REVIEW ARTICLE

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Chronotherapeutic drug delivery systems

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ABSTRACT

Chronobiology is the study of biological rhythms. A lot of diseases have been found that have shown rhythm in their symptoms and severity. For the treatment of such diseases, the timing of drug administration has to be matched with circadian rhythms of the disease and such treatment is called chronotherapy. If the symptoms of a disease display circadian variation drug release should also vary over time. The drug delivery systems are designed to release the drug within the short period of time, immediately after a predetermined lag time. As the name suggests, these systems are meant for chronotherapy, treatment of those diseases that are caused due to circadian changes in the body. Chronotherapeutic systems are developed when zero-order drug release is not desired. Present review of chronotherapeutic gives a comprehensive emphasis on potential disease targets, revisits the existing technologies at hand and addresses the theoretical approaches to emerging the target based on specific molecules.

Key words: Chronotherapeutic, chronotherapy, circadian, hypertension, nocturnal asthma

INTRODUCTION

In daytime, many functions of human body vary considerably. Due to these variations in body, both diseased state and plasma drug concentrations may change.[1] Human circadian rhythm is based on sleep activity cycle, which is directly influenced by our genetic makeup and hence affects the functions of the body during day and night.[1]

Since early times, the daily rhythms in plants and animals have been observed. In 4th century BC, Alexander the Great's Scribe Androsthenes observed some rhythmicity in the leaves of certain trees. He noted that the leaves of certain trees opened during the day and closed at night, which shows clear rhythmicity.[2] Similarly, human brain release number of hormones in the morning while some other are released during sleep. During the h of 6:00 a.m.-12:00 noon, the level of blood pressure and heart rate is at the highest peak.[3]

Several diseases follow circadian rhythm such as - hypertension, asthma, peptic ulcer, and arthritis,[4] for example, - osteoarthritis worsens during the day, and it is most bothersome in the evening. However, in the case of rheumatoid arthritis, the pain usually peaks in the morning and decreases as the day progresses.[5] Cardiovascular diseases such as hypertension, angina, and chest pain also follow a definite circadian rhythm.[5]

The goal of drug delivery research is to develop a formulation to achieve therapeutic need relating to particular pathological conditions.[6] The living systems are predictable dynamic resonating systems which require different amounts of drug at expected times within the circadian cycle which will maximize the desired and minimize the undesired drug effects.[2]

It is not surprising that all the functions of the human body are organized and synchronized in time from the single cell to the genome.[7] Chronotherapeutic drug delivery systems have fulfilled this requirement. Chronotherapeutic drug release in such a system where the drug is released according to the circadian rhythm of disease states, i.e., suddenly after well-defined lag time.[8]

Hence, a novel drug delivery approach; chronotropic systems have been designed for the following reasons.

1. It is designed for chronopharmacotherapy of disease in which circadian rhythms play an important role in their pathophysiology.
2. This delivery is designed to avoid large metabolic degradation of drugs including proteins and peptides in upper gastrointestinal tract (GIT).
3. For programmed delivery of hormones, since continuous release dosage forms may lead to disturbance in normal feedback mechanism of the body.
4. This method is good for the drugs with extensive first-pass metabolism and targeted to a specific site in the intestinal tract, for example, colon.[9]

In these systems, there is a transient release of a certain amount of drug within a short period of time, immediately after a predetermined off- release period. In chronotropic systems, there is a specificity in delivering a higher amount of drug in a burst at circadian timings correlated with the specific pathological disorder to achieve the maximum effect of drug.[10]

Drug release pattern from the device with pulsatile effect is shown in Figure 1.[11]

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CHRONOPHARMACEUTICS

Chronopharmaceutics consists of two words: "Chronobiology" and "Pharmaceutics;" chronobiology is the study of biological rhythms and their mechanisms.[10,12]

Chronotherapeutic drug delivery systems are formulated to deliver the drug to match timings of the disease. The delivery of drugs can be done either after a lag-phase or can be sustained release.

In our body, there are three types of biological rhythms:

Circadian Rhythms

The term "circadian" is derived from Latin words "circa" meaning about and "dies" meaning day. Oscillation in our body that is completed in 24 h is termed as circadian rhythms.

Ultradian Rhythms

Oscillation in our body that is completed in <24 h is termed as ultradian rhythms.

Infradian Rhythms

The oscillation that is completed in more than 24 h is termed as infradian rhythms.[10,12]

Circadian Time Structure

The human circadian time structure is used to depict the peak time of 24 h. Rhythms on a clock like a diagram as shown in Figure 2.[12]

Figure 2 shows the peak time of a selected number of human circadian rhythms in relation to the synchronized routine of most of the human being's. A synchronizer is an environmental time clue that affects the period and phase of rhythms sleep from 10:30 p.m. to 6:30 a.m. activity between 6:00 a.m. and 10:30 p.m.[13]

Blood cell count, basal gastric acid secretion, atrial natriuretic peptide, calcitonin gene related protein peak at late night or early in sleep. Growth hormone, thyroid stimulating hormone, eosinophil number, blood lymphocyte, plasma melatonin and prolactin crest during sleep same as the adrenocorticotropic hormone, follicle stimulating hormone, luteinizing harmone. The peak in plasma cortisol, rennin activity, angiotensin, and aldosterone occurs in the morning as do vascular resistance, arterial compliance, platelet aggregation, and blood viscosity. Hemoglobin and insulin concentration peaks at noon and in the afternoon, same as do the PEF, FEV_1. The circadian rhythms of serum cholesterol and triglycerides crest early in the evening. Through Figure 2, the information conveyed clearly illustrates that physiology and biochemistry of human beings are not constant, they vary along with time, i.e., (during 24 h time structure).[13]

MECHANISM OF BIOLOGICAL TIMEKEEPING

The circadian rhythm of our body is chiefly controlled by suprachiasmatic nuclei that are situated in the hypothalamus and pineal gland.[14,15] The rhythmic activities of the genes which are said to be clock genes such as per^1, per^2, and per^3 clock and the nocturnal secretion of melatonin from pineal gland comprises the central timekeeping mechanism. This master clock controls the duration and phase of the multitude of the circadian clocks present in the cells, tissues, and organ system. Biological timekeeping is an adaptation that has evolved with time due to the cyclic phenomenon being displayed in the environment; therefore, their temporal organizations being executed during the 24-h period ensure the peak functioning of the humans during the day, and restoration and repair during the night time. Furthermore, it proves to be helpful all along the years by making a prior adjustment to changes and challenges related to different seasons of the year [Figure 3].[13]

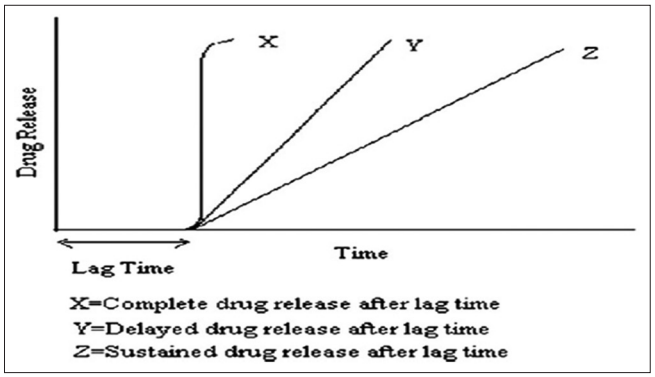

Figure 1: Drug release pattern from the device with pulsatile effect

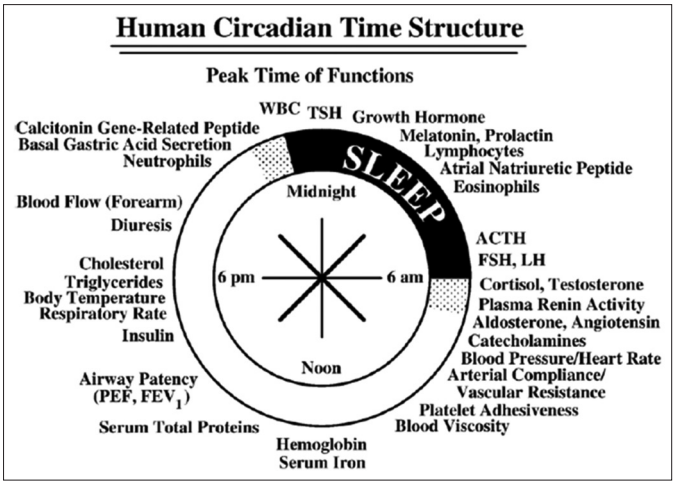

Figure 2: Circadian time structure

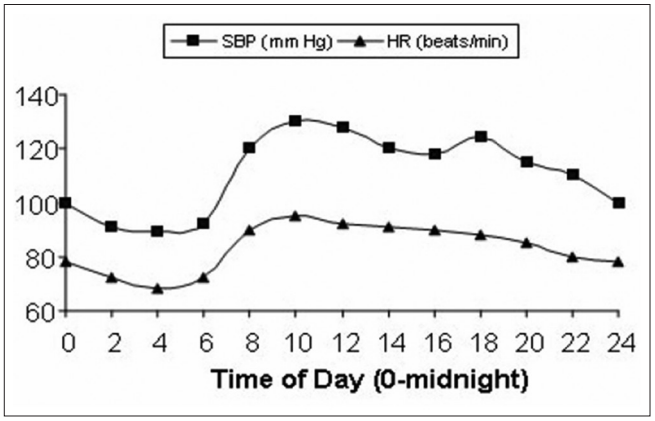

Figure 3: Circadian variation in systolic blood pressure and heart rate[12]

DISEASES WITH ESTABLISHED CIRCADIAN RHYTHMS

Till now, drug delivery systems designs have been governed by the homeostatic theory. This theory is based on the assumption of biological functions that show a constancy over time.[16,17] However, chronobiology studies have established a circadian rhythm for almost all body functions, for example, blood pressure, body temperature, heart rate, plasma concentration of various hormones, gastric pH, and renal function.[17] Pathological states of the disease have circadian rhythms, similar to that physiological functions vary over time. Epidemiological studies have submitted the elevated risk of disease symptoms during the 24-h cycle as shown in Figure 4.

Particular rhythms in the onset and many symptoms were observed in diseases such as myocardial infarction, bronchial asthma, ulcer, diabetes, hypercholesterolemia, and hypertension.[12]

There is a great deal of interest in how chronotherapy can particularly benefit patients suffering from asthma, cancer, cardiovascular diseases, and peptic ulcer diseases.[4] For example, - in case of Asthma, most attacks occur after midnight or in the early morning, the reason behind is low lung function which is promoted by circadian changes at that time.[18] In case of allergic rhinitis, patients suffer their worst symptoms in the early morning when they wake up. In this situation, patients should take a long-acting antihistamine at night rather than taking the medication in the morning. This will get better results from this morning discomfort, and it is very frequently recommended.[1] Diseases showing rhythmicity in their symptoms are enlisted in Table 1 and Table 3 enlists some FDA approved chronotherapeutic formulations.

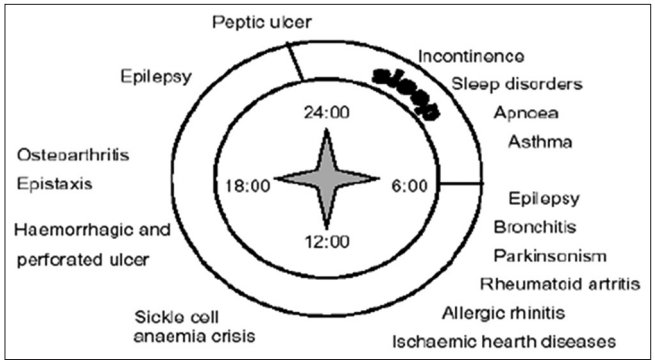

Figure 4: Diseases known to display a circadian rhythm

ANTI-INFLAMMATORY THERAPY

Individuals who suffer from rheumatoid arthritis and related joint disorder, are suggested to take the nonsteroidal anti-inflammatory agents (NSAIDs). These agents are more effective at relieving pain if the drug is administered at least 4–6 h before the pain reaches the peak. If arthritis patient experiences a particularly high level of discomfort in the morning, they should take NSAIDs before bedtime.[19]

ANTI-ASTHMA THERAPY

It has been estimated that symptoms of asthma are mostly found at night than during the day.[20] Many circadian dependent factors appear to contribute to the worsening of nocturnal asthmatic symptoms. For example, cortisol levels reached a maximum at the time of awakening and were lowest in the middle of night and histamine concentrations were found maximum at the time of 4:00 am.[4] Research finding also reveals that theophylline absorption is slower at night. Thus, enhanced understanding of chronobiology impact on the pathology of asthma, and drugs used in its management have led to new approaches to disease management.[21]

CHEMOTHERAPY

Antineoplastic drugs cause cytotoxic effects on both healthy and diseased tissue. Thus, the biological rhythms of both healthy and tumor cells may affect the susceptibility of normal and malignant cells to the agents.[20] It has been noted that "susceptibility rhythms" to drugs may differ between healthy and cancerous tissue. Therefore, the timing of drug treatment should be correct which may help to reduce the host toxicity, increase maximum drug tolerance and finally, result in better tumor management. The pharmacological and pharmacokinetic properties of the drug, mitotic activity, and DNA and RNA synthesis may also influence tumor cell susceptibility.[4] It shows that the timing of drug administration in the treatment of cancer can have a significant impact on treatment success.

CARDIOVASCULAR THERAPY

Cardiovascular disorders such as angina, heart attack, hypertension, stroke and sudden cardiac death have shown

Table 1: Enumerates various diseases with their chronological behavior and symptoms[10]

Disease	Chronological behavior and symptoms	Drugs used
Asthma	Precipitation of attacks after midnight or at early morning hours	Beta-agonist, antihistaminic
Cardiovascular diseases	BP lowers during sleep cycle but rises steeply in early morning hours	Nitroglycerin, calcium channel blockers
Arthritis	Increased concentration of c-reactive protein and interleukin-6 in blood. Pain in the early morning	NSAIDs, glucocorticoids
Diabetes mellitus	Increase in blood sugar level after meal	Sulfonylurea, insulin
Attention-deficit syndrome	Increase in DOPA level in the afternoon	Methylphenidate
Hyper cholestemia	Increased cholesterol synthesis during the night with respect to daytime	HMG CoA Reductase inhibitors
Peptic ulcer	Acid secretion increases in the night as well as in the afternoon	Proton-pump blockers

NSAIDs: Nonsteroidal anti-inflammatory agents

rhythmicity in their symptoms. The differences in patterns of illness between day and night for these disorders have been documented. Dosing schedules have been made; medications have been formulated to provide an appropriate concentration of a drug in body where the drug is most needed. For example, blood pressure of a hypertensive patient increases rapidly after awakening and it peaks in the middle to the late time of the day, decreases in the evening and it is lowest while the patient sleep at night.[1]

Heart attack appears to be greatest in the morning after awakening. At present, there are antihypertensive products in the market that is chronotherapeutic mediations with novel drug delivery systems, releasing drug during the vulnerable period of 6:00 a.m.–noon on administration of medications at 10:00 p.m.

some of these are given in Table 2.

ANTIULCER THERAPY

Patients with peptic ulcer disease experience the greatest degree of pain at the time they go to bed, as the rate of stomach acid secretion is highest at night. Thus, the timing of administration of ulcer medications has a significant impact on their therapeutic effect.

Advantages of Chronotherapy

- Avoidance of undesirable side effects.
- Reduced dose.
- Improved patient compliance.
- Used for drugs with chrono-pharmacological behavior, a high first pass effect, the requirement of night-time dosing and site-specific absorption in GIT.[22]

Disadvantages of Chronotherapy[23]

- It develops a non-24-h sleep-wake syndrome after the treatment as the person sleeps for over 24 h. During the treatment, it is not quite common, but the degree of risk is not known.
- Person going through the therapy may feel unusually hot or cold sometimes.
- Must consult the doctor regularly to avoid side effects.
- Person becomes less productive during chronotherapy and staying awake till the other schedule becomes a bit uncomfortable.
- Person may also be sleep deprived sometimes.

Various Approaches to Design Chronotropic Systems to Achieve Chronotherapeutic Drug Release

Various methods have been developed and applied to design chronotropic systems to achieve pulsatile drug release. These methods are mainly classified into three major categories.[3]

- Time controlled chronotropic systems.
- Stimuli induced pulsatile drug delivery systems.
- Externally regulated pulsatile drug delivery systems.

Time Controlled Chronotropic Systems

In these type of system, the drug releases within a short period of time immediately after a predetermined off release period. These systems are further classified into different types [Figure 5].[3]

a. Time controlled chronotropic systems based on capsule - "Pulsincap system" is one of the most used Pulsatile systems based on the capsule. It consists of an insoluble capsule body, swellable and degradable plugs which are made of approved substances such as bioactive molecules and polymers. The length of plug determines lag time. This total system is locked by a soluble cap of the capsule shell which is dissolved by the presence of dissolution or gastric fluid. After absorbing the gastric media, the plug swells and pushes itself outside the capsule and releases the drug. Many drugs have been formulated in the form of "Pulsincap System" for a Peptic ulcer, hypertension, etc.[24]
b. Time controlled reservoir systems with rupturable polymer coating.

These are either single unit or multi-particulate reservoir systems which are coated with a soluble or erodible barrier. On dissolution or erosion of that barrier, the drug is released from the reservoir.[12]

According to the nature of drug, the mechanism of drug release is either diffusion or dissolution. Time controlled explosion systems for water-insoluble drugs in both single and multi-unit dosage form were discovered by Ueda *et al.*[25-28] Both types

Table 2: Some chronotherapeutic antihypertensive products

Product	Generic name	Manufactures
Innopran XL	Propranolol	Glaxosmithkline USA
Cardizem LA	Diltiazem	Biovail Corporation Mississauga, ON Canada
Verelan PM	Verapamil	Schwarz Pharma Monheim, Germany
Covera HS	Verapamil	G. D. Searle (a division of Pfizer), NY, USA

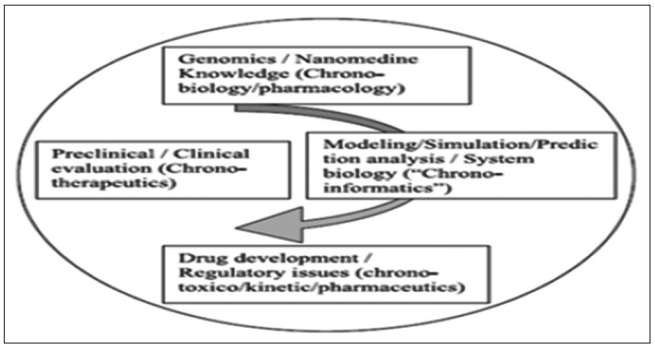

Figure 5: Key steps in designing of chronotropic system

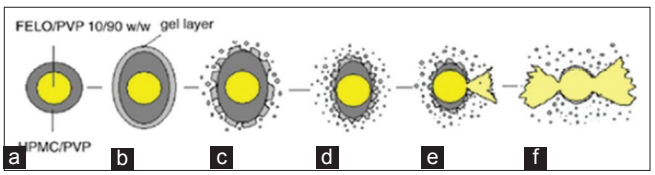

Figure 6: Rupture mechanism of double-walled tablets. (a) Initial tablet, (b) gel forming on the coating layer due to the water penetration and tablet swelling, (c) erosion inception of the coating layer, (d) extended erosion, (e) rapture of the coating layer and initiation of core dissolution, and (f) extended release

Table 3: Examples of FDA approved chronological drug delivery systems in the method

Date of approved by FDA	API	Proprietary name, dosage form	Chronopharmacutias technology	Indication/rationale for chronotherapy
September 1, 1982	Theophylline	Uniphy; extended release tablet	Lontin	Asthma/increased bronchoconstriction in morning
October 15, 1986	Famotidine	Pepcid; tablets	Physical-chemical modification of APZ	Ulcer/increased gastric acid secretion in the evening
December 23, 1991	Simvastatin	Jocor; tablets	Physiochemical modification of API	Hyper choles terolemia/increased cholesterol system overnight
February 26, 1996	Verpami/Hcl	Covera HS; extended-release tablets	OROS	Hypertension/increased BP in the early morning
November 25, 1998	Verapami/Hcl	Verelan PM; extended release capsule	CODAS	Hypertension
August 1,2000	Methylphenidate	Concerta; tablet	OROS	Antipsychotic
February 06, 2003	DiltpazemHclverapmi/HCL	Cardizem LA; extended release tablets	CEFORM	Hypertension
March 12, 2003	Propranolol HCL Vera pami/HCL	Inoperable; extended release capsule	DIFFUCAPS	Hypertension
December 19, 2006	Paliperidone	Invega	OROS	Schizophrenia

CODAS: Chronotherapeutic oral drug absorption system

of dosage form contain a core of drug and osmotic and super disintegrants. The core of drug is then coated with protective polymeric rupturable layers. Water insoluble semi permeable layer which is a rate controlling membrane for influx of water into osmotic core. Different types of release pattern can be obtained different types of dosage forms, for example, rupture mechanism of double-walled tablets as shown in Figure 6.

In case of tablets, the drug is released quickly after the explosion of the outer membrane while in case of pellets or granules, the drug is released with zero-order pattern after a definite lag of time. The lag time increases with increasing coating level and a higher level of talc and plasticizers in the coating. Drug release from time-controlled explosion systems was found to be complete, independent of environmental pH, and drug solubility. However, these systems have a drawback of failing to release drug if swelling agents fail to rupture. The water-insoluble coating and having limited flexibility in the release pattern and maximum lag time of approximately 4 h also noted.

Pulsatile Systems Based on Changed Membrane Permeably

In this system, sigmoid type of release pattern was obtained from pellet cores having drug and succinic acid coated with amino - methyl acrylate copolymer. Succinic acid is dissolved by the water in the medium.[29,30] The permeability of the polymer film is increased by the drug inside and the acid solution. By the presence of different counterions in the medium, the actual permeability and water uptake of acrylic polymer with quaternary ammonium groups can be controlled. Eudragit RS is generally used for this purpose. It contains positively polarized quaternary ammonium group in the polymer side chain, which is accompanied by the hydrochloride counterions. Due to hydrophilic nature of ammonium groups it facilitates the interactions of polymer with water. As the results, water penetrates the active core in the controlled manner and permeability of polymer changes. A small amount of sodium acetate in the pellet core has a significant effect on the drug permeability of the Eudragit film. It leads to the liberation of entire dose within few minutes. Acid containing core can be designed using this system.[2,3]

Stimuli induced pulsatile drug delivery system - these systems are designed based on the physiochemical process of the body. These systems are better classified in two categories:

- Chemical stimuli induced pulsatile drug delivery systems.
- Temperature-induced pulsatile drug delivery system.

Chemical stimuli induced pulsatile drug delivery systems

These systems can be described by certain examples of Chemical stimuli as follows:

pH sensitive pulsatile release chronotropic systems

A particular pH is used as a triggering point of drug release from such delivery system. That devices can be mode of using pH-dependent polymer in such a member that drug will be released after reaching surrounding pH of the device.

Examples of pH-dependent polymer include carboxylmethyl cellulose, phthalates, and various grades of Eudragit.

These polymers help to protect the drug from degradation in upper GIT and attain drug release at a specific part of intestine after a lag time. Akhgari*et al.* studied on the optimum ratio of Eudragit L 100 and Eudragit S 100 for colonic delivery of indomethacin pellets for chronotherapy of rheumatoid arthritis.

Enzyme catalyzed pulsatile chronotropic system

These systems are designed for colonic delivery of drug where release rate is dependent on the catalysis of polymeric membrane be enzymes which are secreted by colonic microflora.

Many natural polysaccharides such as pectin and guar gum have been investigated for their potential in designing colon-specific drug delivery.

Chronotherapy of rheumatoid arthritis has been tried by utilizing these polymers to delivery NSAIDs in the colon after a lag time of 4–6 h to relieve pain in the early morning.[3]

Temperature-Induced Pulsatile Drug Delivery System

Various types of cells inside the body have a different physiological temperature. Some cells pass different temperature with respect to other cells like tumor cells, in which cellular temperature is increased due to their higher metabolic rate. By utilizing thermoresponsive hydrogel system, a pulsatile drug delivery system for targeting tumor can be designed.[3]

Bae YH *et al.* developed indomethacin pulsatile drug delivery system in temperature ranging between 20 and 30°C using reversible swelling properties of copolymers of N-isopropyl acrylamide and butyryl acrylamide.[3]

Externally regulated pulsatile drug delivery system

These systems are modulated to release drug by external stimuli such as electrical effect and magnetic field. When these external forces are applied to the system, conductors present in the delivery system get sensitized to trigger the release of drug from the dosage form.[3]

Magnetic field

Magnetic steel beads can be embedded in a polymer matrix with the model drug. The beads oscillate within the matrix and alternatively creating compressive and tensile forces during the exposure to the magnetic field. This acts as a pump which pushes the increased amount of drug out the matrix.

Satarkar*et al*. have used nanocomposite controlled by remote magnetic field for pulsatile drug delivery. Superparamagnetic Fe_3O_4 was incorporated in negative temperature sensitive poly hydrogels. High frequency alternating magnetic field was applied to trigger the release of drug in a pulsatile manner.[31-35]

Recently Available Different Chronopharmaceutical technologies

OROS technology

This system is used to deliver the drug to the GIT in a time-specific and site-specific manner. It is totally based on osmosis. The active ingredient is guarded by a semi-permeable membrane with a delivery orifice and is formulated into a tablet. This tablet consists of two layers one of the drug layer and another osmotically active agent. When this tablet comes in contact with the fluid, it acquires dispensable viscosity. The osmotic agent pushes the active ingredient away. This technique is used for designing of extended-release tablets.

CEFORM technology

This technology is used for producing uniformly sized and shaped microspheres. The approach is based on "melt spinning" which includes subjecting the solid feedstock to a combination of factors such as temperature, thermal gradients, mechanical forces, flow, and flow rates during processing. These microspheres are almost perfectly spheroid having a diameter about 150–180 mm, thus alluring high drug content. These microspheres can be a part of various dosage forms such as tablets, capsules, and suspensions these can be given coating for a controlled release.

Chronotherapeutic Oral Drug Absorption System (CODAS)® Technology

CODAS technology is a multiparticulate system designed for bedtime dosing. Here, non-enteric coating is applied on drug-loaded beads to delay the release of drug up to 5 h. Here release controlling contains a mixture of both water-soluble and water-insoluble polymers. When this dosage form comes in contact with GI fluid water-soluble polymer gets dissolved slowly, and pores are formed on the coating layer. The drug diffuses through these resulting pores. Water-insoluble polymer acting as a barrier maintains the controlled release fashion like release of verapamil. The rate of release is independent of pH, posture, and food.

TIMERx® technology

It is hydrogel based controlled release device. This technology can provide from zero-order to chronotherapeutic release. It can provide different release kinetic by manipulating molecular interactions. It claims that the "molecular engine" replaces the need for complex processing or novel excipients and allows desired drug release profiles to be "factory set" following a simple formulation development process. Basically, this technology combines primarily xanthan and locust bean gums mixed with dextrose. The physical interaction between these components works to form a strong, binding gel in the presence of water. Drug release is controlled by the rate of water penetration from the GIT into the TIMERx gum matrix, which expands to form a gel and subsequently releases the active drug substance.

DIFFUCAPS® technology

This technology is nothing but capsule-based system containing one or more drug-containing particles (e.g., beads, pellets, and granules). Each bead shows pre-programmed rapid or sustained release profile with or without lag time. It has been already discussed in a system with erodible, soluble, or rupturable membrane section.[36-39]

CHRONOTOPIC® technology

It is also described in a system with an erodible, soluble or rupturable membrane system. It is basically drug-containing core coated with an outer release-controlling layer. Both single and multiple-unit dosage forms such as tablets and capsules or minitablets and pellets have been employed as the inner drug formulation.[40-44]

CONCLUSION

A significant amount of progress has been achieved toward pulsatile drug delivery systems that can effectively treat disease with non-constant dosing therapies such as diabetes. It symptoms of the disease display circadian variation; drug release should also vary over time. Different technologies have been applied to develop time controlled, pulsed, triggered, and programmed drug delivery devices in recent years.

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