1. Introduction

Ever since machines have started taking up physical activities from humans, human lifestyle has gradually shifted to intellectual exertion from physical exertion. Consequently, human body is customised to sedentary occupations engendering increased physical comfort but with concomitant rise in mental stress. In addition, diet habits are also changed drastically. The situations, altogether, instigates numerous physical disorders compelling necessary treatments in form of various medicaments (1-4). Moreover, multiple disorders are also quite common which further enforce multiple uses of drugs. Furthermore, such disorders are seen in young population also and considering lifelong endurance of many of them, their treatment would also become lifelong lasting. In short, burden of drugs on the patient body has greatly increased in these days.

Apparently, drugs/medicines are the chemical compounds which have side effects, normally undergo metabolism and often show drug-drug/drug-food interactions. All of these drawbacks are, in general, dose-dependent which increases with increase in dose. Nevertheless, administration of these life saving drugs cannot be sojourned but if their dosage regimen would be appropriately reduced or adjusted to an optimal effective level, it can minimise associated drawbacks to a certain extent. The task can be rationally fulfilled by delivering the drugs only when it is required. The stated approach is quite befitting especially in the treatment of chronological disorders (5-7).

The chronological disorders exhibit diurnal variations in their amplitudes owing to circadian rhythm of the body. Such disorders are modulated by biological clock of the body and hence require special attention while developing drug delivery systems (5, 8-10). Many disorders are covered under this category with large number of population and different age groups. Few examples of such disorders are asthma, rheumatoid arthritis, angina pectoris, hypertension, peptic or duodenal ulcer, diabetes, hypercholesterolemia, myocardial infarction, attention deficit-hyperactivity syndrome and so on (6, 7, 11, 12).

Evidently, drug delivery and therapeutics has to be designed in an efficient way in order to achieve appropriate drug concentrations at appropriate times, rather than just maintaining constant drug concentrations without concerning biological rhythms. Since

a few years, the disorders that follow rhythmic patterns have offered ascend to the foundation of new drug delivery systems, called chronopharmaceuticals – emerged by integration of chronobiology and pharmaceutics (10, 13-16). Chronobiology is the study of biological rhythms and associated mechanisms in the living systems (17, 18). A biological rhythm can be of – high frequency pulsatile oscillations (tenths of seconds to 1–2 h), ultradian (about 2–20 h), circadian (~24 h), circaseptan (~7 day), circamensual (~1 month) or circannual (~1 year) type in animal or humans beings (19). Amongst all, circadian rhythm is considered one of the most studied and most important biological clock to develop and design drug delivery systems (15). Pharmaceutics is a standout subject among all pharmaceutical arena which deals with scientific and technical aspects of design and manufacture of dosage forms to ensure quality, safety, efficacy and reliability of medicines (20). In this manner, chronopharmaceutics is characterized as a branch of pharmaceutics committed to design and evaluation of drug delivery systems, that provide drug release in accordance with biological requirement of given disorder or disease. Such chronopharmaceuticals synchronize drug delivery with physiological needs at a particular timing of day/night and hence enhance therapeutic efficacy and reduce drug related adverse effects (5, 21, 22). Since these types of formulations are designed to deliver drugs on 'time-dependent' phenomenon, they are broadly termed as chronotherapeutics or in other words 'time-controlled' therapeutics.

Biological rhythms exist in nearly all living structures which might be important for their survival under continuously altering ecological conditions (23-25). The interim of biological rhythms can significantly vary as indicated by the kind of living creature. These biological rhythms are controlled by a biological clock, which exists in the brains of all mammals and gives circadian information to all cells in the body, with a specific end goal to adjust their physiology according to the day timings (26, 27). This endogenous timing system synchronizes the cell physiology with outer environment, including the elements like dark-light cycle, changes in surrounding temperature or even food administration. Everyday reproducible modulation of peaks and troughs is apparent for numerous physiological parameters (28, 29). For instance, the menstrual cycle is an understood physiological function in ladies which obeys a cyclical rhythm of about one month. In humans, the circadian rhythm (~24 h clock) is synchronized with sleep-wake cycle (29-31) to modulate several body parameters such as hormone

production/release, metabolism, body temperature, sleep patterns, cell division, heart rate, and various other biochemical, physiological, and behavioural processes (9, 32). Thus, time-dependent dynamic bio-functions in humans are essentially subject to daily circadian modulations, and therefore continuous release of drugs into the human body appears to be superfluous and unwanted.

Numerous hormones in the body discharges in a recurrent or pulsatile way rather than continuously. Few examples are anterior and posterior pituitary hormones, catecholamines, adrenal glucocorticoids, mineralocorticoids, parathormone, gonadal sex steroids, glucagon, insulin and so on (33). Figure 1.1 displays the normal circadian rhythm dependent secretions of various physiological hormones in a pulsatile manner. In most of the cases, baseline release is consolidated with the pulsed release. Say as, basal discharge of insulin excites the synthesis of proteins and glycogen in muscles and adipose tissues while pulsatile insulin release is seen after ingestion of food to manage body's blood glucose levels. Similarly, administration of food also causes the pulsatile release of gastrointestinal (GI) hormones leading to the release of digestive enzymes from stomach and pancreas. The normal gastric acid secretion generally increases amid the day and almost stops during night. In a similar way, the releases of growth hormones, gonandotropins, leutinizing hormone (LH), follicle stimulating hormone (FSH), leutinizing hormone releasing hormone (LHRH), progesterone and estrogen are also governed in the pulsatile manner in order to maintain the normal physiological conditions (28-30). Typically, the secretion of growth hormones attains peak levels during the sleep hours, whereas the levels of both cortisol and testosterone are characteristically high in the morning (34). The level of cortisol, which is higher in the morning, gradually declines during the day and reaches at nadir during the mid sleep span. Further, the synthesis of cholesterol is normally greater during the night time as compared to day time, with maximum production at around early morning hours (9, 32, 33, 35). The circadian rhythm of such physiological hormones governs numerous biological conditions which thereby exhibit temporal or pulsatile behaviour as well (35). The stated pulsatile behaviour of various physiological hormones is very necessary for maintaining the normal homeostasis since continuous hormonal secretion may not only lead to down regulation of hormonal receptors on the target cell membranes but also inflicts undesirable adverse effects (36).

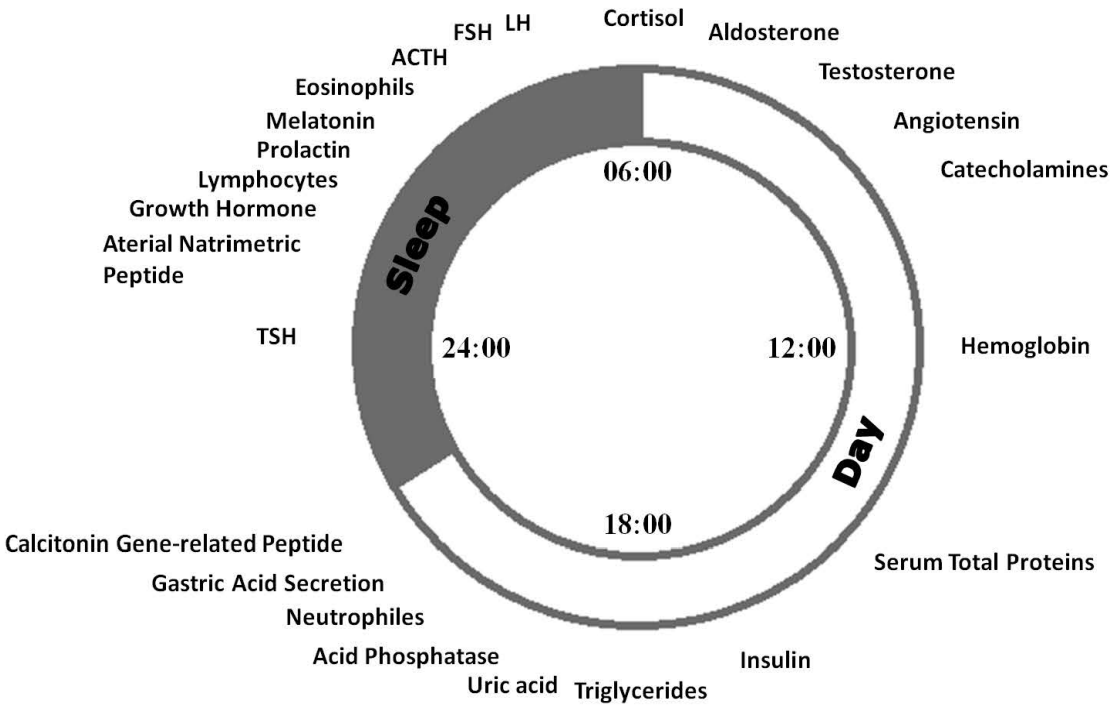

Fig. 1.1 Human circadian rhythm dependent secretion of hormones in a pulsatile manner (9, 11, 15, 37, 38)

Owing to the normal circadian rhythm of hormonal secretions, the occurrence and/or intensity of thereby affected physiological functions/symptoms/disorders also varies throughout the day as displayed in Figure 1.2. Say as, normal lung function experiences circadian modulation that reaches at lower level amid early morning hours. Similarly, blood pressure is also appears to be higher in the morning and up to the late afternoon, but gradually reduces during the night. Accordingly, the severity of many disorders/diseases also alters over a 24 h span (12, 39, 40). The diseases like rheumatic arthritis, bronchial asthma, angina pectoris, myocardial infarction, diabetes, attention deficit hyperactivity syndrome, ulcers, hypertension and hypercholesterolemia exhibit symptomatic changes as a result of biological rhythm. Exacerbation of asthmatic attacks often occurs after midnight or in the early morning as a result of diminished lung capacity promoted by circadian changes around then. Also, cardiovascular disorders like variant/prinzmental's angina, hypertension and myocardial infarction are rather common in early morning hours (12). The circadian variations are also known to contribute in lipid metabolism and complicate normal cholesterol synthesis process (41, 42). Altogether, it can be said that understanding of circadian variations over the day and night is essential to identify appropriate times for drug administration and thus to enhance therapeutic effectiveness of the drugs (43, 44).

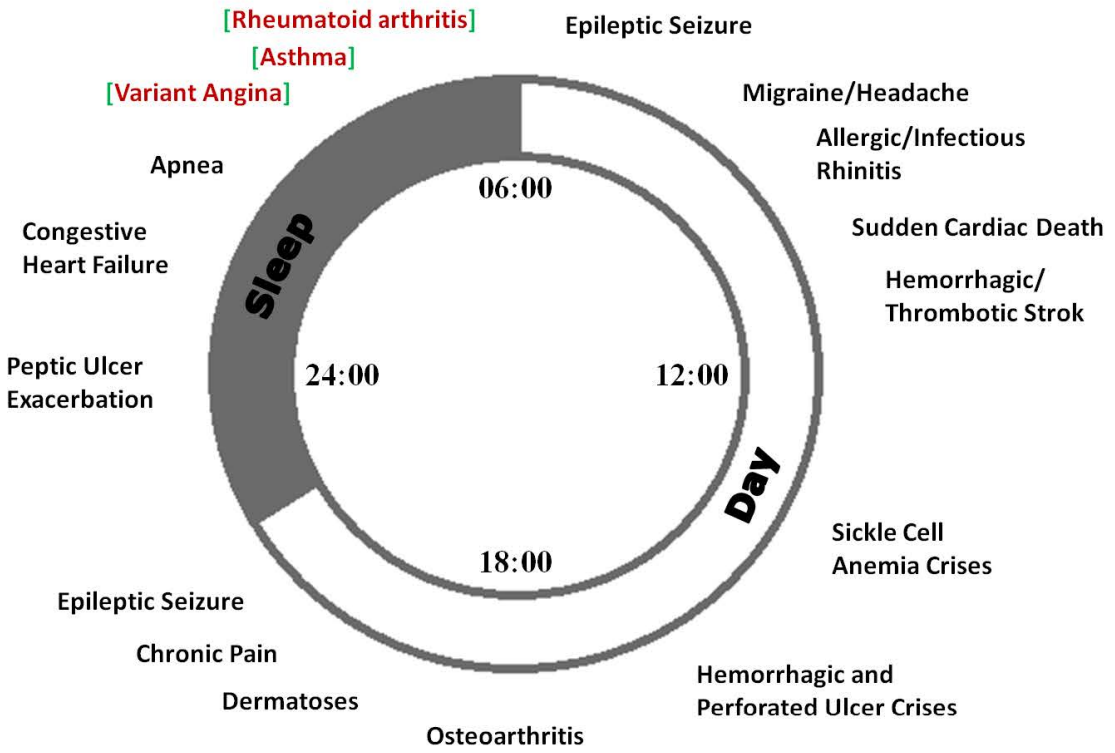

Fig. 1.2 Human circadian rhythm dependent aggravation of chronological diseases/disorders (9, 11, 32, 38)

As shown in Figure 1.2, amongst various chronological conditions, Brochial Asthma (BA), Variant Angina (VA) and Rheumatoid Arthritis (RA) demonstrate peak disturbances in the early morning hours due to the circadian rhythm of the body (9, 11, 12, 15, 37). Associated circadian rhythms and pathophysiologies are briefly discussed below.

Bronchial Asthma (BA): Normal and asthmatic subjects demonstrate circadian variations in the pulmonary functions as determined by spirometric parameters i.e. force expiratory volume (FEV1) and peak expiratory flow rate – which are nearly maximum about 4 pm and minimum at about 4 am (45). A study unveiled that the resistance to airflow gradually rise from 12 midnight to 6 am in sleeping asthmatic patients. Stimulation of vagus tone in both normal and asthmatic patients results broncho-constriction. The stimulation of vagus tone is increased at night which results in decreased airway function. Further, circulating hormones also vary in a circadian manner and contribute to overnight decrease in lung function. Top levels of circulating cortisol happen in the morning subsequent to arousing hours whereas trough levels observed amid 10 pm to midnight (46). Epinephrine, an adrenal hormone, possesses

bronchodilator activity owing to the stimulation of respiratory β_2 receptors and represses release of histamine and other mediators from sensitized mast cells. The greater levels of epinephrine are achieved during afternoon hours and trough levels at early morning hours (46). This circadian behaviour also induces noctural asthma by reducing broncho-dilatation as well as by allowing discharge of spasmogenic mediators from the mast cells. In addition, the levels of serum histamine are also reported to be higher at around 4 am, which is the time of greatest broncho-constriction (46). Thus, overall circadian rhythm increases the risk of asthmatic attacks during the early morning hours and hence the timing of drug administration has to be chosen accordingly in order to obtain maximum drug effect during the same time (45-47). According to Indian, US and British guidelines, oral corticosteroids are one of the most effective medicaments for the management of severe persistent asthma (48, 49).

Rheumatoid arthritis (RA): RA is also a chronic inflammatory disorder which exhibits early morning disturbances owing to circadian rhythm of the body (50). Morning stiffness, joint pain and swelling (i.e. three RA classification criteria) are worst in the morning on account of diurnal changes in the secretion or metabolism of endogenous cortisol and cytokines, particularly Interleukin (IL) 6 (51). Typically, the release of corticotropin-releasing hormone (CRH) from hypothalamus prompts pituitary synthesis of adrenocorticotrophin hormone (ACTH), which in turn stimulates production of glucocorticoid by adrenal cortex. These elements constituting hypothalamic-pituitary-adrenocortical (HPA) axis exhibit distinct circadian pattern (52). Primarily, the ACTH is released in a pulsatile manner, the level of which varies during 24 h span. Typically, the plasma ACTH and the serum cortisol levels are maximum in the morning i.e. at around wakeup time (around 8 am) which gradually decrease during the day and almost reach at nadir during the mid-sleep hours (approximately at 2 am) (53). This situation leads to increased level of pain and inflammation in RA patients. Moreover, the normal cortisol/ACTH secretion is also found to be impaired in RA patients because of relative adrenal-glucocorticoid insufficiency (54). On the other hand, the level of IL6, a potent pro-inflammatory agent which stimulates the production of acute phase of proteins, is also found to be increased from 2 am to 7 am in serum and synovial fluid in RA patients. The higher levels of IL6 bring about increased risk of joint destruction and bone resorption as a result of osteoclastogenesis, and thereby enhances the disease activity in the early morning (55,

56). Overall, clinical signs and symptoms of RA are worst in the early morning on account of diurnal variations of glucocorticoids and pro-inflammatory cytokine levels. Non-steroidal anti-inflammatory drugs (NSAIDs) are known to be amongst the most popular medicaments for the treatment of pain in RA patients. Besides, the corticosteroids, on account of their potent anti-inflammatory and immunosuppressive properties (57), are also considered to be highly effective drugs for the management of pain and inflammation associated with RA (50, 51, 53).

Variant angina (VA): Angina pectoris is a primary form of myocardial ischemia that occurs when coronary blood flow is unable to supply necessary oxygen demand required by heart, inducing a severe chest pain. Basically, the angina can be of three types, i.e. stable angina, unstable angina and variant angina. The variant angina is the type of angina which demonstrates transient ST elevation on ECG during the attack of chest pain. This type of attacks generally occurs at rest typically amid midnight to early morning due to biological/circadian variations (58). It was first described by Prinzmental *et al.* (59) (and hence also called as Prinzmental's angina) as a variant form of angina which is known to be caused by coronary artery spasm (60-62). Prinzmental *et al.* suggested that this type of angina results from temporary blockage of diseased coronary artery as a result of increased tone of vessel wall (59). The circadian pattern of variant angina demonstrates maximum attacks in the duration of midnight to early morning (63). The major underlying mechanisms for variant angina are endothelial dysfunction and increased vascular smooth muscle contraction which is governed by Nitric oxide (NO) synthesized from L-arginine by endothelial NO synthase (NOS) in vascular endothelial cells (64, 65). Under normal circumstances, NO incites relaxation of smooth muscle and vascular dilation in reaction to endothelium vasodilators (66). Kugiyama *et al.* (67) have reported that the coronary artery constricts in response to NG-monomethyl-L-arginine (inhibitor of NOS), in control subject but depict a little response in subject with vasospatic angina. They found that endothelium dysfunction of coronary arteries, which leads to limited baseline secretion of NO, plays a critical part in pathogenesis of coronary artery spasm. Other probable accelerating factors for coronary spasm are disturbance of autonomic nervous activity, chronic inflammation, increased oxidative stress, genetic vulnerability, magnesium deficiency etc. (65, 68). Autonomic nervous system play a crucial part in advancement of coronary artery spasm in subjects with variant angina as incidents of myocardial ischemia are rather common

between midnight to early morning (69). Yasue *et al.* (70) have found that the increased parasympathetic tone, which is usually higher at rest, is responsible in precipitating angina attacks by inciting sympathetic tone that instigates coronary spasm by activating α-receptor in the large coronary arteries. Further, sympatho-vagal imbalance i.e. sympathetic stimulation without parasympathetic amplification, at early in the morning hours also plays a key part in inducing coronary artery spasm (69). Moreover, the plasma levels of Fibrinopeptide A, a product of fibrinogen cleavage by thrombin and a useful indicator of *in vivo* fibrin formation, were also found to be higher between 2 am to 6 am in subjects with variant angina (71). Overall, it was suggested that the circadian rhythm of various chemical mediators evidently provokes the early morning attacks in patients with variant angina. Typically, calcium channel blockers are widely prescribed medicines for the management of variant form of angina (72).

Rationale

Pondering over the circadian rhythm and pathophysiology of BA, RA and VA, it is quite obvious that the effects of the drugs are prominently necessary in the early morning to prevent their attacks. Apparently, the day time control of such disorders can be easily managed by administering the medicaments at appropriate times, but situation is rather difficult in the early morning when patients are asleep and the risk of attack is high. Conventionally, such attacks are managed with night time administration of medicaments in the form of either immediate release (IR) or extended release (ER) formulations. Here, though the effect of medicine is mainly needed in the early morning, the drug is continuously released throughout the night; which eventually necessitate a bit higher amount of dose to extend its effect up to the next morning. If this extra dose which releases throughout the night has no therapeutic benefit, it would be considered utterly harmful in terms of side effects as well as increased metabolic load. Moreover, with the compounds having major long-term side effects or drug-withdrawal effects such as glucocorticoids (73, 74), the situation is even hard-hearted. On the contrary, if the peak effect of drug is specifically targeted in the early morning hours only, maximum administered dose can be utilized solely for therapeutic purpose and better treatment would be possible with relatively lower amount of dose; which subsequently reduce dose dependent side effects. One of the approaches to accomplish above objective is the pulsatile drug delivery system (PDDS) that can restrict the drug release up to predetermined time and thereafter provide burst drug release (8, 11, 75).

Thus, PDDS can be useful for designing of chronopharmacotherapy of diseases which shows circadian rhythms in their pathophysiology. The aim is to deliver the drug according to biological need of a given disease therapy and hence to manage the disease while minimizing treatment's side effects (76).

Hence, the research was undertaken to develop the time-controlled pulsatile release (PR) formulations, so that the administration of such formulations before going to bed (at about 9 pm) will specifically restrict the drug release for specific time and subsequently provide burst drug release to exhibit peak effect in the early morning when the risk of chronological attacks is maximum. By this way, the optimal effect of the drug can be achieved at appropriate time with minimum possible dose.

As stated above, there are several chronological conditions which show early morning disturbances and every single pathological condition is being treated by numerous drugs (5, 8, 11). Thus, there is a wide range of drugs (such as corticosteroids, NSAIDs, calcium channel blockers, tramadol, salbutamol, terbutaline and so on) which need to be fabricated in the form of PR formulations to make them useful for the chronotherapeutic applications (8, 11). Indeed, various researchers have successfully developed the PR formulations of different 'model' drugs by employing different formulation strategies (5-8, 11, 75). However, in practical terms it is often observed that the alteration of a drug candidate in an already developed formulation many-a-times alters the critical formulation attributes above the extent of desired specification limits due to the change in drug properties. For instance, Lin *et al.* (77) have studied the effects of various drugs, i.e. diclofenac sodium, theophylline and salbutamol sulphate, on lag time of compression-coated PR formulations. The lag times obtained with all three drugs were found to be markedly different from each other i.e. 14.6 h, 17.8 h and 21.3 h respectively. The results clearly dictate that the physicochemical properties of the drugs have profound effect on the release characteristics and therefore the formulation developed using any specific 'MODEL' drug cannot be simply employed for any other drug candidate to obtain the same results at all times. In other words, separate drugs require separate development/optimization activity which obviously necessitates extra time and resources. However, this loss of time and resources can be saved by developing a robust platform formulation which can accommodate diverse kind of drug molecules and still exhibit the same target product profile.

Hence, it was a thought of interest to develop the PR platform formulation which will provide same lag time and release characteristics with different type of drugs to make them useful in the treatment of various early morning chronological attacks. Now, as recommended by various regulatory bodies, Quality by Design (QbD) is one of the approaches to obtain the robust quality product; which was explored here for the development of robust platform formulation. To exclusively check robustness of the platform formulation, total six drugs, i.e. prednisone (PRS) (for BA and RA), methylprednisolone (MPR) (for BA), diclofenac sodium (DIC) (for RA), diltiazem hydrochloride (DIL) (for VA), nifedipine (NIF) (for VA) and lornoxicam (LOR) (for RA), were selected based on their wide physicochemical properties and mentioned indications. Importantly, lag time of a PR formulation has to be designed considering drug pharmacokinetics and disease requirements. Here, the time to achieve peak effect for all six selected drugs is about 1-3 h (78-88), and hence the lag time was targeted between 4-6 h so that bedtime administration of the PR formulation (about 9-10 pm) would release the drug only after midnight to exhibit peak effect in the early morning.

The solubility of selected drugs varies over freely soluble class (DIL) to practically insoluble class (NIF). Particularly, NIF and LOR are the poorly soluble compounds for which enhancement of solubility and dissolution rate was obligatory. The doses range from 4 mg (MPR/LOR) to 30 mg (DIL). Further, PRS and MPR are neutral in nature; NIF, LOR and DIC are weakly acidic; whereas DIL is weakly basic. Correspondingly, their pKa are also distributed over a wide range. All of these diversities would comprehensively challenge robustness of the final formulation and conclude whether or not it is a platform technology in real sense.

Various coating strategies such as compression coating, pan coating, fluidised bed coating etc. can be employed to obtain the desired lag time of a PR formulation (7, 8, 10, 11, 75). However, in the present work, we had explored compression coating and pan coating technologies in order to achieve the stated target and further the attempt was made to compare the competence of two processes for the development of PR formulations.

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