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Research Article

CHRONOPHARMACEUTICAL DRUG DELIVERY SYSTEMS: TREATMENT ON BLOOD PRESSURE

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Abstract

Chronopharmaceutical drug delivery systems are gaining a lot of interest as they deliver the drug at the right site of action, right time and right amount, as per the pathophysiological needs of the diseases. These systems are basically time-controlled drug delivery systems in which the system controls the lag time independent of environmental factors like pH, enzymes, GIT motility, etc. These systems are designed for chronopharmacotherapy which is based on the circadian rhythm of the body. The effectiveness and toxicity of many drugs vary depending on dosing time associated with 24 hr. rhythms of biochemical, physiological and behavioral processes under the control of circadian clock. The chronobiology of the various common 24-hour BP profiles seen in hypertensive patients in relation to cardiovascular risk and end-organ injury and ultimately the control and normalization of abnormal BP throughout daytime activity and nighttime sleep. Chronopharmacotherapy provides a means of individualizing the treatment of hypertension according to the circadian BP profile of each patient, and constitutes a new option to optimize BP control and to reduce the risk of cardiovascular disease. Various latest and upcoming marketed technologies of Chronopharmaceutical drug delivery used in treatment of hypertension diseases like OROS®, CODAS®, CEFORM®, DIFFUCAPS®, PULSINCAP®, PROCARDI XL.

Keywords: chronopharmacotherapy, chronobiology, circadian rhythm, cardiovascular diseases, pulsatile drug delivery system.

Introduction

Over the last 35 years the pharmaceutical market has focused increasing preferably for controlled and targeted drug delivery system. Such systems have been focused on constant, variable; sustain drug release or targeting the therapeutic agent to a specific site. Oral controlled drug delivery systems represent the most popular form of controlled drug delivery systems for the obvious advantages of oral route of drug administration. The oral controlled release system shows a typical pattern of drug release in which the drug concentration is maintained in the therapeutic window for a prolonged period of time. [13]

The advancement of technologies in the pharmaceutical field, drug delivery systems have drawn an increasing interest over the last few decades. Nowadays the emphasis of pharmaceutical galenic research is turned towards the development of more efficacious drug delivery systems with already existing molecule rather than going for new drug discovery and development process. [14]

Traditionally, drug delivery has meant for getting a simple chemical absorbed predictably from the gut or from the site of injection. [15] The newer technologies are developing in pharmaceutical field. The most efficacious dosage forms are generated on already existing molecules because many hurdles occur during discovery of the new molecules. Circadian rhythms are a characteristic feature of all human beings and often result in similar physiological phenomena over a period of time. Circadian rhythms can affect many systems within the body, including the cardiovascular and respiratory systems. Circadian rhythm diseases are disorders that are based on biological circadian rhythms and often occur during a predictable period of time. [4,10]

Pulsatile Drug delivery systems are gaining a lot of interest as they deliver the drug at the right site of action at the right time and in the right amount, thus providing spatial and temporal delivery and increasing patient compliance. Pulsatile Drug Delivery systems are basically time-controlled drug delivery systems in which the system controls the lag time independent of environmental factors like pH, enzymes, GIT motility, etc. These systems are designed for chronopharmacotherapy which is based on the circadian rhythm of the body. The major challenge in the development of pulsatile drug delivery system is to achieve a rapid drug release after the lag time. A pulse has to be generated in such a way that a complete and rapid drug release is achieved after the lag time so as to match body's circadian rhythms with the release of drugs.

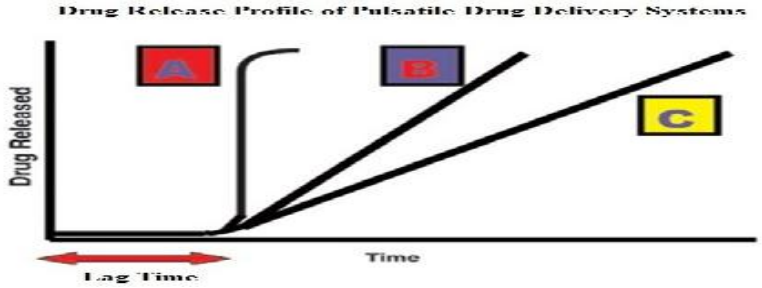

Fig. 1: Drug release profile of PDDS

Where (A) Sigmoidal release after lag time (B) Delayed release after lag time (C) Sustained release after lag time

Pulsatile preparations allow for sudden drug release after a time gap or predetermined lag time that corresponds to the circadian rhythm of a particular disease state. The lag time can be controlled either by osmosis or by the use of an erodible, soluble, or rupturable membrane. [6] The lag time can be incorporated into many dosage formulations, including hard gelatin capsules [21], tablets [22], or pellets [23].

Chronopharmacotherapy

In chronopharmacotherapy (timed drug therapy) drug administration is synchronized with biological rhythms to produce maximal therapeutic effect and minimum harm for the patient. Control release systems for 12 or 24 hr drug release are not suitable for diseases, which follow circadian variation. In that condition there is requirement for time or pulsatile drug delivery system. Several physiological processes in humans vary in a rhythmic manner, in synchrony with the internal biological clock, as shown in Fig.2.

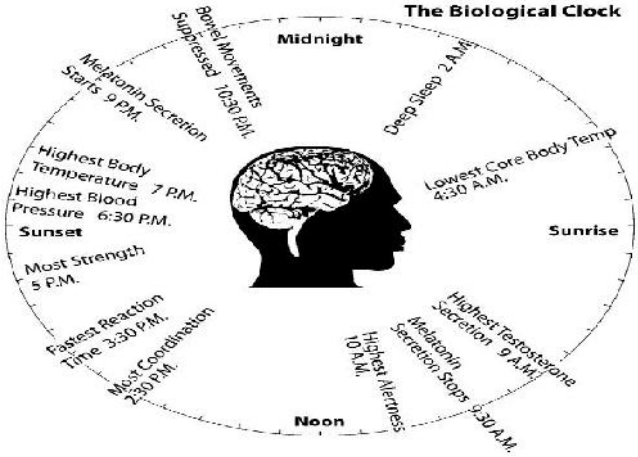

Fig.2: Diseases displaying circadian rhythm Chronopharmaceutics

"Chronopharmaceutics" consist of two words chronobiology and Pharmaceutics. Chronobiology is the study of biological rhythms (circadian, ultradian and infradian) and their mechanisms.[4,5]

Chronobiology is clearly relevant to the fields of medicine, pharmacology, and drug delivery. Clinical studies show that magnitude of rhythmic differences can be to a great extent and a strong determinant of when during 24 hour most morbid and mortal event will occur. For many drugs constant release system is not suitable. [11,12]

Biological rhythm

A biological rhythm is a self-sustaining process inside the human body. It is defined as the process that occurs periodically in an organism in conjugation with and often in response to periodic changes in environmental condition. Our bodies' rhythm, also known as our biological clock.[7,8,9] There are three types of mechanical rhythms in our body, they are

Ultradian: Oscillations of shorter duration are termed Ultradian Rhythms (more than one cycle per 24 h). E.g.90 minutes sleep cycle.[6]

Infradian: Oscillations that are longer than 24 hours are termed as Infradian Rhythms (less than one cycle per 24hours). E.g. Monthly Menstruation.

Circadian: The term circadian is derived from the Latin circa which means "about" and dies which can be defined as "a day". Normally, circadian rhythms are synchronized according to internal biologic clocks related to the sleep-wake cycle. Our circadian rhythm is based on sleep-activity cycle and is influenced by our genetic makeup and thereby affects our bodies' function throughout day and night (24-hour period). Circadian rhythm regulates many body functions in humans like metabolism, physiology, behavior, sleep pattern, hormone production.[1,2,3]

Pharmaceutics: is the discipline of pharmacy that deals with the process of turning a new chemical entity into a medication to be used safely and effectively by patients.

Chronotherapeutics is the purposeful delivery of medications in unequal amounts over time, for example, during the 24 h. Chronotherapeutics takes into account rhythm determinants in (A) disease pathophysiology (chronopathology), (B) chronopharmacology (chronokinetics, chronodynamics, chronesthesy, and chronotoxicology) of medications, and (C) attributes (period, phase, amplitude, and level) of the human circadian time structure to determine the drug-delivery pattern, dose, and administration time to optimize desired or minimize adverse effects.[1,20]

Cardiovascular diseases

In cardiovascular disease capillary resistance and vascular reactivity are higher in the morning and decreases latter in the day. Platelet agreeability is increased and fibrinolytic activity is decreased in the morning, leading to a state of relative hypercoagulability of the blood. Because of this reason the frequencies of myocardial infarction and of sudden cardiac death are more prone during from morning to noon. [31] Ambulatory blood pressure measurements show a significant circadian variation to characterize blood pressure. This variation is affected by a variety of external factors such as ethnicity, gender, autonomic nervous system tone, vasoactive hormones, hematologic and renal variables. Increased heart rate, blood pressure, imbalanced autonomic tone, and circulating level of catecholamines controlling the cardiac arrhythmias show important circadian variation and trigger the genesis of the circadian pattern of cardiac arrhythmias. [32]

Pulsatile hormone secretion

Many hormones in the human body are secreted in a cyclical or pulsatile manner, rather than continuously. Secretions of the anterior and posterior pituitary hormones, adrenal glucocorticoids, mineralocorticoids and catecholamines, gonadal sex steroids, parathormone, insulin, and glucagon are pulsatile. [33] Pulsatile release of gastrointestinal hormones, stimulated by presence of food in the gastrointestinal tract, generally causes the release of digestive enzymes from the pancreas and stomach. Many hormones including follicle stimulating hormone (FSH), leutinizing hormone (LH), leutinizing hormone releasing hormone (LHRH), estrogen, and progesterone are also regulated in the body in pulsatile manner. Numerous biological functions in the body are thus regulated by the temporal and pulsatile release of hormones. [34] If the hormones were continuously secreted, a hormonal imbalance may arise, which would not only induce down regulation of hormone receptors on the target cellular membranes, but might also produce undesired side-effects. [35]

Definition of hypertension

Hypertension is a common chronic condition affecting up to 35% of human adults. This condition is an important risk factor for strokes, heart attacks and other vascular and renal diseases. Pharmacologic treatment of high blood pressure (BP) reduces the

incidence of these complications and prolongs life. [16] Several attributes of the cardiovascular system, including blood pressure (BP) and heart rate (HR), are characterized by predictable changes during the 24 h, for the most part, in synchrony with the rest–activity cycle. [18,19] The chronobiology of the various common 24 hour BP profiles seen in hypertensive patients in relation to cardiovascular risk and end-organ injury and ultimately the control and normalization of abnormal BP throughout daytime activity and nighttime sleep. [17]

Ambulatory BP measurements: criteria for the diagnosis of hypertension [24, 25] and assessment of antihypertensive therapy have thus been established on the basis of mean values determined from data gathered over a single 24-hour span.[26,27,28]

Clinic BP measurements: The diagnosis of hypertension relies on clinic BP, as universally performed using the same static reference thresholds, i.e. 140 and 90 mm Hg for systolic (SBP) and diastolic (DBP) BP. [29] According to the European guidelines, "mean daytime and nighttime values are several mm Hg higher and, respectively, lower than 24-hour means (≥125/80), but threshold values are more difficult to be established, as these are markedly influenced by behavior during day or night". [17]

The Japanese Society of Hypertension also suggested the use of the 24-hour mean (≥135/80) as unique parameter for diagnosis, providing a reference threshold for SBP markedly higher than that suggested later by the European Society. [30]

Clinic versus ambulatory BP measurement

BP determined casually in the physician's office has long been used for the diagnosis of hypertension and for the evaluation of treatment efficacy. [30,36,37] However, these conventional time-unspecified single measurements have major disadvantages. Unfortunately, they are only indicative of the BP status of a brief and small fraction of the entire circadian (24-hour) BP pattern. Moreover, they are often affected by circumstances in the clinic that exert a pressor effect ("whitecoat" effect) [38,39], resulting in higher than actual BP values. Finally, clinical BP measurements can be affected by several potential sources of error [40]; these include defects in instrumentation (lack of proper validation and periodic calibration of the measurement devices, use of inappropriate BP cuff in slim and overweight subjects) and technique of measurement by health personnel (e.g., "digit preference" that leads in observer round-off of an arbitrary last digit, usually 0 or 5). [41-44]

Circadian variation

Circadian rhythm regulates several body functions such as metabolism, physiology, behavior, sleep patterns, hormone production, and so on. The circadian rhythm not only affects most physiological functions but also influences the absorption, distribution, metabolism, and elimination (ADME) of drugs, leading to changes in drug availability and target cell responsiveness.[45-48] the time-dependent dynamic bioprocesses in human body are significantly dependent on circadian variations, and so constant delivery of a drug into the human body seems both unnecessary and undesirable. Timing the administration of some medications in accordance with the body's circadian rhythm may significantly affect the drug's pharmacokinetics and pharmacodynamics. [49] the circadian rhythm influences normal biological processes, the occurrence or intensity of symptoms of these diseases is not constant throughout the day. Several diseases, including arthritis, asthma, allergies, peptic ulcer disease, dyslipidemia, and cancer exhibit predictable circadian variation. Medications and treatments given at the appropriate time according to the body's circadian rhythms will result in more favorable outcomes. [50, 51]

Chronobiology of BP variability

BP is affected by a variety of external factors, including ambient temperature/humidity, physical activity, emotional state (anxiety, anger), alcohol or caffeine consumption, meal composition, and sleep/wake routine. [52-56] the effects of physical and mental activity account for a predominant proportion of the day-night variation [56-58], as demonstrated by studies of shift workers who show a close linkage between activity and BP even during the first 24-hours of night work [59–63]. The intrinsic component of human circadian BP rhythmicity, which is masked by external influences, also plays a role.[64] An endogenous basis for the 24-hour BP variation, i.e., a relationship between the circadian clock and the BP rhythm, is suggested by laboratory rodent studies showing that lesioning of the suprachiasmatic nucleus (the master circadian clock located in the hypothalamus of the brain) abolishes the circadian rhythms of BP and heart rate (HR) without affecting the sleep–wake and motor activity 24-hour cycles. [65,66]

Common types of 24 hour BP patterns

Dipping BP pattern

The predictable changes during the 24 h in environmental and biological variables give rise to the

circadian pattern in BP and HR. In persons with normal BP and uncomplicated essential hypertension, BP declines to lowest levels during nighttime sleep, rises abruptly with morning awakening, and attains near peak or peak values during the first hours of diurnal activity. In the so-called normal dippers, the sleep-time BP mean is lower by 10–20% compared to the daytime mean. In healthy young adults, the immediate morning rise of SBP amounts to about 20-25 mmHg, but in older adults the noncompliant vasculature can give rise to much greater 24-hour in SBP and DBP variation, i.e., 50 mm Hg or more within a single 24-hour span. Significant gender differences in specific features of the BP and HR circadian rhythm have been identified. Typically, men exhibit a lower HR and higher BP than women, the differences being greater for SBP than for DBP [67,68] The extent of the sleep-time decline in BP has been mainly quantified through the so-called diurnal/nocturnal BP ratio, defined as the nocturnal decline in BP relative to the diurnal BP mean, and calculated as 100×(mean diurnal BP-mean nocturnal BP)/mean diurnal BP. Using this ratio, patients have been arbitrarily classified as dippers or non-dippers (diurnal/nocturnal ratio b10%) [69].

Non-dipping BP pattern

The circadian BP variation also comes from the fact that departure from this model profile could characterize overt pathology. Alteration of the circadian rhythm of the neurohumoral factors that affect the autonomic nervous and cardiovascular systems, secondary to various pathological conditions, results in persistent change of the 24-hour BP pattern. [19,70]

A reduced sleep-time decline or even increased sleep-time BP has been reported in patients with orthostatic autonomic failure [71], Shy-Drager syndrome [72], vascular dementia [73], Alzheimer-type dementia [74], cerebral atrophy [75], phaeochromocytoma [76], autonomic neuropathy [77], cerebrovascular disease [78-81], ischemic arterial disease after carotid endarterectomy [82], neurogenic hypertension [83], normotensive and hypertensive asthma [84], chronic renal failure [85-92], severe hypertension [93], salt-sensitive essential hypertension [94], refractory or resistant hypertension [95,96], gestational hypertension [97], essential hypertension with left ventricular hypertrophy [98,99] and cardiac transplantation [100–104] related to immunosuppressive treatment, congestive heart failure (CHF) [105–108], and recombinant human erythropoietin therapy [109]. A circadian profile characterized by daytime hypertension and nighttime hypotension has been described in hemodynamic brain infarction associated with prolonged disturbance of the blood–brain barrier [110]. In these patients, the range of variation in BP between the day and sleep-time level was significantly increased from expected.

Chronotherapy of antihypertensive medications

The pharmacotherapy of hypertension has been strongly influenced by the concept and assumptions of homeostasis. Until the last 15 or so years, the vast majority of the medical community believed systolic blood pressure (SBP) and diastolic blood pressure (DBP) to be relatively constant throughout the 24 hr. [114] In essential hypertension, the relatively constant medication level achieved by conventional (homeostatically styled) antihypertensive therapies may be lower than required in the morning, when BP surges to peak or near peak levels; whereas, it may be higher than required during nighttime sleep, when BP declines, at least in low-risk patients, to their lowest level. [19]

Therapeutic intervention in hypertension consists of adequate control of BP, the goal being to reduce cardiovascular morbidity and mortality. Commonly, the therapeutic strategies used to improve BP control in a hypertensive patient include: increase of the therapeutic dose of the medication, sequential change of antihypertensive drugs or application of drug combinations having synergic effects. All these therapeutic strategies have, in practice, one common element: the administration of antihypertensive medication in a single morning dose (either at the commencement of the diurnal activity span or, more commonly, with breakfast), not only with a single prescribed drug, but also with combination therapy. Results from a recent study indicate that up to 89% of treated hypertensive patients take all their medication in a single morning dose. [111] Once realizing the prognostic implications of an altered circadian BP pattern, this therapeutic approach of using unique single morning dosing could be theoretically valid only if all patients had an adequate dipper pattern of BP variability and if all prescribed antihypertensive drugs had an homogeneous efficacy throughout the 24 hr. Taking into account the fact that most marketed medications fail to provide homogeneous long-lasting efficacy throughout the 24 hr. and there exists a high prevalence of the non-dipper BP pattern. [112,113]

Medications for the treatment of hypertension

The calcium channel blocker controlled-onset, extended-release (COER) Verapamil was the first special drug-delivery tablet medication specifically designed for the chronotherapy of hypertension. [115,116] the drug-delivery technology of this tablet

medication delays the release of verapamil for approximately 4-5 h following its recommended bedtime ingestion. Medication is released thereafter so the highest blood concentration is achieved in the morning around the time of awakening, generally between 6 and 10 a.m., with an elevated level sustained throughout diurnal activity. The half life kinetics of verapamil results in a progressive decline of drug level in the evening and over night, so reduced (trough) concentration occurs during nighttime sleep when BP in uncomplicated essential hypertension is generally lowest. [117] COER - verapamil has been shown to be therapeutic for both dipper and non-dipper hypertensive patients; in non-dippers, it was found to effectively reduce abnormally elevated morning as well as nocturnal BP, particularly SBP, in a dose-dependent manner. [118] Chronotherapeutic oral drug absorption system (CODAS)-verapamil is a second special drug-delivery-based CCB chronotherapy of hypertension. CODAS-verapamil (Verelan PM™; Schwarz Pharma) was approved by the FDA in 1999. Release of verapamil from the polymer-coated beads of this capsule medication following recommended bedtime ingestion is delayed for approximately 4 h. Medication is then dispersed in an increasing amount so that peak blood concentration is achieved in the morning, between 6 and 10 a.m., when SBP and DBP are expected to rise to peak or near peak level in diurnally active uncomplicated essential hypertensive persons. [119] Graded-release long-acting diltiazem (Cardizem LA, Biovail Pharmaceuticals) was approved by the FDA in 2003 for oncedaily dosing either in the morning or evening. Multiple-dose studies show ingestion of the 360 mg dose of this special drug-delivery form of diltiazem at 10 p.m. results in the desired PK profile for a chronotherapy of essential hypertension. [120] The β-antagonist propranolol chronotherapy (Innopran XL™, Reliant Pharmaceuticals) was approved in 2003 by the FDA. Multiple-dose study [121] of this capsule medication shows its ingestion at bedtime as recommended results in trough drug blood concentration toward the latter hours of nighttime sleep (~ 4 a.m. due to the intentional delay of propranolol release for 4–5 h), peak drug concentration between 4 and 10 a. m., and elevated plateau of drug concentration in the afternoon and early evening. Recent findings from 24-hour ABPM trials of this β-antagonist chronotherapy document its potent SBP and DBP reduction in the morning, with persistence of significant BP-lowering activity throughout the entire 24-hour dosing interval [122].

Chronopharmacodynamics of antihypertensive medication

Circadian rhythms in gastric pH and emptying, gastrointestinal motility, biliary function and circulation, liver enzyme activity, blood flow to the duodenum, kidney, and other organs, among other factors. [123,124] Clinically relevant dosing-time differences in the beneficial and adverse effects (termed chronodynamics) of BP-lowering medications are also known. They result from the chronokinetics of medications as well as circadian rhythms in drug-free fraction, rate-limiting steps of key metabolic processes, receptor number and conformation, and/or second messenger and signaling pathways. [125]

Chronopharmacodynamics of Angiotensin II receptor blockers: Angiotensin II receptor blockers (ARB) selectively and specifically antagonize the action of Angiotensin II, a potent vasoconstrictor impacting BP regulation. ARBs are becoming increasingly popular for the treatment of hypertension because they are effective and well tolerated. [19] The ARB valsartan when ingested by stage 1 or 2 essential hypertension patients for 3 months as a immunotherapy, either in the morning upon awakening from nighttime sleep or at bedtime. The highly significant BP reduction after treatment with the 160 mg/day dose of valsartan was similar for both treatment times (17.0 and 11.3 mm Hg reduction in the 24-hour mean SBP and DBP with morning administration, and 14.6 and 11.4 mm Hg reduction in the 24-hour mean SBP and DBP with bedtime administration). Valsartan administration at bedtime as opposed to upon awakening, however, resulted in a highly significant average increase by 6% in the diurnal/nocturnal BP ratio, corresponding to a 73% relative reduction in the number of non-dipper patients.[126] The findings suggest the dosing (i.e., circadian) time of valsartan can be chosen in relation to the dipper status of a given patient to improve therapeutic benefit and reduce cardiovascular risk. These results have been recently corroborated by two independent prospective chronotherapy trials, the first on elderly hypertensive patients characterized by the progressive reduction in diurnal/nocturnal BP ratio with aging [127] and the second on non-dipper hypertensive patients.[128]

Chronopharmacodynamics of α-adrenoceptor antagonists: α Adrenoceptor blockade more effectively reduces peripheral resistance in the early morning hours than at other times of the day and night [129]. Indeed, a single nighttime dose of the α- blocker doxazosin reduces both SBP and DBP throughout day and night, but its greatest effect is exerted early in the morning [130]. Interestingly, the peak effect of doxazosin following nighttime dosing occurs later than predicted based upon its PK [130], suggesting a circadian-stage dependency in the dose response relationship, such as detected for nifedipine [131], enalapril [133], and propranolol. [132]

Chronopharmacodynamics of β-adrenoceptor antagonists: In general, there is a tendency for conventional β-blockers to predominantly reduce diurnal BP, with less effect on night time BP. [134,135] In healthy subjects, a crossover study with propranolol showed a greater decrease in BP and HR during the day than night time hours. [132]The higher impact of β-blockers on the diurnal than nocturnal BP correlates well with the circadian rhythm in sympathetic tone, as gauged by the circadian rhythm of plasma nor adrenaline concentration. [136]

Chronopharmacodynamics of calcium channel blockers (CCB): Several trials have investigated the differential effects of morning vs. evening administration of CCB, including amlodipine [137-139], cilnidipine [140], diltiazem[141], isradipine [142,143], nifedipine [144,145], nisoldipine [146], and nitrendipine [147,148] in presumably diurnally active subjects. A sustained-release formulation of diltiazem was found to be more effective in controlling the 24-hour BP mean when administered at night, while also reducing the diurnal/nocturnal BP ratio towards a more non-dipper profile. [141]

Chronopharmacodynamics of Angiotensin-converting enzyme inhibitors (ACEI): Clinical studies demonstrated a different effect of the ACEI benazepril [149], enalapril [133], perindopril [150], quinapril [151,152], ramipril [153], spirapril [154], and trandolapril [155] when dosed in the morning vs. the evening. In all cases, evening administration of these medications resulted in a more marked effect on nocturnal BP and a significant modification of the circadian BP profile.

Techniques of press-coated chronopharmacotherapy delivery drug systems

Pharmaceutical coating: Pharmaceutical coating is an important technique for the preparation of solid dosage forms, and it is assured that this technique will develop further within the pharmaceutical industry. The main technique employed in the preparation of coated solid dosage forms is based on the deposition of different materials from solution, suspensions, or powders. There are four major coating techniques for applying coatings to pharmaceutical solid dosage forms: (1) sugar coating, (2) film coating, (3) microencapsulation, and (4) press coating. [156,157]

Solventless coating technology: Solventless coating technology can avoid problems of solvent exposure, solvent disposal, and residual solvent in the product. Solventless processing enables a reduction in costs, by eliminating the slow and expensive processes associated with solvent treatment. Moreover, the technology can significantly reduce processing times because there are no drying and evaporation steps. [158,159]

Press coating technology: Press coating, also referred to as double compression coating, compression coating is an old technique first proposed by Noyes in an 1896 patent [160]. An industrial application of this technique was introduced during the period 1950–1960 to allow the formulation of incompatible drugs [161]. Press coating found increasing application during the past two decades; the process does not require solvents, has a relatively short manufacturing process, and achieves a greater increase in mass of the core tablet than solvent-based methods do [162]. The press coating technique offers many advantages, such as protection of hygroscopic, light sensitive, oxygen labile, and acid-labile drugs, isolation of incompatible drugs from each other, and provides a method for both sustained drug release and modification of the drug release profile. [162-164]

Manufacturing process of press coating: There are extensive reports of the use of the press-coating technique for managing drug delivery from the tablets in the literature; the press-coating manufacturing processes employ several steps. The inner core tablet is formulated, and then compressed under appropriate conditions. [165]

Technologies used in chronopharmaceutics

Currently key technologies used in Chronopharmaceutical drug delivery of hypertension diseases includes (Table.1): OROS®, CODAS®, CEFORM®, DIFFUCAPS®, PULSINCAP®, PROCARDI XL.

Table.1: Marketed Technologies of Chronopharmacotherapy drug delivery

Technology	Mechanism	Proprietary name and Dosage form	API	Disease	Advantage
OROS® [166,167]	Osmotic mechanism	Covera-HS®; XL Tablet	Verapamil HCl	Hypertension	Prevent the dangerous surge of BP in the early morning
CODAS® [168-170]	Multiparticulate,pH dependent system	Verelan® PM; XL Release Capsule	Verapamil HCl	Hypertension	Early morning peaks plasma concentration after bed time dosing

DIFFUCAPS® [171,172]	Multiparticulate System	Innopran®; XL tablets	Propranolol HCl, Verapamil HCl	Hypertension	Lag time is 4-5 hours. Release is pH independent
PULSINCAP® [173,174]	Rupturable system	Pulsincap®	Dofetilide	Hypertension	Lag time can be controlled by manipulating the dimension and the position of the plug
PROCARDIA XL® [6]	Sustained release	Procardia XL	Nifedipine	Hypertension	Increase ability to exercise and decrease the frequency of chest pain attacks
CEFORM® [175,176]	Extended Release tablet	Cardizem LA;	Diltiazem HCl, Verapamil HCl	Hypertension	Production of uniformly sized and shaped microspheres

Discussion

Nocturnal hypertension, which is characterized by the loss or even reversal of the expected 10–20% sleep-time BP decline, increases one's risk of cardiovascular and cerebrovascular events, nephrosclerosis, and progression to end-stage kidney failure in renal patients. International guidelines recommend the use of long-acting, once-daily medications that provide 24-hour efficacy. They improve adherence to therapy and minimize BP variability, providing smoother and more consistent BP control. Most antihypertensive medications have been approved to be used once-daily, without specification of ingestion time. Use of a medication with high homogeneous efficacy throughout the 24 h, such as valsartan ingested upon awakening is unlikely to affect the circadian profile of BP and exemplify good treatment choices for dipper hypertensive patients. This therapeutic scheme, however, may not be appropriate for managing non-dippers, since it is important to avoid nocturnal hypertension. The available scientific evidence suggests non-dipper hypertensive may benefit from an evening (as opposed to morning) dosing schedule of certain BP-lowering medications to best reduce abnormally high sleep-time BP and to convert the disturbed non-dipping 24-hour BP profile to the normal dipper one, which is known to be associated with reduced cardiovascular risk. However, because the effects of BP medications can be circadian-stage dependent, that is dependent on ingestion time with reference to endogenous 24-hour rhythms, the specific administration-time-dependent dose–response curve of the drug must be first determined and then taken into consideration to effectively treat hypertensive patients. The non-dipper BP profile in patients with chronic renal failure was normalized with evening, but not morning, four-week isradipine dosing unfortunately did not conduct follow-up to evaluate potential changes in cardiovascular risk, mainly due to the short period of active treatment. On the other hand, recent results have demonstrated that urinary albumin excretion is significantly reduced with bedtime, but not morning, valsartan treatment. The beneficial effects of the chronotherapy of hypertension on urinary albumin excretion, plasma fibrinogen has also been shown to be significantly reduced with bedtime, as compared to morning, valsartan treatment in direct correlation with the increased diurnal/nocturnal BP ratio resulting from the conversion of non-dippers into dippers. The future of chronotherapeutics and delivering drugs in a pulsatile manner seems to be quite promising as in certain diseases states. It exhibit several advantages over the traditional zero or first order drug delivery mechanism. Time controlled or site specific single or multiple units are obtained by pulsatile drug delivery techniques.

Conclusion

Chronopharmaceutical drug delivery shows potential benefits for the diseases which show circadian rhythms like cardiovascular diseases. Several attributes of the cardiovascular system, including BP and HR, are characterized by predictable changes of relatively high amplitude during the 24 h, for the most part in synchrony with the rest-activity cycle. Increasing this ratio towards a more dipper pattern by chronotherapy decreases cardiovascular risk; decreasing the diurnal/nocturnal BP ratio. The basic parameters in the design of polymer based pulsatile systems are the biocompatibility and the toxicity of the polymers used. It can be concluded that Pulsatile drug delivery system provide a unique way of delivering drugs possessing chronopharmacological behaviour, extensive first pass metabolism, necessity of night time dosing, or absorption window in GIT. Pulsatile drug delivery system shall be promising in future. Various latest and upcoming marketed technologies like OROS®, CODAS®, CEFORM®, DIFFUCAPS®, PULSINCAP®, PROCARDI XL.

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