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A REVIEW ON CHRONOTHERAPEUTIC DRUG DELIVERY SYSTEM

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ABSTRACT

Chronotherapeutics refers to the delivery of the drugs according to the human circadian rhythm. Recent development in the pharmaceutical technology has lead to the development of chronotherapeutic drug delivery system. This system minimize the side effects of drugs and highly effective as it is administered with a consideration of biological rhythms of human beings. It is beneficial for the patients suffering from diseases like cardiovascular diseases, arthritis, asthma, cancer, and ulcer. Pulsatile drug delivery system delivers drug at the specific time at specific site.

KEYWORDS: chronotherapy, circadian rhythm, pulsatile drug delivery system.

INTRODUCTION

Chronotherapeutics refers to the treatment of diseases according to human circadian rhythm. Circadian rhythm is the 24 hours internal clock in our brain that regulates physical, mental, behavioral changes. Biological clock regulates circadian rhythm to carry out the important functions like sleep, awakening cycle, blood pressure, hormone secretion, metabolism etc., Circadian rhythm disruption causes due to the environmental factors and genetics. It can affect the hormone release, eating habits, body temperature and digestion. Oral route is the most commonly used drug delivery system due to its advantages and patient compliance. Recently chronotherapeutic drug delivery system is gaining importance in the field of pharmaceutical technology as this reduces the side effects, and it is more effective than any other drug delivery system in calculating the frequency of dose and maximizing the therapeutic effects. Hence the field of chronotherapy paves the way for the advances in the

drug delivery system.

BIOLOGICAL CLOCK

Biological clock regulates the circadian rhythm. Biological clocks are periodic natural changes in the function of the body, or chemicals while circadian rhythm is the periodic bodily, mental and behavioral changes that follow a 24-hour cycle.

TYPES OF BIOLOGICAL RHYTHM

Diurnal	-	day and night
Circadian	-	24 hours
Ultradian	-	less than 24 hour
Sinfradian or Circalunar	-	1 month
Circannual	-	1 year

CIRCADIAN RHYTHM

Circadian rhythm is a sleep-wake cycle pattern for 24 – hour day. It helps to control human's daily schedule for sleep and wakefulness. The time takes for a circadian rhythm to run one cycle is called period of the rhythm. Mostly the natural or innate period of the rhythm is not exactly 24-hours for human beings, due to the regular changes in light and temperature that they experience in their environment which helps to adjust the biological clock.

Figure 1: Circadian rhythm.

MASTER CLOCK

Hypothalamus is the master clock in the human body that coordinates all the biological clocks and keeps them in synchronization. In human beings, the master clock is the group of twenty

thousand neurons found in the region called suprachiasmatic nucleus or SCN.[1] The neurotransmitters present in the SCN involves in the entrainment and control of the rhythms. Neurotransmitters like acetylcholine, glutamate, vasoactive intestinal peptide [VIP], arginine vasopressin [AVP], peptide histidine isoleucine [PHI] have been implicated in the functioning of SCN. These are required for the normal functioning of the clock.

CHRONOBIOLOGY

The study of science dealing with the rhythms in the living organisms is called chronobiology.

CHRONOPHARMACOLOGY

The study of science dealing with the pharmacological variations of the drug is in respect to the biologicaltimings. Chronopharmacology is further subdivided into

Chrono kinetics / Chrono Pharmacokinetics

Chronoesthesy

Chronotherapeutics

CHRONOPHARMACOKINETICS

Chrono pharmacokinetics deals with the time dependent dosage form and predictable rhythmic variations in the parameters used to characterize the bioavailability of the drug. Kinetic changes can occur from the factors like sex, age and phenotype. Physiological factors like cardiovascular, intestinal, renal and hepatic conditions vary according to the time in human beings. Hence dosing time of the drug and the subject synchronization plays a major role in the chrono kinetics.

Drug absorption

Gastric emptying, pH, structure of biomembrane, gastrointestinal blood flow, gastric motility, influences the drug absorption process in oral route administration. Studies on circadian cycle stated that the gastric emptying rates were comparatively higher in the morning than the evening. Most of the lipophilic drugs are absorbed faster in the morning due to higher GI perfusion and gastric emptying in the morning. These changes contribute to the time dependent dosage difference of the drug.

Drug distribution

Blood flow increases during daytime and decreases in the night time due to the sympathetic

and parasympathetic systems which are controlled by the circadian cycle. Hence it affects the distribution of drugs with narrow therapeutic index in the night time which may also lead to mild to moderate level toxicity.

Drug metabolism

By affecting the blood flow in the liver, circadian rhythm affects the clearance of the drugs. Enzymes involved in the phase I, II metabolism and present in the tissues of brain, liver and kidney are controlled by this rhythm. Metabolism rate of drugs depends on the oxidative reactions catalysed by these enzymes. So, when the drug is administered when the oxidative reactions are at lowest, it affects the energy status of the individual resulting inthe metabolic syndrome. This syndrome can be prevented by the deeper understanding of the pathogenesis which helps in fighting against the disease.

Drug excretion

Kidney is mainly responsible for the excretion in human being; lack of sleep can disturb its normal function andblood pressure patterns.

For example, Excretion of urinary sodium, potassium and water is suppressed by the kidney to prevent theloss of nutrients in night time while it does not affect in day time.

Rhythmic changes of excretion are disrupted in patients with chronic kidney disease. In such condition intakeof drug without the knowledge of the kidney cycle can alters the homeostasis and leads to renal dysfunctions.

CHRONOESTHESY

Chronoesthesy is defined as the administration of a drug based on the circadian rhythm differences in the drug pharmacodynamics. Pharmacodynamics deals with the study of biochemical and physiological effects of the drugs on the body and their mechanism of actions at organ / cellular level. Chronoesthesy is the counterpart of the chrono pharmacodynamics. Rhythms in the metabolic pathways, secondary messengers and receptors help to determine this phenomenon. Several drugs have been influenced on their pharmacodynamic properties due tothe timings of administration.

DRUGS SHOWING VARIATION IN THEIR PHARMACODYNAMIC PROPERTIES

Action of local anaesthetics is longest in the noon time.

Anti – anginal drugs like isosorbide dinitrate have high therapeutic effect around 2 A.M

Analgesic drugs like dihydrocodeine and tramadol exert stronger effects in the evening.

Adrenergic β blockers especially propranolol peak concentration is achieved between 8 A.M. and 2 A.M. Calcium channel blockers are effective in lowering blood pressure during night time than day time.

NSAIDs are effective in pain reduction when taken in the morning.

As the pharmacodynamic properties of each drug differ from each other, right time administration of thesedrugs should be chosen by performing clinical trials.

CONCEPT OF CHRRDS

The therapeutic action of the drug for a whole day is not important in this system as it releases drug at once as a pulse after the time lag based on the circadian rhythm of the diseased state. The drug is thus available at the right time to produce therapeutic action and to meet the needs. Chronotherapy can be achieved by controlled drug release or delayed drug release or pulsed drug release.

Delayed release formulations includes time controlled drug release and site specific dosage forms.[2] By timing administration of the drug, the plasma peak is achieved at an optimal rate and the frequency of the dose can be reduced.

CONTROLLED DRUG RELEASE

The United States Pharmacopeia (USP) defines the modified release (MR) dosage form as "the one for which the drug release characteristics of time course and / or location are chosen to accomplish therapeutic not offeredby conventional dosage form such as solution, ointment, promptly dissolving dosage form".

DELAYED DRUG RELEASE

This term is used for enteric coated dosage forms that are intended to delay the release of the medicament until it has passed through the stomach. Capsules, tablets may be coated, or encapsulated to restrict the releasing of drug in the gastric fluid of the stomach where a delay is important to alleviate potential problems like drug inactivation and gastric mucosal irritation.

PULSATILE DRUG DELIVERY SYSTEM

Pulsatile drug delivery system can be defined as the rapid release of drug within a short time period immediately after a predetermined lag time.[3] In various disease we can recommend the pulsatile drug delivery system such as duodenal ulcer, cardiovascular disease, asthma,

neurological disorder, cancer, hypertension and hypercholestemia etc.

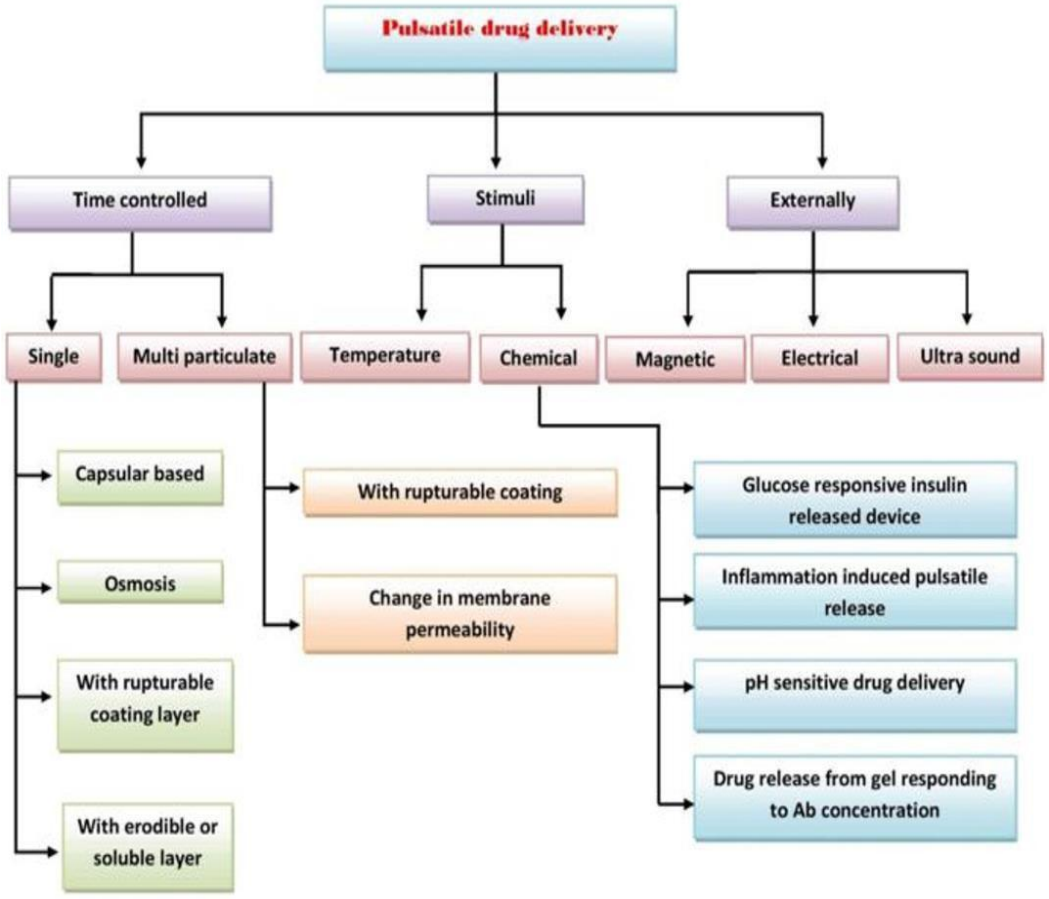

Figure 2: Classification of pulsatile drug delivery system.

TIME CONTROLLED PULSATILE DRUG DELIVERY

Release of the drug within a short time period of time immediately after a pre – determined lag time is called as time-controlled release system. The drug release is independent of the gastrointestinal transit time, motility, pH and enzymes.

Single unit system [tablets and capsules]

Single unit system consists of a core, swelling agent and a coating film of ethyl cellulose. Core contains thedrug and a disintegrating agent.

Capsule based

Capsule based pulsatile drug delivery system consists of capsule with swellable plug or system based osmosis and capsule based on expandable orifice. In capsule with swellable plug, a insoluble body contains drug and aplug. The plug is removed after the predetermined time lag due to swelling, erosion, or dissolution. The plug material consists of permeable and

swellable polymers like polyvinyl alcohol and polyethylene oxide.

Capsule based system osmosis consists of a capsule enclosed in a semi permeable membrane. The capsule contains an insoluble plug and an osmotically active agent along with the drug. When it comes in contact with the body fluids, water diffuses across the semi permeable membrane. Due to increase in pressure, the plug is ejected after a time.

Capsule based on expandable orifice contains a liquid drug layer, an osmotic engine, push layer and semi permeable membrane coating. When the system is in contact with the aqueous surrounding, water permeates across the rate controlling membrane and activates the osmotic layer. The osmotic layer is activated when the system is in contact with the water. The expansion of the osmotic layer results in the development of pressureinside the system, which results in the delivery of the liquid. 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.

Osmosis based system

Osmosis capsule have micropores at the bottom of the capsule made up of ethyl cellulose. A swellable layer is present in the bottom of the capsule body. Drug reservoir contains drug, lactose and starch. After administration of the drug, water molecules penetrate through micropores, hydration and swelling increases internal osmotic pressure results in explosion of the capsule and the drug releases after that burst.[4]

With rupturable coating

This system consists of a reservoir system coated with rupturable membrane. When water enters into the system, the swellable layer expands resulting in the rupture of film with rapid drug release. The effervescent excipients, swelling agents provide the necessary pressure for the rupture of the coating.[5]

With erodible or soluble layer

This system consists of a drug reservoir coated with soluble or a erodible barrier. Outermost erodible layer consists of ethyl cellulose, plasticizer, diethyl phthalate, hydroxy propyl methyl cellulose. Barrier layer erodes in the aqueous environment and the drug is released rapidly.[4]

MULTIPARTICULATE SYSTEM [pellets]

In this system, drug is coated on non-pareil seeds followed by a swellable layer and an

insoluble layer.[5]

With rupturable coating

The drug is coated with a non-pareil sugar seeds, the release is independent of environmental factors like drugsolubility and pH.

Change in membrane permeability

The capsule contains many coated particulates to deliver therapeutic agents into the body, drug release can beachieved by changing the permeability of the coating layer.

STIMULI INDUCED RELEASE SYSTEM

Temperature

When the temperature is high, drug releases in the swollen state.

CHEMICAL STIMULI INDUCED SYSTEM

In glucose responsive insulin release device, drug releases after the stimulation by any biological factors. It delivers drug in exact amount at the exact time of need unlike other drugs. These devices are developed with a sensor. The swelling of the polymer is caused by change in pH. The system turns to deswelling mode when theblood glucose level is reduced and the gluconic acid level is also decreased.

In inflammation induced pulsatile release, hydroxyl radicals are produced from the inflammation responsive cells, it can be treated with hyaluronic acid gels. This system can be used for treating inflammatory diseases.[6]

pH sensing drug delivery releases the drug in response to the change in pH, pH dependent polymers are used inthis system for releasing the drug at specific location.[7]

Novel gels were developed which responses to the change in concentration of the bio active compounds. Drugs can be released from gels in body when there is change in antibody concentration.[8,9]

EXTERNAL STIMULI PULSATILE RELEASE SYSTEM

Magnet induced release

Oscillating magnets are incorporated to the polymer matrix, it receives magnetic field from materials like nickel, iron and cobalt. The travel speed of the drug through the stomach and

intestine can be controlled by an external magnet which changes the absorption of the drug.

Electric induced release

This system is prepared with polyelectrolytes that contain ionisable groups, under the influence of electric field or change in pH hydrogels swell and release the drug.

Ultrasound induced release

Polymer undergoes degradation during the ultrasound exposure, by improving the strength of ultrasound theamount of drug release can be increased.[10]

DISEASES AND CHRONOTHERAPEUTICS

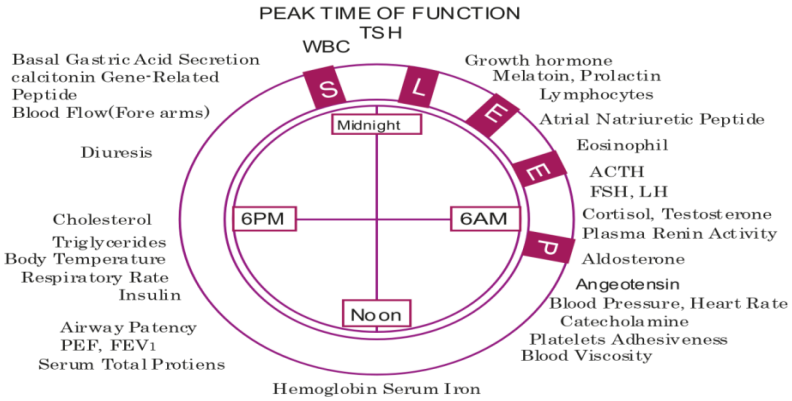

Figure 3: Human circadian time structure.

Circadian rhythm of human body plays a major role in the treatment of diseases, both physiological functions and pathological states of diseases follow rhythmic process. Treatment of diseases according to the chronological behaviour can benefit patients suffering from ulcer, allergic rhinitis, asthma, hypertension, arthritis etc., Mostly heart attacks appears to be increase in early morning so release of antihypertensive drug during the vulnerable period of 1 am to 6 am can decrease the risk of cardiac arrest.

Acid secretion in the stomach is highest at night time, intake of anti-ulcer medications in the night time has adominant impact than taking it during the day time.

Likewise in the case of asthma, cortisol secretion is high at the time of awakening so the anti-asthmatic medications can developed with delayed drug release method which delivers the drug during morning uponnight administration of the drug.

CONCLUSION

The main goal of the chronotherapeutic drug delivery system is to provide therapeutic action by targeting the specific site at specific time. This system can increase the benefits for the patients and decrease the side effects of the drug. Pulsatile drug delivery system plays a key role in correlating the biological rhythms. Chronotherapy is an important tool to overcome the drug delivery problems. Currently there are some anti-hypertensive agents that are modulated according to human circadian rhythm which are more effective than other hypertension medications.

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