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CHRONOTHERAPY: A CONCEPT, PAUPERISM AND APPROCHES

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ABSTRACT

In the modern era of treatment many new approaches have been evolved for more efficient administration of drugs. One of such approach is the administration of drugs at times at which they are most effective and best tolerated. Chronotherapy is the approach where the availability of drug is timed to match rhythms of disease or disorders in order to optimize therapeutic responses and minimize side effects, which makes it a profound and purposeful delivery of medications in unequal amounts over time. Number of systems such as pulsatile drug delivery systems which can use stimuli from magnetic, electric, ultrasound, chemicals, enzymes etc. for drug release in the form of pulse when actually required, core in cup tablets, compression coated/press coated tablets, double coated hard gelatin capsules and double coated tablets, chronomodulating infusion pumps, controlled-release microchip, Layered systems, sigmoidal release systems hydrogels, osmotic drug delivery systems etc have been successfully used for effective chronotherapeutic drug delivery systems.

Keywords: Chronology, Circardian rhythm, Pulsatile systems, Hydrogels, Chronsthesy.

INTRODUCTION

The term "chrono" basically refers to the study that every metabolic happening undergoes rhythmic changes in time [1]. Chronotherapeutics refers to a Therapy in which *in vivo* availability of drug is timed to match rhythms of disease or disorders in order to optimize therapeutic responses and minimize side effects, which makes it a profound and purposeful delivery of medications in unequal amounts over time (during the 24 h). It is based on the observation that there is an interdependent relationship between the peak-to-trough rhythmic activity in disease symptoms and risk factors, pharmacologic sensitivity, and pharmacokinetics of many drugs [2].

The chronotherapy of a medication may be accomplished by the appropriate timing of conventionally formulated tablets and capsules, and the special drug delivery system to synchronize drug concentrations to rhythms in disease activity [3]. One approach to increasing the efficiency of pharmacotherapy is the administration of drugs at times at which they are most effective and/or best tolerated. Chronotherapeutics takes into account rhythm determinants of the human circadian time structure to determine the drug-delivery pattern, dose, and administration time to optimize desired and/or minimize adverse effects [4, 5].

Which are as follows:

1. **Chronopathology (disease pathophysiology):** Study of biological rhythms in
disease processes and morbid and mortal events.
2. **Chronopharmacology:** is the study of the manner and extent to which the kinetics and dynamics of medications are directly affected by endogenous biological rhythms, and also how the dosing time of medications affect biological punctuality and the features (period, level, amplitude, and phase) of biological rhythms [5-9]. Thus it involves both the investigation of drug effects as a function of biologic timing and the investigation of drug effects upon rhythm characteristics.

- ***Chronokinetics***- This term includes both rhythmic changes in the drug bioavailability, pharmacokinetic and its excretion [5,6,10,11].
- ***Chronodynamics***- Chronodynamics refers to dosing-time, i.e., rhythm-dependent, differences in the effects of medications.5, Such administration- time differences are due to rhythms in the free-to-bound drug fraction, number

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and conformation of drug-specific receptors, second messenger and ion channel dynamics, and ratelimiting step(s) in metabolic pathways [10,12]. Both the desired/ beneficial and undesired/adverse effects of medications can vary significantly according to their administration time.

- ***Chronesthesy-*** chronopharmacology studies sometimes reveal great differences in their effects with different biological times of application, even through the pharmacokinetics and concentration are the same. This phenomenon is termed chronesthesy, which is the circadian change in the susceptibility of any biosystem to a drug (including organ systems, tumors) parasites, etc.

- ***Chronotoxicology*** - Chronotoxicology, is an aspect of chronodynamics; it refers specifically to dosing-time, i.e., rhythm-dependent, differences in the manifestation and severity of adverse effects and thus intolerance of patients to medications [5,13-15] certain classes of drugs that have high risk of adverse effects and relatively narrow therapeutic range are likely to show significant dosing-time differences in safety (i.e., chronotoxicology).

3. **Rhythm Attributes:**

Circadian rhythms are self-sustaining, endogenous oscillations that occur with a periodicity of about 24 hours also termed as sleep-wake cycle. It is derived from two words *circa,* meaning "about" and *dies*, meaning day which corresponds to approximately 24-hour cycles endogenously generated by an organism. These are controlled by an inherited master clock network composed of the paired suprachiasmatic nuclei (SCN) that are situated in the hypothalamus and the pineal gland [16]. Most people sleep at night and rise in the morning. In night-shift workers, most circadian rhythms are shifted to match their sleep-wake cycle [17, 18]. This master clock network orchestrates the period and phase of the large number of acquiescent peripheral circadian clocks located in cells, tissues, and organs. The end-effect is a wonderful chronological organization of biological processes and functions. A biological rhythm is a self-sustaining oscillation of endogenous origin. It is defined by the characteristics of period, level, amplitude, and phase.

- ***Period*** - Period is the duration of time required to complete a single cycle. Intermediate-period rhythms show oscillations as short as a few hours to as long as 6 days. Included in this category are the ultradian (< 20 h), circadian (-24 h), and infradian (>28 h) rhythms. Finally, long-period rhythms show oscillations of roughly a week, month, and year.

- ***Phase*** - Phase refers to the clocking of specific features, such as the peak and trough values, of a rhythm relative to the corresponding time scale.
- ***Amplitude-*** It is a measure of the magnitude of the predictable in time variability due specifically to a biological rhythm. The amplitude of rhythms may change with aging. For example, in diurnally active young adults the circadian rhythm in antidiuretic hormone (ADH), which regulates urine formation and volume, is of very high amplitude. Peak ADH concentration occurs during the nighttime to ensure reduced urine formation and volume during sleep; thus, in young adults urine formation and volume are much greater during diurnal activity than nocturnal sleep. However, with aging the amplitude of the ADH rhythm decreases; as a consequence, the peak of the circadian rhythm in urine formation and volume shifts to the middle of the night, resulting in frequent disturbances of sleep because of the need to urinate [19].

- ***Level*** - Level is the baseline around which rhythmic variation occurs. The level of circadian rhythms oscillates in a predictable-in-time manner during the month in young women and over the year in men and women, giving rise, to menstrual and annual biological rhythms.

Many functions of the human body vary considerably in a day. These variations cause changes both in disease state and in plasma drug concentrations. Human circadian rhythm depends on sleep-activity cycle, is influenced by our genetic makeup and therefore, affects the body's functions day and night (24-hour period) [20, 21]. Circadian changes in the effects of various chemical agents, neurotransmitters and harmones have been documented viz.histamine, sodium salicylate, acetylcholine, halothane, prostaglandine F, reserpine, cyproheptadine, ethanol, insulin, chlorothiazide, oxymetholone, orciprenalin and SCH 1000 (bronchodilators), indomethacin, ACTH, cortisol and various synthetic corticosteroids.

DISEASES AND CONDITIONS REQUIRING CHRONOTHERAPY

Chronotherapy needs to be applied into those diseases and disorders which specifically follow circardian rhythms or in those diseases which are caused due to distrupted circardian rythms eg insomnia.

The symptomatic intensity of many diseased conditions and the occurrence of severe health emergencies show quite specific timings.

- Gout, gallbladder, and peptic ulcer attacks are more frequent at night.
- Acute pulmonary edema, congestive heart failure, and asthma get worse at night.

- Symptoms of allergic rhinitis and rheumatoid arthritis are either most intense overnight or in the morning upon wakening.
- Migraine headache typically is triggered during rapid eyeball movement (REM) episodes during nighttime sleep or in the early morning hours after awakening.
- Angina pectoris, ventricular arrhythmia, acute myocardial infarction, sudden cardiac death, stroke, fatal pulmonary embolism, and hypertensive crises all are most frequent in the morning as are other cardiovascular conditions.
- Depression is most severe in the morning.
- Symptoms of osteoarthritis worsen during the course of daily activity, being most intense typically in the late afternoon and evening.
- Perforated and bleeding ulcer is reported to be most common in the afternoon.
- Some seizure disorders are triggered during specific sleep stages and/or by transitions between sleep and wakefulness.

The following are the diseases with established oscillatory rhythm in their pathogenesis,

Asthma:

Symptoms of asthma occur 50 to 100 times more often at night than during the day. Many circadian dependent factors appear to contribute to the worsening of nocturnal asthmatic symptoms.[22] For example, level of cortisol which is an anti-inflammatory substance , were generally highest at the awakening time and lowest during the midnight, and level of histamine which is a mediator of bronchoconstriction, peaked with the greatest degree of bronchoconstriction at 4:00 am in the morning.

Pain:

Pain threshold follow the different pattern in different tissues. The sensitivity threshold of the gingiva to a cold stimulus was maximal at 6:00 pm and reached a peak at 03:00 am. Tooth sensitivity was lowest between 03:00 pm and 6:00 pm, with a peak in pain intensity at 08:00 am.

Arthritis:

The plasma concentration of C - reactive protein and interleukin-6 of patients with rheumatoid arthritis follow circardian rhythm. Patients with osteoarthritis have less pain in the morning and more at night; while those with rheumatoid arthritis have pain that usually peaks in the morning and decreases throughout the day.

Thus chronotherapy for all forms of arthritis using NSAID's such as ibuprofen should be timed to make sure that the highest blood levels of the drug coincide with peak pain [23].

Cardiovascular diseases:

A number of functions of the cardiovascular system like hypertension, heart rate, stroke volume, cardiac output, blood flow follow circadian rhythms. For example

- Capillary resistance and vascular reactivity are higher in the morning and decline later in the day.

- Platelet agreeability is increased and fibrinolytic activity is decreased in the morning, leading to a state of relative hypercoagulability of the blood. Hence there is an increase in the incidence of early-morning myocardial infarction, sudden cardiac death, stroke, and episodes of ischemia [24]. Modification of these circadian triggers by pharmacologic agents may lead to the prevention of adverse cardiac events.

- Blood Pressure is at its lowest during the sleep cycle and rises steeply during the early morning awakening period. Most patients with essential hypertension have a similar circadian rhythm of BP as do normotensive persons, although hypertensive patients have an upward shift in the profile. They have quite a marked rise in blood pressure upon awakening - called 'the morning surge' which is due to high catecholamine concentration in the early morning.

Duodenal ulcer:

In peptic ulcer patients, gastric acid secretion is highest during the night [25]. Thus suppression of nocturnal acid is an important factor in duodenal ulcer healing.

Cancer:

Chemotherapy may be more effective and less toxic if cancer drugs are administered at carefully selected times that take advantage of tumor cell cycles while less toxic to normal tissue [26]. Normal human bone marrow DNA synthesis peaks around midday DNA synthesis in malignant lymphoma cells peaks near midnight. Therefore by treatment at mid night, more tumor cell could be killed with same dose of S-phase active cytotoxic therapy and with relatively little bone marrow damage.

Hypercholesterolemia:

Hepatic cholesterol synthesis follows circadian rhythm. It is generally higher during the night than during daylight, and diurnal synthesis may represent up to 30%–40% of daily cholesterol synthesis. Although cholesterol is synthesized during the night as well as daylight; the maximal production occurs early in the morning, i.e. 12 h after the last meal. Studies with HMG CoA reductase inhibitors have suggested that evening dosing was more effective than morning dosing [27].

Diabetes:

The goal of insulin therapy is to mimic the normal physiologic pattern of endogenous insulin secretion in healthy individuals, with continuous basal secretion as well as meal-stimulated secretion. Providing basal insulin exogenously to patients with diabetes inhibits hepatic glucose production. Exogenous administration of mealtime doses promotes peripheral glucose uptake (i.e. it prevents postprandial increases in blood glucose concentration) as well as reducing hepatic glucose release [28].

Ankylosing Spondylitis:

Ankylosing spondylitis is characterized by swelling and discomfort of the joints of the back [29]. Overall, back stiffness and pain were a problem throughout the 24 hours, but pain intensity was rated 2 to 3 times higher and stiffness about 8 times greater between 06:00 am to 09:00 am.

Renal diseases:

Renal osteodystrophy is a condition due to chronic kidney disease and renal failure, with elevated serum phosphorus levels, low or normal serum calcium levels, and stimulation of parathyroid function, resulting in a variable admixture of bone disease. This condition can be managed with calcium supplements, vitamin-D metabolites or Calcitrio. It has been reported that a higher dose of oral D3 is more effective and safe after dosing at evening in patients with renal osteodystrophy [30].

Neurological disorders:

Neurologic disease: Alzheimer disease is a neurological disease associated with circadian rhythm disturbance; however, irregular sleep-wake cycles also can be seen in other neurodegenerative diseases. Alzheimer disease is characterized by sleep disruptions with awakenings and confusion (sundowning phenomenon) [31]. In children with autism spectrum disorder, both sleep onset and sleep maintenance insomnia have been described [32].

CHRONOTHERAPEUTIC DRUG DELIVERY SYSTEMS

Chronotherapeutics refers to the clinical practice of synchronizing drug delivery in a manner consistent with the body's circadian rhythm to produce maximum therapeutic activity and minimum side effects by determining the best biological time for drug dosing. The basic concept for new drug delivery systems for safety and efficacy of the drug by coordinating the peak plasma concentration of the drug with the circadian rhythm of the body is to synchronize drug release with the circadian rhythm of the body. Several techniques have been developed and applied to design chronopharmaceutic delivery systems for desired drug release. These techniques are broadly classified into following three major categories:

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

Time Controlled Chronotropic Systems

In time controlled chronotropic systems, drug is released as a burst within a short period of time immediately after a programmed off release period. This system can again be classified as

a. Time controlled chronotropic systems based on capsules

These systems are composed of an insoluble capsule body, swellable and degradable plugs made of hydrophilic polymers (eg- hydroxyl propyl cellulose, poly vinyl acetate, polyethylene-oxide), lipids and bioactive molecule. The lag time is controlled by plug, which is pushed away by swelling or erosion and drug is released as a pulse from the insoluble capsule i.e. Pulsincap® a swellable hydrogel seals the drug contents into the capsule body. The hydrogel plug swells after coming in contact of fluid and after a lag time, the plug pushes itself outside the capsule and rapidly releases the drug [33].

b. Time controlled reservoir systems with rupturable polymer coating / time controlled explosion system

These have been developed for both single and multiple unit dosage forms.[34, 35] In both cases, the core contains the drug, an inert osmotic agent and suitable disintegrants. Individual units can be coated with a protective layer and then with a semipermeable layer, which is the rate controlling membrane for the influx of water into the osmotic core. Pressure required to rupture the coating can be achieved by using swelling agents, gas producing effervescent agents or osmogens [35-38]. Swelling agent includes superdisintegrents like carboxy methylcellulose, sodium starch glycollate, L-hydroxy propyl cellulose. Polymers like polyacrylic acid, polyethylene glycol etc, and a mixture of tartaric acid and sodium bicarbonate is used as effervescent agent. Water access to system causes the coating to swell, rupture and release of drug occurs. Release of drug is independent of pH or solubility of drug. Lag-time can be varied by varying thickness of coating or by changing amount of plasticizers in the outermost layer. Rapid release of drug after lag-time can be observed with increase in the concentration of the osmotic agent

c. Time controlled reservoir systems with soluble or eroding polymer coating

In these types of systems drug core is coated with a solube or eroding polymer eg- Ethylcellulose. The lag

period can be predetermined by varying the particle size of particlesize used the longer the lag time obtained, suggesting the particle size [39].

Pulsatile Systems

Pulsatile drug delivery systems are time and site-specific drug delivery systems, thus providing special and temporal delivery and increasing patient compliance The release of the drug as a pulse is designed in such a way that complete and rapid release of the drug follows the lag time [40].

Stimuli induced pulsatile drug delivery system

The drug release from these systems occurs due to stimulus which depends on the physiochemical processes of body. These systems are designed for site specific targeted drug delivery by the induction of various physiochemical stimuli at target site.

Biological stimuli like release of enzymes, hormones, antibodies, pH of the target site, temperature of the site, concentration of biomolecules like glucose, neurotransmitters, inflammatory mediators etc acts as stimuli to trigger the release of drug from these types of drug delivery systems. These systems can be classified into following sub categories:

a. Chemical stimuli induced pulsatile drug delivery systems*:*

Those which use concentration of biomolecules like glucose, neurotransmitters, inflammatory mediators etc acts as stimuli for triggering drug release. In Diabetes-mellitus Type-1 there is an increase in blood glucose concentration rhythmically. Several systems were developed which responded to changes in glucose concentration. One such stimuli induced system includes pH sensitive hydrogel containing glucose-oxidase enzyme immobilized in hydrogel. As the blood concentration of glucose rises, glucose-oxidase converts glucose into gluconic acid, which changes the pH of system. Due to change in pH, swelling of polymer takes place and this result into insulin release. Insulin decreases the blood glucose level and consequently the gluconic acid level also declines and system turns to deswelling and hence decreasing the insulin release [41].

b. ***pH sensitive pulsatile release chronotropic systems***

These system uses pH at specific site as a stimuli for drug release. These systems take the advantage of fact that there exists different pH environment at different parts of gastrointestinal tract. Hence utilizing pH dependent polymers, targeting at specific site of gastrointestinal tract is possible as well as a desired lag time can be achieved due to dependency of polymer solubility only at a particular pH of gastrointestinal tract. Generally pH dependent polymers are utilized for enteric coating to protect the drug from degradation in upper G.I.T and attain ethylcellulose or any polymer. The smaller the EC drug release at specific part of intestine after a predetermined lag time [42]. A number of chronotropic systems have been developed and marketed for chronotherapy utilizing pH dependent polymers for asthma, angina, rheumatoid arthritis, cancer, diabetes and ulcer e.t.c. Akhgari *et al*., studied on the optimum ratio of eudragitl100 and Eudragit S1000 for colonic delivery of indomethacin pellets for chronotherapy of rheumatoid arthritis [43].

c. Enzyme catalyzed pulsatile chronotropic systems

These systems are generally developed for colonic delivery of drug as release rate of drug is dependent upon the catalysis of polymeric membrane by enzymes secreted by colonic microflora. Therefore these systems are more specific for targeting, independent of pH variations along the gastrointestinal tract. Numerous natural polysaccharides have been investigated for their potential in designing colon specific drug delivery. Chronotherapy of rheumatoid arthritis has been tried by utilizing these polymers to deliver NSAIDS in colon after a lag time of 4-6hours to relieve pain in early morning [44].

d. Temperature induced pulsatile drug delivery systems

These are system which uses temperature of the site as stimuli for drug release. Certain cells posses different temperature with respect to other cells like tumor cells, in which cellular temperature is raised due to their higher metabolic rate. For targeting tumors, a pulsatile drug delivery system can be designed by utilizing thermo-responsive hydrogel system. As the name suggests, these polymers undergo swelling/deswelling phenomena in response to temperature change (at different metabolic rates of tumors cells) which modulates drug release from these systems. A reversible swelling properties of copolymers of N-isopropyl acrylamide and butyrylacrylamide can be utilized to developed indomethacin pulsatile drug delivery system in temperature range of 20^0C -30^0C [45].

Externally Regulated Pulsatile Drug Delivery Systems

These systems release the drug on getting the stimuli from various external sources like ultrasound, magnetic field, electrical effect and irradiation to control the drug release.. When these external stimuli are applied on the delivery system, conductors present in the delivery system get sensitized to activate the release of drug from the delivery system. Eg- Magnetic beads prepared by interfacial polymerization of polyamide microcapsules shows drug release by this type of delivery mechanism.

Ultrasound Based drug delivery systems

Ultrasound is an enhancer for improvement of drug penetration through biological barriers such as skin,

blood vessels etc. The ultrasound effect enhances degradation of the polymer in which the drug molecules are incorporated. The drug can be released by repeated ultrasound exposure. Pulse delivery is achieved by on-off application of ultrasound [46, 47].

Magnetic Based drug delivery systems

This method of drug delivery involves immobilization of drug or radionuclide in biocompatible magnetic nano or microspheres or in magnetic liposomes. The drug & an appropriate ferrofluid are formulated into a pharmaceutically stable formulation which is usually injected through the artery that supplies the target organ or tumor in the presence of an external magnetic field. Prolonged retention of the magnetic drug carrier at the target site alleviates or delays the RES clearance & facilitates extravascular uptake. This process is based on competition between forces exerted on the particles by macro & microcirculation, the characteristics of the magnetic particles (size, configuration) & the applied magnet [48, 49].

Electric Based drug delivery systems system

This technique generates an electrical potential gradient that facilitates the movement of solute ions across the membrane. Because of charged nature and relatively large molecular size of proteins and peptides, iontophoresis may provide means for their effective delivery [50].

Radiation Based drug delivery systems.

Physical energy in the form of radiation can be used to activate inert oncologic drugs for the cancer treatment. X-rays have an advantage over other forms of physical energy because tissue penetration and precise localization can be achieved. Radiation can be used to control drug delivery through radiation-inducible gene therapy. Radiation-guided drug delivery systems involve the targeting of immunoconjugates to radiation-inducible neoantigens induced by irradiation of neoplasms [51].

Dosage forms used for chronotherapy

A number of commercially available chronotherapeutic drug-delivery systems have been developed for desired drug release. They are administered in the evening and delay the release of drugs until the early morning hours, when the symptoms of the disease are worst. Parenteral chronotropic systems are getting more accepted. The most widespread application is that of the insulin pump, which is used to administer insulin for the treatment of diabetes mellitus. Time programmed regimens for cytotoxic drug delivery by intravenous infusion are also an example of chronotherapeutic system.

Core in cup tablets

These systems are made up of a core tablet containing active ingredient, an impermeable outer shell and a top cover layer-barrier of a soluble polymer. The cover layer erosion is responsible for drug release [52].

Compression coated/press coated tablets

Delayed release and intermittent release formulations can be achieved by press-coating or compression coating. Hydrophilic cellulose derivatives are used in these systems. The major drawbacks of this technique are that relatively large amounts of coating materials are needed and it is difficult to position the cores correctly for the coating process [53].

Double coated hard gelatin capsules and double coated tablets

These are rupturable pulsatile drug delivery systems in form of hard gelatin capsules /tablets which releases the drug in time controlled manner. Capsules are filled with active pharmaceutical ingredient either for single pulse or multi-pulse release (in form of multiparticulates) and coated with a swelling layer followed by an external water insoluble semipermeable polymeric coating. A threshold hydrodynamic pressure due to water absorption is required to rupture the outer coating (rate controlling step) and allowing the release of contents in surrounding medium and fulfills the purpose of desired lag time required in chronotherapy of disease [54].

Chronomodulating infusion pumps

These system contains core having drug (low bulk density solid or liquid lipid material) and disintegrant. Core is coated with cellulose acetate polymer. When the system comes in contact with water, water penetrates the core, displaces the lipid material. After depletion of lipid material, internal pressure increases until a critical stress is reached, which causes rupture of coating and release of drug for chronotherapeutic applications.

Pulsincap systems

Pulsincaps are composed of a water insoluble body and a water soluble cap, and a drug which is sealed with a hydrogel plug. At a predetermined time after administration, the swollen plug is ejected from the capsule and the drug is then released into the small intestine or colon [55].

Controlled-release microchip

A microchip device can store one or more compounds inside of the microchip in any form (solid, liquid, or gel), and can release these compounds when there is demand.

It contains a large number of reservoirs, each covered by a thin membrane of a material that serves as an anode in an electrochemical reaction. There are other electrodes on the surface of the microchip that serve as cathodes in an electrochemical reaction. Each reservoir is

filled with a compound for release. When release from a particular reservoir is desired, an electrical voltage (approximately 1 volt) is applied between the anode covering that reservoir and a cathode. The cathode remains intact during this process but the anode membrane dissolves due to an electrochemical reaction. Thus the reservoirgetsopentoallow the material inside to diffuse out into the surrounding fluid. Each reservoir on the microchip can be activated and opened individually, allowing complex release patterns to be achieved [56].

Hydrogels as carriers in chronotherapeutic systems

Hydrogels are used as chronotherapeutic carriers due to their physicochemical and biological properties. Hydrogels are three-dimensional structures that can absorb a large amount of water. They are composed of swellable hydrophilic polymers. Hydrogels containing hydrophilic groups swell to a higher degree. Swelling of stimuli sensitive hydrogels can be brought about by the change of the temperature, ionic strength and pH of the swelling medium. The swelling kinetics of hydrogels can be diffusion-controlled (Fickian) and relaxation-controlled swelling. Various hydrogels are used in the formulation of chronotherapeutic delivery systems like,

1. Stimuli-sensitive hydrogels - Environmentally sensitive hydrogels are responsive to changes in their external environment. They can exhibit dramatic changes in their swelling behavior, network structure, permeability, or mechanical strength in response to changes in the pH, ionic strength, or temperature of the surrounding fluid [57].

2. Temperature-sensitive hydrogels -Temperature-sensitive hydrogels are gels whose properties, especially their equilibrium swelling ratio, vary in response to change in the temperature of the environment. Temperature-sensitive hydrogels can be classified into positive and negative thermosensitive types. Positive thermosensitivity hydrogels contain mostly hydrophilic monomers; they increase in swelling with rise in temperature. Negative thermosensitivity hydrogels are composed of monomers such as N-methylacrylamide, N, N-dimethylacrylamide, and N-isopropylacrylamide, which contain hydrophobic substituents; they increase in swelling with decline in temperature [58, 59].

3. Physical, Chemical and Analyte-sensitive, such as light, magnetic field sensitive hydrogels.

When constant drug plasma levels need to be avoided, as in chronotherapy, time-controlled or pulsed-release formulations are preferable, especially in the treatment of early morning symptoms. By timing drug administration, plasma peak is obtained at an optimal time and the number of doses per day can be reduced. Saturable first-pass metabolism and tolerance development can also be avoided. Various technologies to develop timecontrolled peroral drug delivery systems have been extensively studied in recent decades.Some of these systems are discussed in the following subsections.

Layered systems

These are one or two impermeable or semipermeable polymeric coatings (films or compressed) applied on both sides of the core [60]. To allow biphasic drug release, a three-layer tablet system was developed. The two layers both contain a drug dose. The outer drug layer contains the immediately available dose of drug. An intermediate layer, made of swellable polymers, separates the drug layers. A film of an impermeable polymer coats the layer containing the other dose of drug. The first layer may also incorporate a drug-free hydrophilic polymer barrier providing delayed (5 h) drug absorption. Conte *et al* has also studied a multi-layer tablet system (Geomatrix®). It consists of a hydrophilic matrix core containing the drug dose. This kind of three layer device has been used in the treatment of Parkinsonian patients using L-dopa/benserazide [61].

Sigmoidal release systems (SRS)

For the pellet-type multiple unit preparations, SRS containing an osmotically active organic acid have been coated with insoluble polymer to achieve different lag-times [62-63]. By aplying different coating thicknesses, lag times *in vivo* of up to 5 hours can be achieved. Release rates from SRS, beyond the lag time, has been found to be independent of coating thickness.

CONCLUSION

It has been well established fact that human body follows the discipline during its normal functioning through circardian rythyms which work like a clock. It has also been found that various disease display circardian variation in the form of varied severity of disease over the time period i.e diseases usually exhibit chronopathophyisiology. Also the drugs if administered on different times show different rate of effectiveness as well as adverse effects. Wise and more meaningful drug delivery systems such as chronotherapy therefore aim at providing the drug when required, depending upon disease intensity to maximize benefits and reducing side effects. Advantages of chronotherapy are very vast and can be explored more in present and future for effective treatment of many more disease and disorders.

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