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Review Article

A Review on Types and Methodologies of Pulsatile Drug Delivery System

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ABSTRACT
Pulsatile drug delivery systems (PDDS) are gaining importance as these systems deliver the drug at specific time as per the pathophysiological need of the disease, resulting in improved patient therapeutic efficacy and compliance. Diseases wherein PDDS are promising include asthma, peptic ulcer, cardiovascular diseases, arthritis, attention deficit syndrome in children, and hypercholesterolemia. PDDS can be classified into time controlled systems wherein the drug release is controlled primarily by the delivery system; stimuli induced PDDS in which release is controlled by the stimuli, like the pH or enzymes present in the intestinal tract or enzymes present in the drug delivery system and externally regulated system where release is programmed by external stimuli like magnetism, ultrasound, electrical effect and irradiation. The current article focuses on the diseases requiring PDDS, methodologies involved for the existing systems, recent update and PDDS product currently available in the market.

Keywords: PDDS, Lag time, Circadian rhythm, erodible plug.

1. INTRODUCTION

1.1 Pulsatile drug delivery system

Traditionally, drug delivery has meant for getting a simple chemical absorbed predictably from the gut or from the site of injection. A second-generation drug delivery goal has been the perfection of continuous, constant rate delivery of bioactive agents. However, living organisms are not ‘‘zero-order’’ in their requirement or response to drugs. They are predictable resonating dynamic systems, which require different amounts of drug at predictably different times within the circadian cycle which will maximize desired and minimize undesired drug effects. Till early nineties efforts have been made to design the drug delivery system which will release the drug at fairly constant rate. In fact these systems turned to be one of the most successful systems in delivering the drug molecule. But still for many of the drugs; use of such systems is not suitable because of a number of reasons. This is particularly true in cases where the drug is subjected to large metabolic degradation. Due to ‘first pass effect’ there will be reduction in the bioavailability of the drug because; gradual release can result in greater degradation. Secondly drugs with short half-life need to be administered repeatedly which results in patient non-compliance. Further, in case of chronic treatment, where the drug is given in sustained release dosage form, continuous exposure of the drug to body may lead to adverse effect. For example, diabetes mellitus requires chronic treatment with sustained release formulations of drugs like sulfonylurea, which will damage the pancreas earlier than the corresponding immediate release dosage form. Lastly, drugs that exhibit tolerance should not be delivered at a constant rate, since the drug effect decreases with time at constant drug level. In addition drug toxicity increases with time when drug levels are held constant. In such cases it is preferable to use dosage form, which will provide desired concentration of drug at particular time point only.

Nowadays, concept of chronopharmaceutics has emerged, wherein, research is devoted to the design and evaluation of drug delivery systems that release a therapeutic agent at a rhythm that ideally matches the biological requirement of a given disease therapy. Diseases where a constant drug levels are not preferred, but needs a pulse of therapeutic concentration in a periodic

manner acts as a push for the development of **"**Pulsatile Drug Delivery Systems". In this system, there is rapid and transient release of a certain amount of drug molecules within a short time-period immediately after a predetermined off release period. Various techniques are available for the pulsatile delivery like pH dependent systems, time dependent systems, micro-flora activated systems, etc. which can be designed as per the physiology of disease and properties of the drug molecule.

In the body several physiological functions such as metabolism sleep pattern heart attacks are regulated by pulsed or transient release of bioactive substances at a specific time and site. Therefore to mimic the function of living system it is necessary to achieve pulsed release of certain amount of bioactive compounds at predetermined interval. Thus release pattern of such drug delivery is circadian pattern. The release of some drug is preferred in pulses (Fig.1). A single dosage forms provided 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 pulses of drug release. The ability to deliver a bioactive compound and therapeutic agent to a patient in pulsatile release profile is major goal in the drug delivery. This system is also called as time controlled system because the release is independent of the environment [1,2].

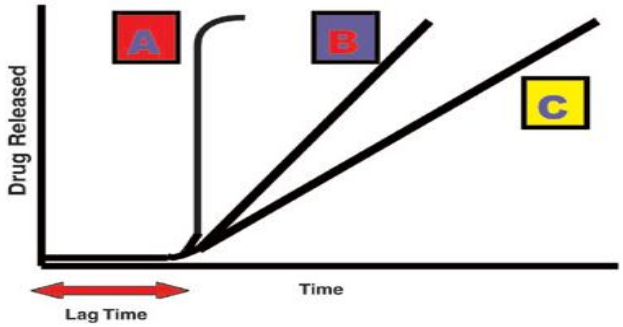

Fig. 1: Pulsatile release profile; A- release of drug as a pulse after a lag time, B - delivering the drug rapidly and completely after lag time and C – constant drug release over prolonged period of time after lag time.

1.2. Desirable properties PDDS

1. Drug should act locally.
2. It should have absorption window in GIT.
3. It should have an extensive first pass metabolism.
4. It should develop biological tolerance.
5. It should develop zero order release.

1.3. Advantages of PDDS:

1. The system is cost effective.
2. The number of dose per day can be reduced.
3. Improved patient compliance.
4. Adverse effect can be reduced.
5. As the pharmacokinetic and pharmacodynamic profile of the most drugs are subject to circadian variation pattern effective drug level are reached which could improve the therapy outcome.
6. It is useful in targeting drug delivery.
7. It is useful for drug, which develop tolerance or with an excessive first pass metabolism e.g. Beta blocker.[2,3]

1.4. Disadvantages of PDDS

1. There may be increased toxicity due to doe dumping.
2. Drug absorption is site specific.
3. Capsular system requires special equipments and manufacturing steps therefore large scale production is complicated.[2,3]

2. DISEASES REQUIRING PULSATILE DRUG DELIVERY

Thorough understanding of the disease physiology is required before designing the pulsatile drug delivery system. A disease where rhythmic circadian organization of the body plays an important role, pharmacokinetics and/or pharmacodynamics of the drugs is not constant within 24 h. Table1 enumerates various diseases showing such a chronological behavior. Asthma is one such disease where pulsatile drug delivery system can be useful. Circadian changes are seen in normal[2,3].

Table 1: Chronological behavior of diseases and drugs used

S. No.	Disease	Chronological behavior	Drugs used
1	Peptic ulcer	Acid secretion is high in the afternoon and at night	H_2 blockers
2	Asthma	Precipitation of attacks during night or at early morning hours	β_2 agonist, antihistaminic
3	Cardiovascular diseases	BP is at its lowest during the sleep cycle and rises steeply during the early morning awake	Nitroglycerin, Calcium channel
4	Arthritis	Pain in the morning and more pain at night	NSAIDs, Glucocorticoids
5	Diabetes mellitus	Increase in the blood sugar level after meal	Sulfonylurea, Insulin, Biguanide

3. METHODLOGIES FOR PULSATILE DRUG DELIVERY

Trigger systems are designed to alter rate of drug delivery in response to stimuli like changes in specific molecule, magnetic or electric field, ultra sound, temperature, light or mechanical forces. Different methodologies for the PDDS are:

1. **Time controlled**

Fabrication of delivery system that releases its contents after predetermined period.

2. **Stimuli induced**

Development of system that can respond to change in the local environment.

3. **Externally regulated**

3.1) Time controlled pulsatile release System

In time controlled drug delivery systems pulsatile release is obtained after a specific time interval in order to mimic the circadian rhythm. Such type of pulsatile drug delivery system contains two components: one is immediate release pulse and second is plug responsible for lag time.

3.2) Stimuli induced pulsatile systems

In these systems there is release of the drug after stimulation by any biological factor like temperature, or any other chemical stimuli (Fig.2). These systems are further classified in to temperature-induced systems and chemical stimuli induced system, on the basis of stimuli.

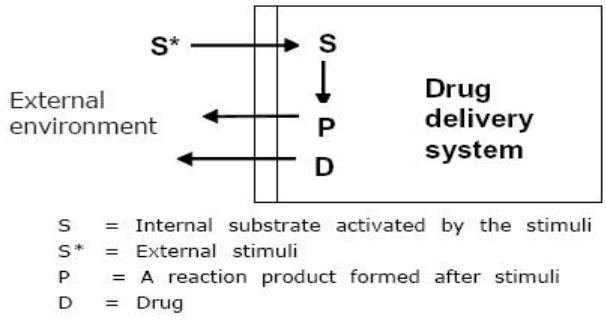

Fig. 2: Stimuli induced PDDS

3.3) 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 drug release in swollen state. Y.H. Bae et al developed indomethacin pulsatile release pattern in the temperature ranges between 20^0C and 30^0C by using reversible swelling properties of copolymers of N-isopropylacrylamide and butyrylacrylamide. Kataoka et al developed the thermosensitive polymeric micelles as drug carrier to treat the cancer. They used functionalized poly (N-isopropylacrylamide) to prepare corona of the micelle which showed hydration and dehydration behavior with changing temperature.

3.4) Chemically induced systems

3.4.1) Glucose-responsive insulin release

Devices in case of diabetes mellitus there is rhythmic increase in the levels of glucose in the body requiring injection of the insulin at proper time. Several systems have been developed which are able to respond to changes in glucose concentration. One such system includes pH sensitive hydrogel containing glucose oxidase immobilized in the hydrogel. When glucose concentration in the blood increases glucose oxidase converts glucose into gluconic acid, which changes the pH of the system. This pH change induces swelling of the polymer, which results in insulin release. 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. An example of the pH sensitive polymers includes N, N dimethylaminoethyl methacrylate, chitosan, polyol etc[1,6]

3.4.2) Inflammation-induced pulsatile release

On receiving any physical or chemical stress, such as injury, fracture etc., inflammation take place at the injured sites. During inflammation, hydroxyl radicals are produced from these inflammation-responsive cells. Yui and co-workers focused on the inflammatory induced hydroxyl radicals and designed drug delivery systems, which responded to the hydroxyl radicals and degraded in a limited manner. They used hyaluronic acid (HA), which is specifically degraded by the hyaluronidase or free radicals. Degradation of HA via the hyaluronidase is very low in a normal state of health. Degradation via hydroxyl radicals however, is usually dominant and rapid when HA 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.[1,6]

3.4.3) Drug release from intelligent gels responding to antibody concentration

There are numerous kinds of bioactive compounds which exist in the body. Recently, novel gels were developed which responded to the change in concentration of bioactive compounds to alter their swelling/deswelling characteristics. Special attention was given to antigen-antibody complex formation as the cross-linking units in the gel, since such interactions are very specific. Utilizing the difference in association constants between polymerized antibodies and naturally derived antibodies towards specific antigens, a reversible gel swelling/deswelling and drug permeation change occurs.

3.4.4) pH sensitive drug delivery system

Such type of pulsatile drug delivery system contains two components one is of immediate release type and other one is pulsed release, which releases the drug in response to change in pH. In case of pH dependent system advantage has been taken of the fact that there exists different pH environment at different parts of the gastrointestinal tract. By selecting the pH dependent polymers drug release at specific location can be obtained. 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. In one of the study carried out by Mastiholimath et al, attempt was made to deliver theophylline into colon by taking the advantage of the fact that colon has a lower pH value (6.8) than that of the small intestine (7.0–7.8). So, by using the mixture of the polymers, i.e. Eudragit L and Eudragit S in proper proportion, pH dependent release in the colon was obtained[5].

3.4.5) Externally regulated systems

For releasing the drug in a pulsatile manner, another way can be the externally regulated systems in which drug release is programmed by external stimuli like magnetism, ultrasound, electrical effect and irradiation. Magnetically regulated system contains magnetic beads in the implant. On application of the magnetic field, drug release occurs because of magnetic beads. In case of ultrasonically modulated systems, ultrasonic waves cause the erosion of the polymeric matrix thereby modulating drug release. Miyazaki et al, evaluated the effect of ultrasound (1MHz) on the release rates of bovine insulin from ethylene vinyl alcohol copolymer matrices and reservoir-type.Drug delivery systems in which they found sharp drop in blood glucose levels after application of ultrasonic waves. Mathiowitz et al developed photochemically controlled delivery systems prepared by interfacial polymerization of polyamide microcapsules. For this purpose, azobisisobutyronitrile (AIBN), a substance that photochemically a nitrogen gas, was incorporated. Due to exposure of azobisisobutyronitrile to light, nitrogen is released with increase in the pressure causing ruptures of the capsules and releasing the drug[1]

4. Classification of PDDS

PDDS can be classified as:

1) Single unit pulsatile system- it can be sub classified as:

1. Osmotic systems
2. Capsule based systems
3. Delivery systems with soluble or erodible membranes
4. Delivery systems with rupturable coating

2) Multiple unit pulsatile systems are further classified as:

1. Systems based upon change in membrane permeability
2. Systems based upon rupturable coating

4.1.1 Osmotic systems

It consists of capsule coated with a semipermiable membrane. An insoluble drug consisting of the osmotically active agents and drug formulations are incorporated inside the capsule. When this capsule comes in contact with dissolution fluid, the semipermiable membrane allows the entry of water, which causes development of pressure and the insoluble plug expels after a lag time (Fig.3). Such systems are utilized to deliver methylphenidate[1,4].

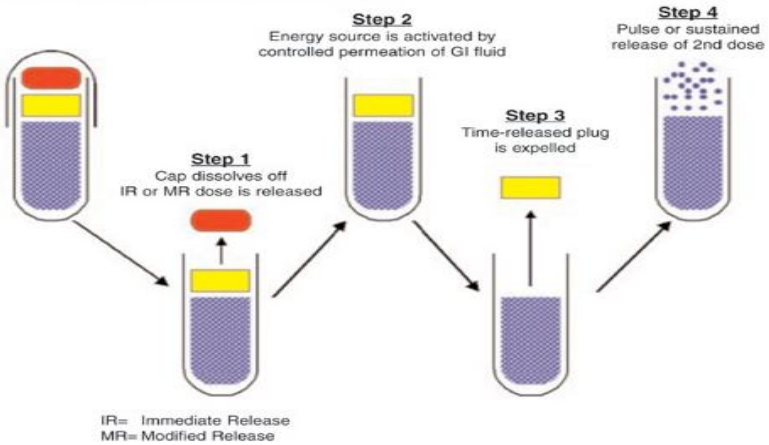

Fig. 3: Osmotic pulsatile drug delivery system

4.1.2 Capsule based system with release controlling plug

Single- unit systems are mostly developed in capsule form (Fig.4). A plug, which gets pushed away by swelling or erosion, controls the lag time and the drug is released as a “Pulse” from the insoluble capsule body. These systems contain release-controlling plug between immediate release compartment and pulsed

release compartment. On contact with aqueous fluids, the cap rapidly dissolves thereby releasing the immediate release component followed by pulsed release component. The lag time is provided by the plug, which is inserted in the body. In an approach used by Jimoh et al, pulsatile release was achieved by generation of hydrostatic pressure inside the capsule.

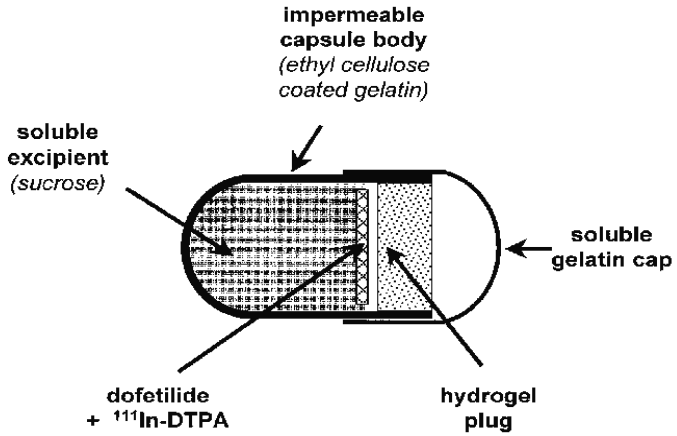

Fig 4: Capsule release based system with controlling plug.

4.1.3. Delivery systems with rupturable coating layer

These systems consist of an outer release controlling water insoluble but permeable coating subject to mechanically induced rupture phenomenon. Recently different systems based on hard gelatin capsules and tablet core were described, all coated by inner swellable and outer rutpurable layer. Including swelling, osmotic or effervescent additives in the reservoir may attain the film rupture. By optimizing the system, drug release can be obtained at specific time interval. Sungthongjeen et al developed a tablet system consisting of core coated with two layers of swelling and rupturable coatings wherein they used spray dried lactose and microcrystalline cellulose in drug core and then core was coated with swelling polymer croscarmellose sodium and an outer rupturable layer of ethylcellulose (Fig.8). Further development of osmotic drug delivery using swellable core technology where in a formulation consists of a core tablet containing the drug and a water swellable component, and one or more delivery ports[5]

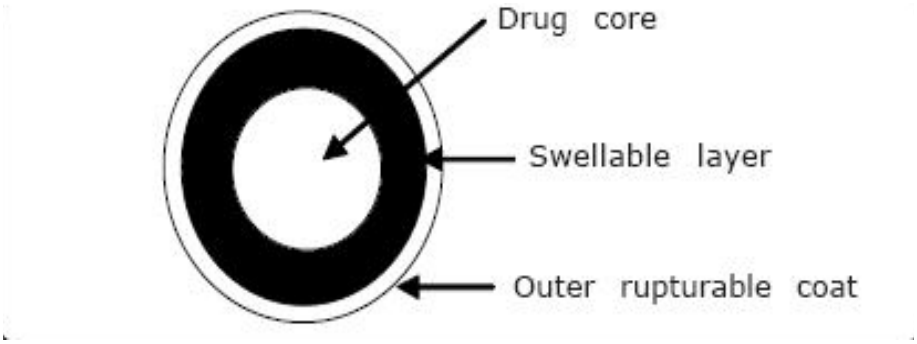

Fig. 5: Delivery systems with rutpurable coating layer.

4.1.4. Delivery systems provided with erodible coating layers

In such systems the drug release is controlled by the dissolution or erosion of the outer coat, which is applied on the core-containing drug (Fig. 6, 7). Time dependent release of the active ingredient can be obtained by optimizing the thickness of the outer coat. An oral dosage form devised to release drugs following a programmed time period after administration based on this concept. System is composed of a drug-containing core and a hydrophilic swellable polymeric coating of HPMC, which is capable of delaying the drug release through slow interaction with aqueous fluids.[5-7]

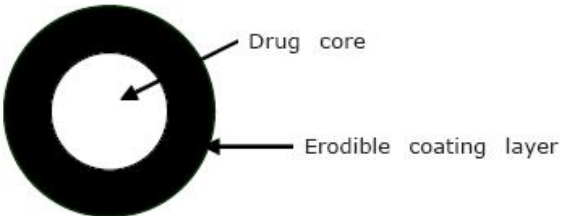

Fig.6: Delivery systems with erodible coating layers.

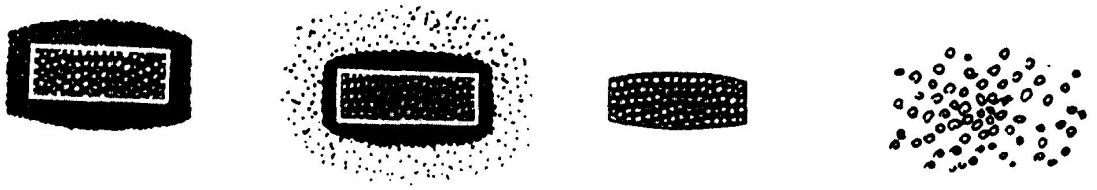

Fig. 7: Delivery systems with erodible coating layers and erosion of core.

4.2) Multiparticulate Unit Systems

The units of multiparticulate systems are distributed freely throughout the GIT; their transport is affected to a lesser extent than the single unit formulations by the transit time of food. Multiple unit pulsatile systems are further classified as:

a. Systems based upon change in membrane permeability

b. Systems based upon rupturable coating

4.2.1) Systems based upon change in membrane permeability:

In this system drug is designed in such a way that the drug releases in divided doses over timed intervals throughout a day to produce a pulsatile curved concentration with a time. The drug is formulated in a capsule form containing three types of pellets. Each pellet contains a core that comprises a drug and water-soluble modulating agent (e.g. Sodium chloride). The core is held in place with the help of binding agent like PVP. Each core is enclosed with water insoluble and water permeable film forming and a hydrophilic agent. The thickness of the coating depends upon kind of pellet. When the capsule is exposed to the physiological environment it gets dissolved and pellets are exposed to the gastric environment. The rate of release is controlled by the relative thickness on the pellets, the proportion of

hydrophobic agent in coating and the proportion of osmotic agent in the pellet. The coating of pH independent material is given to ensure that it does not disturb preset release time intervals.

4.2.2) Pulsatile systems with rupturable coating

Drug delivery controls the rupture of membrane. The timing of release is controlled by the thickness of coating and amount of water-soluble polymer to achieve the pulsed release. The individual particle has the same composition of internal core but the thickness of the external coating may be varied. Multiparticulate system offers more advantages over single unit system. These include no risk of dose dumping, flexibility of blending units with different release pattern and short gastric residence time. Many polymers and type of devices are used to provide a pulsatile release of a drug. The devices are classified according to the type of polymer used.

5. Floating - pulsatile drug delivery system

Retention of drug in the stomach prolongs overall gastrointestinal transits time and improves the oral bioavailability of the drugs having site specific absorption, pH dependant solubility and absorption window in stomach. FPDDS system having bulk density lower than that of gastric fluid thus remain buoyant on gastric fluid. Combination of floating and pulsatile drug delivery system is with the advantage that drug can be released in upper GI tract after definite time period of no drug release i. e. lag time. The lag time is defined as the time between the administration of pharmaceutical dosage form containing the drug and the beginning of absorption. Floating pulsatile drug delivery system is promising drug delivery for site and time specific release of drugs acting as per chronotherapy of diseases e. g. Verapamil HCl in ischemic heart diseases.

Floating pulsatile dosage forms floats on gastric fluid for predetermined lag time (no drug release) followed by rapid pulse release of drug. Using this principals it is possible to formulate one or two pulse release dosage forms, this systems releases two drug dosages at different time points as per chronotherapy of disease. Gorden L. and et al (2005) developed capsule system as two pulse dosage form containing first pulse of immediate release followed by lag time and then a second pulse of control release. For formulation of this multiobjective drug delivery system the pharmacokinetic parameter of drug and chronotherapy of disease are the important factors. In short floating pulsatile concept was applied to increase the gastric residence of dosage forms having lag phase followed by burst release. Such novel drug delivery has been attempted for:

i) Chronopharmacotherapy of diseases which show circadian rhythms in the pathophysiology

ii) For those drugs having absorption window in upper GI tract.

iii) For drugs having pH dependant solubility e.g. Verapamil HCL

iv) Gastro retentive: Better absorption from upper part of GIT for those drugs that are insoluble in lower GIT, thus avoid degradation. [8,9]

6. Chronotherapeutices

Chronotherapeutices is a new and advanced class of drug delivery system. It depends upon number of terms among them some of the important terms are as below:

6.1) Chronobiology

A human body has its own natural way to fight against diseases and maintain the normal homeostasis, which not only depend upon age, sex, gender, genetics, but also on various biological rhythms.

6.2) Chronopharmacology

Chronopharmacology is the study of how biological rhythms affect medication. It is an understanding of behavior of therapeutic agent with respect to time profile.

6.3) Chronokinetics

It refers to effects of biological rhythm on drug absorption, distribution, metabolism and excretion. Adrenergic receptor antagonists theophylline and NSAIDs are few example of prescribed medications that show the difference in kinetics that are dependent on administration time (circadian rhythm).

6.4) Biological rhythm

A biological rhythm is any cyclic change in the level of a bodily chemical or function. The different biological rhythms can be as follows:

i) Internal (endogenous) - Controlled by the internal biological clock e.g. Body temperature cycle.

ii) External (exogenous) - Controlled by synchronizing internal cycles with external stimuli.

e.g. Sleep/wakefulness and day/night. These stimuli are called ‘zeitgebers’ from the

German meaning “time givers”. These stimuli include environmental time cues such as sunlight, food, noise, or social interaction. Zeitgebers help to reset the biological clock to a 24 h day.

iii) Circadian rhythms – Endogenously generated rhythms with a period close to 24 h.

iv) Diurnal rhythms – a circadian rhythm that is synchronized with the day/night cycle.

v) Ultradian rhythms – biological rhythms (e.g. feeding cycles) with a period much shorter (i.e., frequency much higher) than that of a circadian rhythm.

vi) Infradian rhythms – biological rhythms with a cycle of more than 24 h (e.g. the human menstrual cycle).

vii)

6.4.1) Circadian Rhythms

Circadian is derived from a Latin phrase meaning "about a day'' [about (circa) and a day (dia)] Circadian rhythms are physiological and behavioral rhythms include:

- Sleep/wakefulness cycle
- Body temperature
- Patterns of hormone secretion
- Blood pressure
- Digestive secretions
- Levels of alertness reaction times
- Circadian rhythms have a period of approximately 24-25 h.
- When the rhythm is synchronized with the day/night cycle it is termed diurnal rhythm

6.4.2) Circadian Clock

In humans (and other mammals), a circadian clock is located in the suprachiasmatic nuclei (SCN).

The SCN is in the hypothalamus and it is a tiny cluster of about 10 thousand nerve cells.

This circadian clock is synchronized to the external cycles of light and darkness and social contact. The synchronized rhythm is called the diurnal rhythm.

Disruption of the clock or its synchronization occurs during jet-lag, shift work and old-age.

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6.5) Circadian rhythm dependencies

Various body functions shows dependency on circadian rhythm and these variations ultimately affect the diagnostic parameter in different diseases. e. g. the erythema and indurations reaction of intradermal allergen is two to three fold greater in the late afternoon and in the early evening, than in the morning. Determination of the blood pressure is affected by the time of measurement to a great extent Systolic and diastolic blood pressure is highest in the afternoon. In the evening it begins to decline attaining lowest level during sleep. The variation is attributed to temporal pattern in activity, stress and posture during 24 h. and circadian rhythm in nervous and endocrine system. Similarly patient response to the glucose tolerance test is greater in the morning than the evening. It has found that most of the organ systems perform their function in circadian rhythm pattern. e. g. pulmonary, cardiovascular, renal, hematological, immunologic, motor function and general physiologic function such as organ blood flow, organ coordinated rhythm in cell cycle phase, distribution and drug metabolism. At the cellular level, many cell functions, enzyme activities, protein phosphorylation protein and hormone and hormone receptor concentration and gene expression have also been shown to vary predictably as a function of time of day[11]

6.5.1) some of the physiological activities showing circadian rhythms

i) Intraocular Pressure (IOP)

In glaucoma patients IOP peaks at 4 am and has a trough in the afternoon, opposite that of people with normal IOP.

1. Hormone Secretion

Growth hormone and melatonin are produced at night where as testosterone and cortisol in the early morning hours.

2. Gastric Motility

Slower at night, which can impact controlled-release Product design.

3. Blood Coagulation

Even with constant heparin infusion rate, thromboplastin time and risk of bleeding vary significantly during the day.

4. Asthma Treatment

Evening dosing can improve lung function during sleep.

7) Chronotherapy

Chronotherapeutic products can synchronize drug delivery with circadian rhythms in order to optimize efficacy and minimize side-effects. This is one avenue to extend the useful life of a drug substance and create new dosage forms. A less expensive development proposition with potentially higher returns given the time to develop a product based on new chemical entity or even a combination product for a new indication. Various diseases like asthma, hypertension and acidity show circadian variation. To follow this principle one must have

to design dosage form such that it can be given at the convenient time e.g. bed time for the above mentioned diseases with drug release in the morning. Drug pharmacokinetic too show circadian variation for various anti-inflammatory drug like the indomethacin, ketoprofen and diclofenac sodium which have grater absorption in the morning as compared to evening and site specific absorption from the small intestine. The outdated western theory of "homeostasis" taught that the probability of risk or intensity of disease was equal throughout a specific period. However, Chronobiology (the quantitative study of the rhythmic temporal relationships of biological phenomena) has quite clearly been proven across many biological functions. It is time optimized therapy i.e. chronotherapy can refer to the time within the circadian cycle, menstrual cycle, or other longer biological cycles such as yearly cycles. The important fact is chronotherapy generally does not involve new medication but old ones are used in such way that they will produce drug effect in time-controlled manner and the desired drug release should be time specific as well as site specific too.[7-12]

10) Cancer drug administration and chronotherapy

The goal of developing chronotherapeutic products to optimize the desired effects of a drug and minimize its undesired ones can be achieved in certain disease states. The benefits of chronotherapy are well established in the treatment of cancer, and the timing of chemotherapy drug administration can improve treatment tolerability and permit higher, more efficacious dosing. Furthermore, there is a high incidence of disease symptoms and adverse events in the morning hours, so ensuring that adequate plasma levels of a drug are present in the morning can be critical to effective treatment of many diseases, including cardiovascular disease Development of suitable chronotherapeutic oral dosage forms can be achieved using delayed- and/or pulsatile-release technologies. In the present work, an attempt has been made to formulate and evaluate floating pulsatile drug delivery system of captopril based on impermeable cylinder.[1]

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