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Current status of chronotherapeutic drug delivery system: An overview

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ABASTRACT

Chronotherapeutics drug delivery system is useful in the treatment of disease, in which drug availability is timed to match rhythms of disease, in order to optimize therapeutic effect and minimize side effects. The specific time that patients take their medication is very important as it has significant impact on success of treatment. If symptoms of a disease display circadian variation, drug release should also vary over time. Drug pharmacokinetics can also be time-dependent; therefore, variations both in a disease state and in drug plasma concentration need to be taken into consideration in developing drug delivery systems intended for the treatment of disease with adequate dose at appropriate time. Various technologies such as time-controlled, pulsed, triggered and programmed drug delivery devices have been developed and extensively studied in recent years for chronopharmaceutical drug delivery. These, as well as pertinent issues, are addressed in this review.

Key words: Cicardian rhythm, Chronotherapeutics, Chronopharmacology, chronotherapeutic drug delivery system.

INTRODUCTION

In order to increase the effectiveness of drug there are many approaches have been applied , here one of the technique is described which is chronotherapeutic drug delivery system. 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 is based on sleep-activity cycle, is influenced by our genetic makeup and hence, affects the body's functions day and night (24-hour period) [1]. The dependence of bodily functions in certain disease states on circadian rhythm is well known. A number of hormones are released by the brain in the morning,

while others are released during sleep. Blood pressure and heart rate are highest during the hours of 6.00 a.m. to 12.00 noon [2].

To introduce the concept of chronopharmaceutics, it is important to define the concepts of chronobiology and pharmaceutics. Chronobiology is the study of biological rhythms and their mechanisms. Biological rhythms are defined by a number of characteristics [3]. The term ‘‘circadian’’ was coined by Franz Halberg from the Latin circa, meaning about, and dies, meaning day . Oscillations of shorter duration are termed ‘‘ultradian’’ (more than one cycle per 24 h). Oscillations that are longer than 24 h are ‘‘infradian’’ (less than one cycle per 24 h) rhythms. Ultradian, circadian, and infradian rhythms coexist at all levels of biologic organization [3]. Pharmaceutics is an area of biomedical and pharmaceutical sciences that deals with the design and evaluation of pharmaceutical dosage forms (or drug delivery systems) to assure their safety, effectiveness, quality and reliability .

It can be defined as a branch of pharmaceutics devoted to the design and evaluation of drug delivery systems that release a bioactive agent at a rhythm that ideally matches the biological requirement of a given disease therapy. Ideally, chronopharmaceutical drug delivery systems (ChrDDS) should embody time-controlled and site-specific drug delivery systems [4]. Advantages are safer, more effective and reliable therapeutic effect taking into account advances in chronobiology and chronopharmacology, system biology [5] and nanomedicine [6]

Diseases, such as hypertension, asthma, peptic ulcer, arthritis, etc, follow the body's circadian rhythm [7]. Many systems in the human body such as cardiovascular, pulmonary, hepatic and renal systems show variation in their function throughout a typical day. They are naturally synchronized by the internal body clocks and are controlled by the sleep wake cycle. Each bodily system exhibits a peak time of functionality that is in accordance with these rhythmical cycles. Similarly, disease states affect the function of some of these systems in the body and therefore, they too exhibit a peak time of activity within a circadian rhythm [8]

This can be understood by taking an example of Pain. Many new drug formulations, new products, and new drug delivery systems have been developed , but pain treatment is still inadequate. We are convinced that not enough attention has been given to time- of -day patterns of pain intensity and medication requirements. The pain intensity is rarely constant over a 24-hour period. Indeed, many clinical studies report during a day time or active at night episodes of pain exacerbation. Therefore, when asking a patient about the characteristics o f his/her pain, it is as important to be precise not only where or how it hurts but also when the pain is least and worse . In fact, several studies have been conducted over the years on the time dependent variation in the perception of pain, its neurochemistry, and on drug treatment . T he daily pain profile must be used to determine the best time to administer an analgesic drug to a patient.

Ideal Characteristics of Chtonotherapeutic Drug Delivery System :

Ideal ChrDDS should:

- be non-toxic within approved limits of use,
- have a real-time and specific triggering biomarker for a given disease state,
- have a feed- back control system (e.g. self-regulated and adaptative capability to circadian rhythm and individual patient to differentiate between awake – sleep status),
- be biocompatible and biodegradable, especially for parenteral administration,
- be easy to manufacture at economic cost,
- be easy to administer in to patients in order to enhance compliance to dosage regimen.

To our knowledge such ideal ChrDDS is not yet available in the market. The majority of these features may be found at the interface of chronobiology, chronopharmacology, system biology and nanomedicine.

Chronotherapeutics :

The f irst chronotherapy to be widely applied in clinical practice was introduced in the 1960s — the alternate-day morning schedule of conventional tablet corticosteroid medication [9]. Other chronotherapies have since been widely used in clinical medicine in the U S, Europe , and Asia ; these include special evening theophylline systems for chronic obstructive pulmonary disease , conventional evening H_2 -receptor ant agonists for peptic ulcer disease , and conventional evening cholesterol medications for hyperlipidemia [21].

Chronopharmacology and chronotherapeutics are the two scientific domains that study specifically when drugs produce their best effectiveness and least side effects. Biological rhythm markers have been identified to guide the chronotherapy of many diseases,

The term "chrono" basically refers to the observation that every metabolic event undergoes rhythmic changes in time. Researchers have concluded that all living organisms are composites of rhythms with varying frequencies that may range from seconds to seasons. Perhaps the best known and studied chronobiologic frequency is the circadian rhythm which approximates the earth's 24-hour rotation around the sun [10]. Researchers have recently concluded that both disease states and drug therapy are affected by a multitude of rhythmic changes that occur within the human body [11].

Chronotherapeutics refers to a treatment method in which in vivo drug availability is timed to match rhythms of disease in order to optimize therapeutic outcomes and minimize side effects. 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 [12].

The tradition of prescribing medication at evenly spaced time intervals throughout the day, in an attempt to maintain constant drug levels throughout a 24-hour period, may be changing as researchers' report that some medications may work better if their administration is coordinated with day-night patterns and biological rhythms [13].

Circadian time structure :

The biological rhythm studies help in defining the temporal organization of human beings. One means of illustrating the human circadian time structure is to depict the peak time of 24-h rhythms on a clock--like diagram like that shown in Fig. . This figure shows the peak time of a select number of human circadian rhythms in relation to the typical synchronizer routine of most human beings — sleep in darkness from 10:30 p.m. to 6:30 a.m. and activity during the light of the day between 6:30 a.m. and 10:30 p.m. The peak in The results of numerous biological rhythm studies help define the temporal organization of human beings. One means of illustrating the human circadian time structure is to depict the peak time of 24-h rhythms on a clock basal gastric acid secretion, white blood cell count (WBC), calcitonin gene-related protein, and atrial natriuretic peptide occurs late at night or early in sleep. Growth and thyroid stimulating hormone (TSH), blood lymphocyte and eosinophil number, and plasma melatonin and prolactin crest during sleep as do the adrenocorticotropic (ACTH), follicle stimulating (FSH), and luteinizing (LH) hormones. Plasma cortisol, renin activity, angiotensin, and aldosterone peak in the morning as do arterial compliance, vascular resistance, platelet aggregation, and blood viscosity.

Hemoglobin and insulin concentrations peak at noon and in the afternoon, as do the spirometric measures of airways caliber — FEV1 (forced expiratory volume in 1 s) and PEF (peak expiratory flow rate). The circadian rhythms of serum cholesterol and triglycerides and urinary diuresis crest early in the evening. The information conveyed in this figure clearly illustrates that the biochemistry and physiology of human beings are not constant; rather, they are variable in a predictable and coordinated manner during the 24 h.

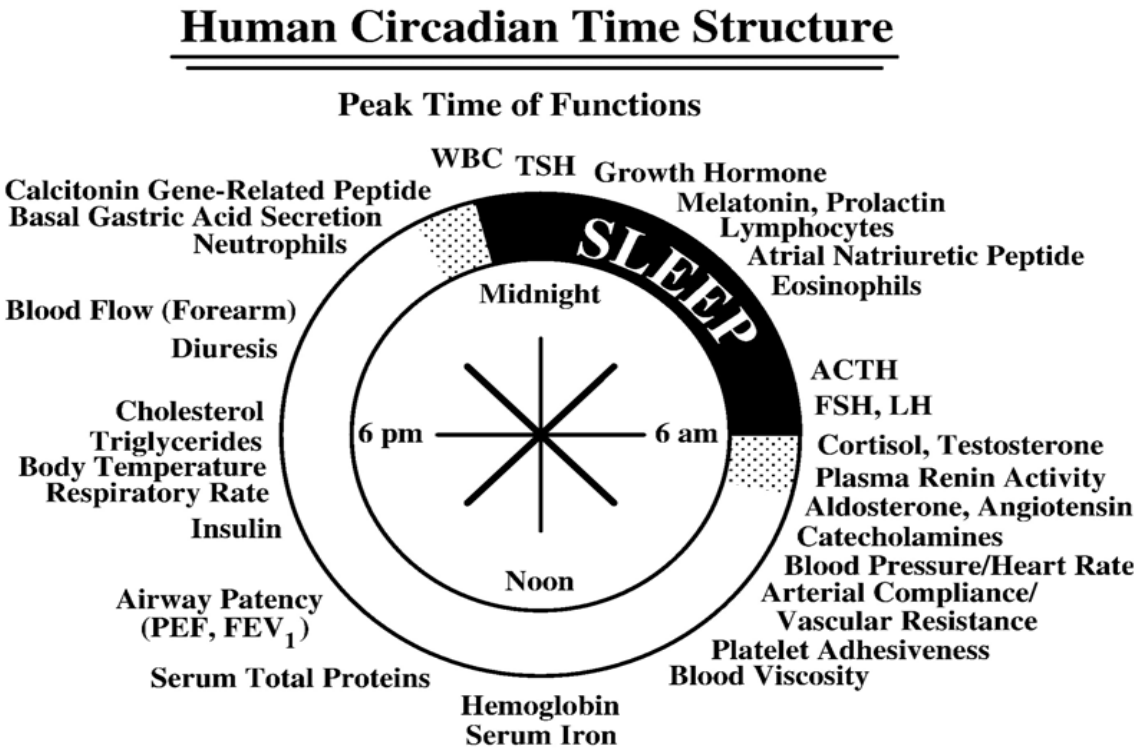


Fig. 1. Human circadian time structure

[Shown is the approximate peak time of circadian (24-h) rhythms of selected biological variables in persons adhering to a normal routine of daytime activity (6–7 a.m. to 10–11 p.m.) alternating with nighttime sleep. The activity in light-sleep in darkness daily routine determines the phasing of all circadian rhythms. The circadian rhythms of white blood count (WBC), thyroid stimulating hormone (TSH), growth hormone, melatonin, prolactin, atrial natriuretic peptide, and esosinophil and lymphocyte cell numbers in blood peak between bedtime and early hours of sleep. Circadian rhythms in the blood level of adrenocortical tropic hormone (ACTH), follicle stimulating hormone (FSH), luteinizing hormone (LH), testosterone, cortisol, catecholamines, renin activity, aldosterone, and angiotensin peak near the end of nighttime sleep or start of daytime activity. The morning peak of the rhythm in vaso-active entities contributes to the morning peak time of the circadian rhythms in heart rate, blood pressure, arterial compliance, and vascular resistance in normotensive and uncomplicated essential hypertension persons, and the morning peak of the circadian rhythm in blood catecholamines gives rise to the morning peak of the circadian rhythm in platelet aggregation. Circadian rhythms of hemoglobin and serum iron peak around mid-day and total serum proteins and airway caliber — PEF (peak expiratory flow rate) and FEV1 (forced expiratory volume in 1 s)—peak in the afternoon. Circadian rhythms of body temperature and respiratory rate and blood insulin, cholesterol, and triglycerides peak late in the afternoon, while those of urine production (diuresis), forearm blood flow, neutrophils, basal gastric acid production, and calcitonin-generelated peptide (a vascular dilator) peak late in the activity span. Together, the phasing (peak time) of these and numerous other 24-h rhythms in biological processes and functions make up the circadian time structure of human beings, giving rise to day–night patterns in disease activity, with the potential for varying-in-time requirements for pharmacotherapy, as well as administration-time differences in the kinetics and dynamics of medications.]

Mechanisms of biological timekeeping :

Circadian rhythms are controlled by an inherited master clock network composed of the paired supra chiasmatic nuclei (SCN) that are situated in the hypothalamus and the pineal gland [14,15]. The rhythmic activities of specific, so-called, clock genes, like per1, per2, per3, bmal, clock, and CRY, among others, and their gene products, plus the cyclic (nocturnal) secretion of melatonin from the pineal gland comprise the central timekeeping mechanism. This master clock network

orchestrates the period and phase of the multitude of subservient peripheral circadian clocks located in cells, tissues, and organ-systems. The end-effect is a rather exquisite temporal organization of biological processes and functions. Biological timekeeping is an evolutional adaptation to an environment that is organized in time, displaying discrete and important cyclic phenomena. Thus, the temporal organization of biological processes and functions during the 24-h period ensures peak functioning of the diurnal human species during daytime activity and restoration and repair during nocturnal rest; during the menstrual cycle, it ensures fertility and perpetration of the species; and during the year it ensures a priori biological adjustment to predictable-in-time changes and challenges associated with the different seasons of the year.

Chronopharmacology:

The concept of homeostasis implies that the kinetics and dynamics of medications are comparable no matter the time of day, day of menstrual cycle, and month of year of their administration. However, facts dispute the validity of this assumption; the time with reference to circadian rhythms of the ingestion, injection, infusion, or cutaneous application of medications can affect their behavior, sometimes markedly.

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 timekeeping and the features (period, level, amplitude, and phase) of biological rhythms. Studies show that the time of drug administration, especially with reference to circadian rhythms, can impact the kinetics and dynamics of various classes of medications. Several concepts of chronopharmacology, as discussed below, are relevant to the drug discovery and drug delivery sciences.

- **Chronodynamics :**

Chronodynamics refers to dosing-time, i.e., rhythm-dependent, differences in the effects of medications . Such administration- time differences are due to rhythms in the free-to-bound drug fraction, number and conformation of drug-specific receptors, second messenger and ion channel dynamics, and ratelimiting step(s) in metabolic pathways . Both the desired/ beneficial and undesired/adverse effects of medications can vary significantly according to their administration time. Many examples of chronodynamics can be cited. One is the constant infusion over 24 h of ranitidine, an H2-antagonist prescribed to treat duodenal ulcer disease. The therapeutic effect of ranitidine — inhibition of gastric acid secretion and increase (alkalinity) of gastric pH—is poorer during the overnight hours of drug infusion than during the daytime hours of drug infusion, indicating that there might be a partial nocturnal resistance to H2- receptor blockade . Similar findings have been found for heparin as reported and reviewed by Decousus et al. [72,73]. The anticoagulant effect of constant-rate heparin infusion over the 24 h on deep-vein thrombosis (DVT) patients exhibits profound circadian differences. In normally diurnally active patients, the anticoagulant effect of constant-rate heparin infusion can be too great overnight, posing the risk of hemorrhage as an adverse effect, while the anticoagulant effect of the same infused heparin dose in the morning in the same patients can be sub therapeutic, posing the risk of further aggravation of the DVT condition. This circadian-rhythm-dependent effect is also found when heparin is administered by other routes, as discussed by Haus in this special issue [74].

Another example is the non-steroid class of anti-inflammatory drugs (NSAIDs), as discussed in detail in this special issue by Bruguerolle and Labrecque . NSAIDs are prescribed to manage the pain, stiffness, and inflammation of rheumatoid and osteoarthritis. A number of clinical trials with NSAIDs have shown that they exert better therapeutic effect on the aggravating morning symptoms of rheumatoid arthritis, and are better tolerated, when ingested around or at bedtime

than in the morning upon arising. On the hand, NSAIDs are more effective in reducing the afternoon and evening peak intensity of osteoarthritis symptoms when ingested in the morning or around lunch time, although the likelihood of gastric intolerance and other adverse effects is greater when they are routinely ingested in the morning as opposed to evening.

- **Chronopharmacokinetics :**

Chronopharmacokinetics entails the study of temporal changes in drug absorption, distribution, metabolism and excretion [16]. Pharmacokinetic parameters, which are conventionally considered to be constant in time, are influenced by various physiological functions displaying circadian rhythm. Circadian changes in gastric acid secretion, gastrointestinal motility, gastrointestinal blood flow, drug protein binding, liver enzyme activity, renal blood flow and urinary pH may play a role in time-dependent variation of drug plasma concentration [17]. Numerous chronopharmacokinetic studies have been conducted over the last 20 years. The results of these studies demonstrate that time of administration affects drug kinetics. Studies in man have been reported, particularly in relation to cardiovascular active drugs, non-steroidal anti-inflammatory drugs (NSAIDs), local anaesthetics, anticancer drugs, psychotropic drugs, antibiotics and anti-asthmatic drugs [17]. Most of the drugs seem to have a higher rate or extent of bioavailability when they are taken in the morning than when they are taken in the evening.

Theoretical and formal approaches to chronopharmaceutics :

When treating human diseases, the overall goal is to cure or manage the disease while minimizing the negative impact of side effects associated with therapy. In this respect, chronopharmaceutics will be a clinically relevant and reliable discipline if pharmaceutical scientists could delineate(describe) a formal and systematic approach to design and evaluate drug delivery system that matches the biological requirement. The key component for the success of ChrDDS design for the treatment of diseases is the elucidation of control-relevant models for drug delivery [18] .

A control-relevant model is the one that has: (i) predictive capability in terms of the process input – output behavior; and (ii) utility in performing on-line calculations for control or optimization purposes. Because of the complexity of identified biological oscillators, two physical descriptors have been discussed to illustrate the mathematical description of such system: the linear mass -spring oscillator and the non-linear electrical oscillator described by vanderPol . The latter provides a simple example of an oscillator in which the variation of one parameter alters the system from being relatively insensitive to noise to one that is very sensitive [19] . A general introduction to the mathematics of biological oscillators can be found in the monograph by Pavlidis [20] .

A number of modeling approaches are available in the broad area of hemodynamic variable regulation, cancer chemotherapy, and glucose concentration control. The advantages and disadvantages of some of the modeling approaches can be found elsewhere and are beyond the scope of this manuscript.

Modeling cardiovascular diseases :

Modeling works on blood pressure (BP) control available in the literature includes empirical tuning of controllers using linear models [22,23], nonlinear approaches [24,25], and formulation of a finite number of multiple linear models [26,27]. An alternative to either the empirical or fundamental modeling approaches for BP control is the construct of fuzzy set theory models and the corresponding rule-based controllers [28,29]. Moreover, the two following harmonic

regression equations for the frequency of onset of myocardial infarction according to plasma creatine kinase MB (CK-MB) activity were suggested by Muller et al. [30]:

$$\frac{dn_{mi}}{dt} = 29.3 - 6.74\cos\left(\frac{2\pi \times t}{24}\right) + 5.03\sin\left(\frac{2\pi \times t}{24}\right) + 0.78\cos\left(\frac{4\pi \times t}{24}\right) - 3.55\sin\left(\frac{4\pi \times t}{24}\right)$$

where,
dnmi/dt is the number of myocardial infarctions per hour and t is the time of day in hours

Modeling cancer chemotherapy :
The modeling approaches to cancer chemotherapy can be classified into two major groups: lumped parameter models (e.g. Gompertz model) and cellcycle models [31,32]. Some oncology groups use the Gompertz model to describe tumor growth, but allow for more complicated tumors, behavior heterogeneity, and spatial variations within tumor, different tumor types, cellular, micro- and macro-environments, and many other factors through statistical techniques and Monte Carlo simulations [48]. Cell-cycle models describe cancer tumor behavior based on the number of cells in a given phase of the cell cycle [31,32]: resting phase (G0), RNA and protein synthesis (G1), DNA synthesis (S), construction of mitotic apparatus (G); and mitosis (M). Each cell-cycle is governed by
its own differential equation [32].

$$X_{G0} = -(T_{G0} + d_{G0})X_{G0}(t) + 2rT_M X_M(t)$$

$$X_{G1} = -(T_{G1} + d_{G1})X_{G1}(t) + 2(1-r)T_M X_M(t)$$

$$X_s = -(T_S + d_S)X_S(t) + T_{G1}X_{G1}(t)$$

$$X_{G2} = -(T_{G2} + d_{G2})X_{G2}(t) + T_S X_S(t)$$

$$X_M = -(T_M + d_M)X_M(t) + T_{G2}X_{G2}(t)$$

Here the number of cells in a particular stage is given by Xi, the transition rate between stages is Ti, the death rate for cells in a particular stage is di, and of the cells that undergo mitosis, r enter the resting stage, and (1_r) return to the RNA/protein synthesis stage. The model formulation assumes that each stage is subdivided into only one compartment. Goldbete and Claude also discussed the implications of modeling studies to improve the temporal patterning of drug administration. They showed the importance of time patterned signals in physiology focused on the insights provided by a modeling approach using examples of pulsatile intercellular communication. They also showed that time-patterned treatments of cancer involve two distinct lines of research: clinical trials (e.g. circadian chronomodulation of anticancer drugs) and theoretical studies (e.g. resonance phenomenon with the cell-cycle length).

Chronotherapeutic drug delivery systems :
Controlled release formulations can be divided into subgroups of rate-controlled release, delayed-release and pulsed-release formulations. Delayed-release formulations include time-controlled release and sitespecific dosage forms [33-35]. 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 [36]. 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.

- **Enteric-coated systems :**

Enteric coatings have traditionally been used to prevent the release of a drug in the stomach Enteric coatings are pHsensitive and drug is released when pH is raised above 5 in the intestinal fluid. These formulations can be utilised in time-controlled drug administration when a lag time is needed. Because of the unpredictability of gastric residence, such systems cannot be the first choice when a time-controlled release is required. In the treatment of nocturnal asthma, a salbutamol formulation containing a barrier coating which is dissolved in intestinal pH level above about 6, has been successfully used [37]. The system contains a core which is film coated with two polymers, first with HPMC and then with a gastro-resistant polymer (Eudragit® L30D). In this system the duration of the lag phase in absorption can be controlled by the thickness of the HPMC layer.

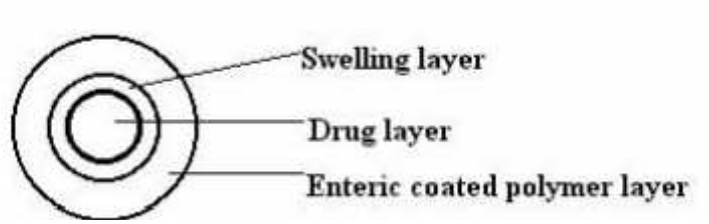


Fig. 2 : Schematic representation of Enteric coated system

- **Layered systems :**

These are one or two impermeable or semipermeable polymeric coatings (films or compressed) applied on both sides of the core [38]. 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 [39]. Night-time problems and early-morning symptoms of Parkinsonism can be avoided by using a dual-release Geomatrix@ formulation, which allows daily doses of drug to be reduced and leads to extent of bioavailability 40 % greater than when a traditional controlled release formulation is employed

- **Time-controlled explosion systems (TES) :**

These have been developed for both single and multiple unit dosage forms [40,41] . 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. As water reaches the core,

osmotic pressure is built up. The core ultimately explodes, with immediate release of the drug. The explosion of the formulation can also be achieved through the use of swelling agents. Lag time is controllable by varying the thickness of the outer polymer coating .

- **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 [42-44]. By applying 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.

- **Press-coated systems :**

Delayed-release and intermittent-release formulations can be achieved by press-- coating. Press-coating, also known as compression coating, is relatively simple and cheap, and may involve direct compression of both the core and the coat, obviating the need for a separate coating process and the use of coating solutions. Materials such as hydrophilic cellulose derivatives can be used and compression is easy on a laboratory scale. On the other hand, for large-scale manufacture, special equipment is needed. The major drawbacks of the technique are that relatively large amounts of coating materials are needed and it is difficult to position the cores correctly for the coating process [45].

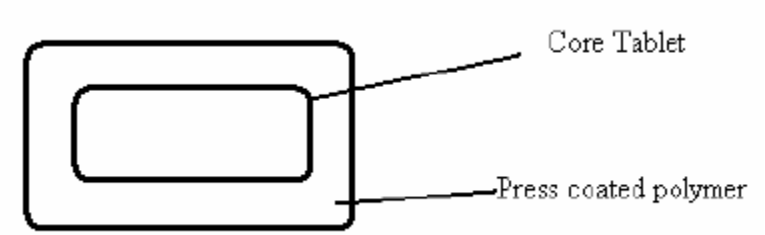


Fig. 3 : Schematic representation of press coated system

In recent years, various controlled release, especially time-controlled release, drug delivery systems based on compression coating technology have been studied. Most of such formulations release drug after a lag phase, followed by a rapid dissolution of the core. Conte *et al* have developed a press coated device in which the inner core contains the drug and the outer coat is made of different types of polymers. The outer barrier, which controls drug release, can be either swellable or erodible. Lag times can be varied by changing the barrier formulation or the coating thickness [46,47]. Hydrophilic polymers such as hydroxypropyl methylcellulose and sodium alginate have been used in the coat to control drug release.

- **Drug-delivery systems for peptides and proteins :**

There has been rapid progress in the development and synthesis of new proteins and peptides as potential therapeutic agents, there has been little progress in the formulation and development of associated delivery systems. The formulation and development of protein and peptide delivery systems are of equal importance due to problems of poor stability, low bioavailability, and short half-life. The stability of protein and peptide drugs during the preparation of products and administration constitutes a major problem.

A small change in environmental temperature, pH, or ionic strength can disrupt the tertiary structure, thus destroying biological activity.

Low stability results in low drug bioavailability. Bioavailability is defined as the degree and rate at which a substance like a medication is absorbed into the living system .

There is current interest in drug-delivery systems that are able to release neuroendocrine and other therapies in synchrony with biological rhythm-determined requirements as discussed by Haus [48] in his contribution to this issue. The treatment of hypopituitary dwarfism by human growth hormone-releasing hormone (GHRH) has been shown to be more effective when administered in a pulsatile than constant-rate manner , and this may be the case for other peptides as well [48]. Considering the advantages and disadvantages of the various choices of peptide administration, we are focused on developing the subcutaneous route for pulsatile drug-delivery systems. The purpose of this work is to design novel subcutaneously injectable chronotherapeutic systems that make possible the delivery of pulses of therapeutic agents at predetermined intervals.

Hydrogels as drug-delivery systems for chronotherapeutics :

The aim of this work is to create a chronotherapeutic drugdelivery system for protein administration. Proteins are highly vulnerable and require a protective system to ensure acceptable bioavailability. Hydrogels are a natural choice due to their unique properties, such as its biocompatibility. This section provides a brief background about hydrogels, their properties, their classification as a stimuli sensitive material, and their application as drug delivery systems.

Hydrogels are three-dimensional structures composed of hydrophilic polymers that can imbibe water . They are not soluble but swell due to the presence of chemical or physical cross links. The physical crosslinks can be crystalline regions, inter-polymer entanglements, orweak interactions such as van der Waals forces or hydrogen bonds. The degree of crosslinking, which is controlled by the chosen feed crosslinking ratio and solvent content during preparation, is the most important factor affecting the swelling property of hydrogels. The crosslinking ratio is defined as the ratio of one mole of crosslinking agent to one mole of polymer repeating units. The greater the incorporation of the crosslinking agent into the hydrogel structure, the greater the crosslinking ratio. Highly crosslinked hydrogels have a tighter structure and swell less than the same hydrogels of lower crosslinking ratio. Crosslinking hinders the mobility of the polymer chain, thereby lowering the swelling ratio. The swelling ratio of hydrogels is also affected by the chemical structure of the polymer. Hydrogels containing hydrophilic groups swell more than ones composed of hydrophobic groups. Hydrophobic groups aggregate, and this leads to collapse of hydrogel structure in the presence of water thereby minimizing their exposure to the water molecule. As a result, hydrogels containing hydrophobic groups swell less than hydrogels containing hydrophilic groups. The swelling of environmentally sensitive hydrogels can be affected by specific stimuli. Swelling of temperature-sensitive hydrogels can be affected by change in temperature of the swelling medium. Ionic strength and pH affect the swelling of ionic strengthsensitive and pH-sensitive hydrogels, respectively. There are many other specific stimuli that can affect the swelling of other environmentally responsive hydrogels.

Applications of hydrogels to drug delivery :

A number of strategies have been proposed to achieve drugdelivery systems for efficient therapy. Among them, hydrogels have attracted considerable attention as excellent candidates for controlled-release, bioadhesive, or targetable devices of therapeutic agents. Hydrogel-based delivery devices can be used for oral, rectal, ocular, epidermal, and subcutaneous application.

1. Peroral drug delivery :

The most common choice of drug delivery for pharmaceutical applications using hydrogels is the oral route. With peroral administration, hydrogels can deliver drugs to four major specific sites—

mouth, stomach, small intestine, and colon.By controlling the swelling properties or bioadhesive characteristics in the presence of a biological fluid, hydrogels can be a useful device for releasing drugs in a controlled manner at these desired sites. Additionally, they can also adhere to certain specific regions in the oral pathway, leading to locally increased drug concentration, thus enhancing drug absorption at the release site.

2. Drug delivery in the oral cavity :

Drug delivery to the oral cavity can have versatile applications in the local treatment of diseases of the mouth, such as periodontal disease, stomatitis, fungal and viral infections, and oral cavity cancers. Long-term adhesion of the drug-containing hydrogel against the copious salivary flow that bathes the oral cavity mucosa is required to achieve this local drug delivery. For this purpose, many types of bioadhesive hydrogel systems have been devised since the early 1980s. Some are already marketed. For example, a bioadhesive tablet developed by Nagai and his coworkers is commercially available under the brand name Aftach®. This product—a local delivery system of triamcinolone acetonide for the treatment of aphthous ulcers—is composed of a double layer, i.e., a bioadhesive layer made of hydroxypropyl cellulose and poly(acrylic acid) and a lactose non-adhesive backing layer.

3. Drug delivery in the gastrointestinal tract :

The gastrointestinal tract is unquestionably the most popular route of drug delivery because of the ease of drug administration, adherence to therapy, and large surface area for systemic drug absorption. It is, however, the most complex route; therefore, versatile approaches are needed to deliver drugs for effective outcomes.

4. Rectal drug delivery :

The rectal route has been used to deliver many types of drugs although patient acceptability is variable due to discomfort arising from the administered dosage forms. Its primary applications have been the local treatment of diseases of the rectum, such as hemorrhoids. Additionally, it is well known that drugs absorbed from the lower part of the rectum drain directly into the systemic circulation. Thus, the rectal route is useful for those drugs undergoing extensive first-pass metabolism. Conventional suppositories, hitherto adapted as dosage forms for rectal administration, are solids at roomtemperature and melt or soften at body temperature. A problem associated with the rectal administration of conventional suppositories is that drugs diffusing from the suppositories in an uncontrolled manner are unable to be sufficiently retained at a specific position in the rectum and sometime migrate upwards to the colon. This often leads to variation of the bioavailability of certain drugs, in particular, those that undergo extensive first-pass elimination.

5. Ocular drug delivery :

Successful drug delivery to the eye is difficult because of the many physiological constraints, such as the protective mechanisms of effective tear drainage, eyelid blinking, and low cornea permeability. Medications that are administered as conventional drop solutions tend to be eliminated rapidly from the eye; thus, they have only limited absorption and poor ophthalmic bioavailability. Additionally, due to the very short-term retention of drugs, a frequent dosing regimen is often required to achieve therapeutic efficacy for a sufficiently long duration. These challenges have motivated researchers to develop drug-delivery systems that provide a prolonged ocular residence time

Examples of chronopharmaceutical technologies :

Currently key technologies in chronopharmaceutics includes: CONTINR, physico-chemical modification of the active pharmaceutical ingredient (API), OROSR, CODASR, CEFORMR, DIFFUCAPSR, chronomodulating infusion pumps, TIMERxR, threedimensional printing, controlled-release (CR) erodible polymer and CR microchip strategies. Readers may find advantages and disadvantages of each technology depending on their specific needs on the website of each developer/marketer website before selection. Informations on FDA approval status and dosage formed were compiled from the FDA electronic orange book [49]. We will focus on the principle and application of each of these technologies.

- **CONTINR technology :**

In this technology, molecular coordination complexes are formed between a cellulose polymer and a non-polar solid aliphatic alcohol optionally substituted with an aliphatic group by solvating the polymer with a volatile polar solvent and reacting the solvated cellulose polymer directly with the aliphatic alcohol, preferably as a melt. This constitutes the complex having utility as a matrix in controlled release formulations since it has a uniform porosity (semipermeable matrixes) which may be varied [50]. This technology has concretely enabled the development of tablet forms of sustained-release aminophylline, theophylline, morphine, and other drugs. Research suggested that evening administration of UniphylR (anhydrous theophylline) tablets represented a rational dosing schedule for patients with asthma who often exhibit increased bronchoconstriction in the morning. Patients demonstrated improved pulmonary function in the morning compared with use of twice-daily theophylline when once-daily UniphylR was administered in the evening. Thus, evening administration of once-daily theophylline may block the morning dip in lung function commonly seen [51]. CONTINR technology provides for closer control over the amount of drug released to the bloodstream, and benefits patients in terms of reducing the number of doses they need to take every day, providing more effective control of their disease (particularly at night), and reducing unwanted side effects .

- **Physico-chemical modification of the API :**

In this strategy, a proprietary method is used to modify the physicochemical properties (e.g. solubility, partition coefficient, membrane permeability, etc.) of the API to achieve the chronopharmaceutical objective. The rationale for such approach is based on the published work demonstrating that solubility and permeability are critical factors governing drug bioavailability [52]. Typical examples of the use of this strategy in chronotherapy are those of antihyperlipidemic statins (HMG-CoA reductase inhibitors) [53,54] and antiulcerative agents (histamine H2 receptor-antagonists) . Basically, the introduction a methyl group in the chemical structure of lovastatin (C24H36O5, 404.54 MW) leads to the production of simvastatin (C25H38O5, 418.56 MW). Such modifications change the melting point (m.p.) of these compounds from 174.5 to 135–138 jC for lovastatin and simvastatin, respectively [55]. Based on the work of Yalkowsky et al. [56], it is now established that molecular weight and m.p. of compounds are related to their solubility. In fact, water solubility data for lovastatin is unavailable, but that of simvastatin is 0.03 mg/ ml [55]. Physicochemical modifications affect the time to reach the maximum plasma concentration (Tmax) for these compounds. The Tmax varies from 2 to 4 h for lovastatin and simvastatin, respectively. Prodrug approach may also be used to obtain a ChrDDS. For example, lovastatin and simvastatin are lactone prodrugs that are modified in the liver to active hydroxyl acid forms. Since, they are lactones, they are less water soluble than other statins [57].

- **OROSR technology :**

OROSR technology [58] uses an osmotic mechanism to provide pre-programmed, controlled drug delivery to the gastrointestinal tract. The dosage form comprises a wall that defines a

compartment. The active drug is housed in a reservoir, surrounded by a semi-permeable membrane/wall (e.g. cellulose esters, cellulose ethers and cellulose ester–ethers) and formulated into a tablet. The tablet is divided into two layers, an active drug layer and a layer of osmotically active agents (e.g. poly(ethylene oxide)) comprising means for changing from a non-dispensable viscosity to a dispensable viscosity when contacted by fluid that enters the dosage form. For example, water from the gastrointestinal tract diffuses through the membrane at a controlled rate into the tablet core, causing the drug to be released in solution or suspension at a predetermined rate. This creates a 'pump' effect that pushes the active drug through a hole in the tablet. This technology, especially the OROSR Delayed Push– Pullk System, also known as controlled onset extended release (COER) was used to design Covera-HSR, a novel anti-hypertensive product. It actually enabled delayed, overnight release of verapamil tohelp prevent the potentially dangerous surge in BP that can occur in the early morning [59]

- **CODASR technology :**

The Chronotherapeutic Oral Drug Absorption System (CODASR) [60] is a multiparticular system which is designed for bedtime drug dosing, incorporating a 4–5 h delay in drug delivery. This delay is introduced by the level of non-enteric release-controlling polymer applied to drug loaded beads. The releasecontrolling polymer is a combination of water soluble and water insoluble polymers. As water from the gastrointestinal tract comes into contact with the polymer coated beads, the water soluble polymer slowly dissolves and the drug diffuses through the resulting pores in the coating. The water insoluble polymer continues to act as a barrier, maintaining the controlled release of verapamil [61]. The rate of release is essentially independent of pH, posture and food. The nighttime dosing regimen of (CODASR-Verapamil) was not associated with excessive BP reductions during the sleeping hours. The CODASR-verapamil extended release capsules (VerelanR PM) as ChrDDS actually provided enhanced BP reduction during the morning period when compared with other time intervals of the 24-h dosing period [62].

- **CEFORMR technology ;**

The CEFORMR technology [63] allows the production of uniformly sized and shaped microspheres of pharmaceutical compounds. This ChrDDS approach is based on ''melt-spinning'', which means subjecting solid feedstock i.e. biodegradable polymer/bioactive agents combinations to the combination of temperature, thermal gradients, mechanical forces, flow, and flow rates during processing. The microspheres obtained are almost perfectly spherical, having a diameter that is typically 150–180 Am, and allow for high drug content. The microspheres can be used in a wide variety of dosage forms, including tablets, capsules, suspensions, effervescent tablets, and sachets. The microspheres may be coated for controlled release either with an enteric coating or combined into a fast/ slow release combination. This technology has been actually used to develop CardizemR LA, 1-day diltiazem formulation as ChrDDS [64].

- **DIFFUCAPSR technology :**

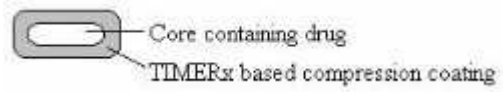
In the DIFFUCAPSR technology [65], a unit dosage form, such as a capsule for delivering drugs into the body in a circadian release fashion, is comprising of one or more populations of drug-containing particles (beads, pellets, granules, etc.). Each bead population exhibits a pre-designed rapid or sustained release profile with or without a predetermined lag time of 3–5 h. The active core of the dosage form may comprise an inert particle or an acidic or alkaline buffer crystal (e.g. cellulose ethers), which is coated with an API-containing film-forming formulation and preferably a water-soluble film forming composition (e.g. hydroxypropylmethylcellulose, polyvinylpyrrolidone) to form a water-soluble/dispersible particle. The active core may be prepared by granulating and milling and/or by extrusion and spheronization of a polymer

composition containing the API. Such a ChrDDS is designed to provide a plasma concentration–time profile, which varies according to physiological need during the day, i.e. mimicking the circadian rhythm and severity/manifestation of a cardiovascular disease, predicted based on pharmacokinetic and pharmacodynamic considerations and in vitro/in vivo correlations. This technology has been used to formulate the first and recently FDA approved propranolol-containing ChrDDS (InnopranR XL) for the management of hypertension

- **Chronomodulating infusion pumps :**

Externally and internally controlled systems across a range of technologies including pre-programmed systems, as well as systems that are sensitive to modulated enzymatic or hydrolytic degradation, pH, magnetic fields, ultrasound, electric fields, temperature, light and mechanical stimulation have been reviewed in detail elsewhere [66]. To our knowledge infusion pumps on the market that have been referred to as chronomodulating for drug delivery application include the MelodieR programmable SynchromedR , PanomatR V5 infusion [67], and the RhythmicR pumps. The portable pumps are usually characterized by a light weigh (300–500 g) for easy portability and precision in drug delivery. For example portable programmable multi-channel pumps allowed demonstration of the clinical relevance of thechronotherapy principle in a sufficiently large patient population. Specifically, a clinical phase III trial involving several patients with metastatic gastrointestinal malignancies compared a flat versus the chronomodulated three-drug regimen, and demonstrated large, simultaneous improvements in both tolerability and response rates in patients with metastatic colorectalcancer receiving chronotherapy

- **TIMERxR technology :**



The TIMERxR technology (hydrophilic system) [68] 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 gastrointestinal tract into the TIMERxR gum matrix, which expands to form a gel and subsequently releases the active drug substance. This system can precisely control the release of the active drug substance in a tablet by varying the proportion of the gums, together with the third component, the tablet coating and the tablet manufacturing process. A chronotherapeutic version of this technology platform is being tested in clinical trial with a bioactive agent known as AD 121 against rheumatoid arthritis. Potential application ofthis technology is the development of an oral, CR opioid analgesic oxymorphone [69].

- **Controlled-release microchip :**

An alternative method to achieve pulsatile or chronopharmaceutical drug release involves using microfabrication technology. Santini et al. [70] reported a solid-state silicon microchip that can provide controlled release of single or multiple chemical substances on demand. The release mechanism was based on the electrochemical dissolution of thin anode membranes covering microreservoirs filled with chemicals in solid, liquid or gel form. Initially the authors conducted proof-of-principle release studies with a prototype microchip using gold and saline solution as a model electrode material and release medium, and demonstrated controlled, pulsatile release of ch poly(L-lactic acid) and had poly(D,L-lacticco- glycolic acid) membranes were fabricated that released four pulses of radiolabelled dextran, human growth hormone or heparin in vitro [71].

This technology has the potential to be used in the design of ChrDDS with a better control over drug release kinetic in order to match biological requirement over a versatile period of time.

CONCLUSION

Chronopharmaceutics will certainly improve patient outcome and optimize disease management in the future. Research in chronopharmacology has demonstrated the importance of biological rhythms in drug therapy and this has led to a new approach to the development of drug delivery systems. Optimal clinical outcome cannot be achieved if drug plasma concentrations are constant. If symptoms of a 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. Since it is seems that timing of drug administration in disease therapy has significant impact upon treatment success, chronotherapeutics remains an important area for continuing research.

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