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Chrono-Pharmaceutical : Future of Pharmaceutics

Snehal S More[1], Sanket S Gadhe[2], Shrikant K Ainor[2], Shriram K Thorat[3]
Department of Quality Assurance Techniques, Siddhant College of Pharmacy, Pune, Maharashtra, India[1]
Department of Pharmaceutics, Sanjivani, College of Pharmaceutical Education & Research, Kopargaon[2]
Department of Pharmaceutics, AISSMS College of Pharmacy, Pune, Maharashtra, India[3]

Abstract: *The term "chrono-pharmaceutics" is a combination of chronobiology and pharmaceutics. In chronobiology, biological rhythms (circadian, ultradian and infradian) and their mechanisms are discussed. Circadian rhythms, which last about one day, are themost studied type of biological rhythm. The term "circadian" comes from the Latin words for about (circa) a day (Diem). Body rhythms of shorter duration are termed "ultradian" 6'hr (more than one cycle per 24 h). Body rhythms that are longer than 24 h are "infradian" (less than one cycle per 24 h) rhythm. 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. Coordination of biological rhythms with medical treatment is called chrono-therapy.*

Keywords: Chrono-pharmaceutics, chrono-therapy, circadian, chrono-theranostics.

I. INTRODUCTION

It has been reported that approximately 100,000 deaths and more than 2 million hospitalizations annually in the United States are due to properly prescribed medications [1, 2]. These adverse drug reactions could be related to multiple factors (e.g. disease determinants, environment, and genetics). However, in drug delivery in biology of living species, time is a fundamental dimension that has been long over looked in drug design and delivery. It is now documented that cycles of different scales exist in biological activities ranging from veryshort (ultradian) rhythms to rhythms with a period of approximately one day (circadian) and rhythms with longer cycles, of a week, a month, a season, or even longer. Instead of being a passive response to external changes, these rhythms are generated by endogenous biological clocks, i.e., time-keeping structures. In mammals, the central pacemaker is the suprachiasmatic nucleus (SCN) [3]. For example, ithas been reported that non-pharmacological (light therapy, sleep deprivation, and rhythm therapy) and pharmacological (lithium, antidepressants, and agomelatine) therapies of affective disorders influence circadian rhythms [3]. Beside familial advanced sleep-phase syndrome [4], the importance of the biological rhythm in drug dosing [5], metabolic syndromes [6] have also been demonstrated. Therefore, a plethora of data both from studies ranging from basic chronobiology to clinical applications (chrono-therapy) have been recently compiled for readers interested in comprehensive background information on this emerging and promising research topic [7]. The foregoing facts suggest that it is now known that in drug dosage forms design, the notion that "one size fits all at all times" is not correct. Among strategies to address this concern, traditionally, patients and health care providers attempted better controlled over the administration of conventional dosage forms with respect to time (a proven concept referred to as chrono-therapy [8]). Additionally, a promising strategy to improve the efficacy and safety of old and new drugs is to revisit our current drug discovery and formulation approaches based on knowledge gained from chronobiology forfuture chrono-theranostics of human diseases whenever a clinical or therapeutic advantage can be proven. Clearly, there is a critical an durgent need at least in cases such as asthma, cancer and heart diseases for novel chrono-pharmaceutical drug products either for therapy or prevention. Such novel drug dosage forms should be effective, safe, robust (predictable drug release rate in biological systems) and clinically justified, with spatial and temporal control ability after administration by different routes. Theoretically, such ideal drug delivery system (preferably a noninvasive system with affordable cost) would potentially improve the safety, efficacy and Patient compliance of old and new drugs. This ideal goal of the "magic pill" remains elusive due to several hurdles or bottlenecks. After a brief overview of the current status of chrono-pharmaceutical drug delivery, this review focuses on the three major hurdles that should be overcome for the chrono-pharmaceutical drug formulation concept to transition from hype to real hope in future clinical practice.

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1.1 Chronotherapy

The knowledge of 24 hr rhythm in the risk of disease plus evidence of 24 hr rhythm dependencies of drug pharmaco kinetics, effects, and safety constitutes the rationale for pharmacotherapy (chrono-therapy).20) One approach to increase the efficiency of pharmacotherapyis the administration of drugs at times at which they aremost effective and work best tolerated. The chrono-therapy of a medication may be accomplished by the appropriate timing of conventionally formulated tablets and capsules, and a special drug delivery system to synchronize drug concentrations to rhythms in disease activity. Chronotherapy is especially relevant in the following cases. The risk and work intensity of the symptoms of disease vary predictably over time as exemplied by allergic rhinitis, arthritis, asthma, myocardial infarction, congestive heart failure, stroke, and peptic ulcer disease. The therapeutic-to-toxicity ratio of a medication varies predictably according tochrono biological determinants as exempliˆed byantitumor medications. The pharmacokinetics and pharmaco dynamics of a medication vary depending onbiological rhythms. The goal of pharmacotherapy ishormonal substitution to mimic the rhythmic variation of hormone levels in healthy individuals. Also on thehorizon are drugs to ˆx broken biological clocks, perhaps a factor in all illness in the opinion of some physicians. Table 1 shows several examples of chrono-pharmacotherapy [9]

1.2 Chrono-Drug Delivery System (chrono-DDS)

The effectiveness and toxicity of many drugs vary depending on the 24 hr rhythms of chemical, physiological and behavioral processes. Also, several drug scan cause alterations to the 24 hr rhythms leading toillness and altered homeostatic regulation. The alteration of biological rhythm is a new concept of adverse effects. It can be minimized by optimizing the dosing schedule. [10] Many researches demonstrate the rationale behind chrono-therapy [11] however, drug delivery research has focused on a constant drug release rate. The reason why the majority of DDS is designed without emphasis on proven oscillatory phenomenamay be in drug delivery imitations. Advances inchronobiology and global market constraints changes the traditional goal of pharmaceutics such as a constant drug release rate. The increasing research interest on Chrono-DDS may create a new sub-discipline in chrono-pharmaceutics. The technologies in chrono-pharmaceutics includes: CONTIN}, physicochemical modification of the active pharmaceutical ingredient, OROS}, CODAS},CEFORM}, DIFFUCAPS}, chrono-modulating infusionpumps, TIMERx}, three-dimensional printing,controlled-release erodible polymer and controlled release microchip strategies.39) As examples of Chrono-DDS on the market, there are compounds such as theophylline(Uniphyl}), famotidine (Pepcid}), simvastatin(Zocor}), COER-verapamil (Covera-HS}, Verelan}PM), diltiazem (Cardizem} LA) and propranolol(InnoPran} XL).39) Most data have been compiled from the FDA electronic orange book,40) specific product package inserts and United States patents and specific pharmaceutical company websites. Future development in chrono-0pharmaceutics may be performed by the new technology such as system biology and Nanomedicine.**[12]**

1.3 Chrono-Pharmaceutics: Definition and Concept

The term “chrono-pharmaceutics” is a combination of chronobiology and pharmaceutics. In chronobiology, biological rhythms (circadian,ultradian and infradian) and their mechanisms are discussed. Circadianrhythms, which last about one day, are themost studied type of biologicalrhythm. The term “circadian” comes from the Latin words for about(circa) a day (Diem). Body rhythms of shorter duration are termed“ultradian” (more than one cycle per 24 h). Body rhythms that arelonger than 24 h are “infradian” (less than one cycle per 24 h) rhythm[13, 14, and 15]. Pharmaceutics is an area of biomedical and pharmaceutical sciences that deals with the design and evaluation of pharmaceuticaldosage forms (or drug delivery systems) to assure their safety, effectiveness, quality and reliability. Coordination of biological rhythms with medical treatment is called chrono-therapy while chrono-the rapeuticsis concerned with the delivery of drugs according to inherent activities of a disease over a certain period of time. The potential benefits of chrono-therapeutics have been demonstrated in the management of a number of diseases. Recent studies have revealed that a number of diseases have a predictable cyclic rhythm and thuschrono-therapy can be a good approach to their treatment [16, 17, 18, and 19].Diseases where chrono-therapy is promising include diabetes mellitus, asthma, peptic ulcer, cardiovascular diseases, arthritis, attention deficit syndrome in children, and hypercholesterolemia. These conditions require that such system has to be designed in which the drug should not be released at all during the initial phase of dosage form administration.

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In other words the drug should be released as a "pulse" after a lag time. Such systems are known as pulsatile drug delivery systems (PDDS),time-controlled systems, or sigmoid release systems. PDDS have been developed in close connection with emerging chrono-therapeutic views. This delivery is gaining much interest and attention because time specific and site-specific delivery of drugs in the right amount is obtained from this device [20,21].

II. BIOLOGICAL RHYTHMS

Concepts and terminology of chronobiologya biological rhythm is a self-sustaining oscillation of endogenous origin. It is defined by the characteristics of period, level,amplitude, and phase. Biological rhythms and the clocks that orchestrate them are adaptive traits. The ambient environment is organized in space, interms of its geography, and in time, in terms of its cycles, the most obvious being the 24-h and annual photo-periodicities. Ecological studies show that the same niche (same geography) displays a rather precise temporal organization; its functionality is optimized by different species using it at different, and generally no overlapping, times. Diurnally active species use it during the dayand nocturnally active species use it during the night for complementary purposes. The organization of the milieu interioris like that of the ambient environment. It is precisely structured in space, from the sub cellular to the organ-system level, which defines its anatomy, and it is precisely structured in time with bio periodicities that match those of the natural environment, which defines its temporal anatomy. The ecological niches of the external environment show predictable-in-time differences during the 24 h in specific activities, and this is also the case for the endogenous environment. All endogenous biological processes and functions are programmed-in-time during the 24 h for the conduct of specific activities at discrete times.

2.1 Period

Period is the duration of time required to complete a single cycle. The spectrum of biological rhythms is broad Short-period rhythms of a second or so are quite common; the high frequency oscillations in the electrical impulses of the central and autonomic nervous systems and the high frequency pulsatile secretions of the neuroendocrine system are but a few examples.

Intermediate-period rhythms show oscillations as short as a few hours to as long as 6 days. Included in this category are the ultradian (b20 h), circadian (~24 h), and infradian (N28 h)rhythms. Finally, long-period rhythms show oscillations of roughly a week, month, and year 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, respectively, to menstrual and annual biological rhythms.

2.2 Amplitude

Amplitude is a measure of the magnitude of the predictable-intime variability due specifically to a biological rhythm. Some biological rhythms are of very high amplitude, accounting for 25–50%of the total variability observed in a given process or function during the 24 h. The amplitude of rhythm may change with aging .For example, in diurnally active young adults the circadian rhythmin 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 inurine formation and volume shifts to the middle of the night, resulting in frequent disturbances of sleep because of the need tourinate. The amplitude of certain circadian rhythms may also vary with change in health status. For example, the amplitude of the circadian rhythm in airway caliber of normal lungs is quite small, equal to about 5% of the 24-h level; however, in mildasthma it is typically increased to 25%, and in severe asthma it can be increased to 50–60%of the 24-h mean level. Thus, both the amplitude and 24-h level, which is also often markedly decreased, of this circadian rhythm are targets of the chrono-therapy of asthma, as discussed in this issue by Smolensky et al.

2.3. 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. For example, the phase of the high-amplitude circadian

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Rhythm of serumcortisol concentration is defined by its prominent morning peak (~20 µg/dl) around 8 a.m. and its trough (as low as0 µg/dl) during nighttime sleep.

2.4 Circadian Time Structure

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-like diagram like that shown in. 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 indarkness 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 basal gastric acid secretion, white blood cell count

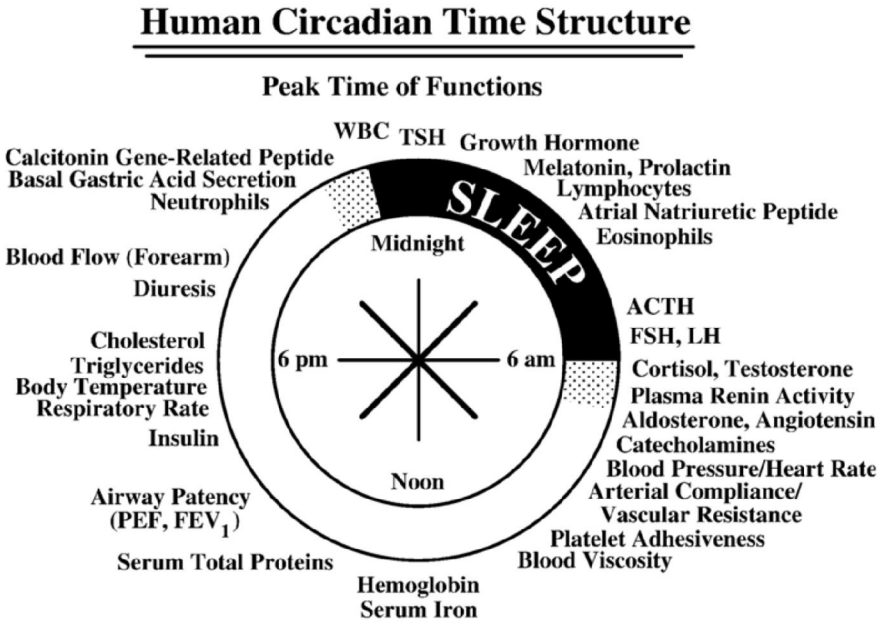

Figure 1: Human circadian time structure

Shown is the approximate peak time of circadian (24-h) rhythms of selected biological variables in persons adhering to anormal 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 eosinophil and lymphocyte cell numbers in blood peak between bedtime and early hours of sleep. Circadian rhythms in the blood level ofadrenocortical tropic hormone (ACTH), follicle stimulating hormone (FSH), luteinizing hormone (LH), testosterone, cortisol, catecholamine, renin activity, aldosterone, and angiotens in 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 essentialhypertension persons, and the morning peak of the circadian rhythm in blood catecholamine 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, andtriglycerides peak late in the afternoon, while those of urine production (diuresis), forearm blood flow, neutrophils, basal gastric acid production, and calcitonin-generelatedpeptide (a vascular dilator) peak late in the activity span. Together, the phasing (peak time) of these and numerous other 24-h rhythms in biological processesand 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. (WBC), calcitonin gene-related protein, and atrial natriureticpeptide occurs late at night or early in sleep. Growth andthyroid stimulating hormone (TSH), blood lymphocyte andeosinophil number, and

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plasma melatonin and prolactin crestduring sleep as do the adrenocorticotropic (ACTH), folliclestimulating (FSH), and luteinizing (LH) hormones. Plasmacortisol, renin activity, angiotensin, and aldosterone peak in themorning as do arterial compliance, vascular resistance, platelet aggregation, and blood viscosity. Hemoglobin and insulinconcentrations peak at noon and in the afternoon, as do thespirometric measures of airways caliber — FEV1 (forcedexpiratory volume in 1 s) and PEF (peak expiratory flow rate).The circadian rhythms of serum cholesterol and triglyceridesand urinary diuresis crest early in the evening. The information conveyed in this figure clearly illustrates that the biochemistryand physiology of human beings are not constant; rather, theyare variable in a predictable and coordinated manner during the24 h. [22]

III. Conclusion

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-like diagram like that shown in. 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.

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