delivery from a polyanhydride matrix during ultrasonic irradiation is reported. [29]

Light induced pulsatile release

The interaction between light and material can be used to modulate drug delivery. This can be accomplished by combining a material that absorbs light at a desired wavelength and a material that uses energy from the absorbed light. Gold nanoshells are a new class of optically active nanoparticles that consist of a thin layer of gold surrounding a core. The optical properties of the nanoshells can be turned over the visible and near IR spectrum. When exposed to near-infrared light, nanoshells absorb the light and convert it to heat, raising the temperature of composite hydrogel above its lower critical solution. The hydrogel collapses and this result in an increased rate of release of soluble drug held within the matrix.[30]

Mechanical force induced pulsatile release

Drug delivery can also be achieved by mechanical stimulation of an implant. To achieve mechanical force induced pulsatile release, alginate hydrogels which release vascular endothelial growth factor in response to compressive forces of varying strain amplitudes were prepared. Free drug present within the polymer matrix is expelled during compression, once the strain is removed hydrogel returns to its original volume. This is similar to squeezing the drug out of a sponge.[29]

Pulsatile release systems for vaccine and hormone products

To produce protective immunity, vaccines are administered as an initial shot of an antigen followed by repeated booster shots. The frequency of the booster shots, and hence the exact immunisation- schedule is antigen dependent. Also, co-administration of vaccine adjuvant is often needed to enhance the immune response to achieve protective immunity. Pulsatile drug delivery systems 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.[31]

CONCLUSION

Circadian rhythm of the body is an important concept for understanding the optimum need of drug in the body. Diseases have certain circadian rhythms and hence the timing of medication regimens is very significant in treating chronic conditions There exists a constant need for new delivery systems that can provide increased therapeutic benefits to the patients by delivering drug at the right time, right place & in right amounts to coincide with circadian rhythm of body. Hence chronopharmaceutical drug delivery can be used in case of chronopharmacotherapy of diseases which shows circadian rhythm in their patho physiology which can tackle the problems as it is modulated to release the drug according to the biological clock. It holds good promises of benefit to the patients suffering from chronic problems like arthritis, asthma, hypertension etc. Thus designing of proper chronopharmaceutical drug delivery system with a pulsatile release will enhances the patient compliance, optimum drug delivery to the target site and minimizes the undesired effects. Various methodologies are employed for developing pulsatile drug delivery like time controlled, stimuli induced, externally regulated system and multiparticulate drug delivery system. The commercial products based on novel drug delivery systems have significantly increased in the past few years. As timing of drug administration in disease therapy has significant impact upon treatment success, in future is certainly going to gain popularity.

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