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Review Article

THE EMERGENCE OF TIME PROGRAMMED DRUG DELIVERY SYSTEM: CHRONOTHERAPY OF CARDIO VASCULAR DISEASES

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ABSTRACT

Time programmed drug delivery system is a system that promises to deliver a drug at a point of time when it is most required, as it is programmed beforehand. Though the delivery system is a boon to the pharmaceutical research due to its desired release profile feature and application to numerous disease areas like hypercholesterolemia, asthma, cardiovascular disease, peptic and duodenal ulcers and cancers of various categories, its special significance is due to its potential applications in chronotherapeutic drug delivery, where the pinnacle aim of devising this drug delivery system is to obtain a programmed release at desired time points, with a lag time where no drug is released. Lot of work is being carried out lately, to understand the relationship between the rhythmicity in disease symptoms and the biological clock, but a special mention is required in case of diseases associated with cardiovascular functions. Cardiovascular system works on a frequency cycle and it resonates hour to hour with the biological clock except in cases of disturbances from any external stimuli, which leads to CVS disorders. Correcting the rhythmicity of the frequency cycles of heart, which are apparently in sync with the master clock, can be done or achieved by delivering the drug exactly at the point of time when it is needed the most. This will minimize the side effects and maximize the benefits of the administered dose. This review focuses on the importance of circadian rhythm and chronotherapy in the management of CVS and overall physiology, scientific evidences of their relationship, role and importance of PDDS in formulation management and finally the work done in this direction and the marketed chronotheraptics delivery systems available for CVS disorders.

Keywords: Pulsatile drug delivery system, Chronotherapy, Cardiovascular diseases, Pulsatile technology.

INTRODUCTION

Industrial pharmacy came into the picture when researchers realised that the "eureka" moment of discovering a drug molecule is insufficient to convert a drug into a delivery system. That simply lipophilicity and hydrophobicity can not decide the fate of a molecule, through its journey of getting transformed into a successful dosage form. Also, various health conditions, disorders and diseases don't basically respond to a drug but to a delivery system and the failure of delivery system becomes the failure of the drug. Though still maximum drugs were doing well with their immediate release profiles, conditions like cancer and AIDS were continuously challenging the researchers to make the specific delivery of such drugs more efficient. So controlling the release of the drug through the delivery system came into picture in 1960s via mucosal inserts, implants (e. g., subcutaneous or intramuscular), oral capsules (release in the GI tract), topical patches (applicable on skin), and they were getting approved for clinical use[1]. The time period between 1980s and 90s became the era of controlled release delivery and selective drug targeting. The huge popularity of controlled release delivery systems and drug targeting at that time, also brought Ehrlich's imagined concept of the "Magic Bullet" to certainty [1]. After the increasing success of controlled delivery systems, Time controlled drug delivery came as a bifurcation and modification of the same, as it was realised that ordered/structured release may not always be the requirement of the disease condition, but tailor made burst release may be required, by some diseases, as per the disease pathophysiology and on-set patterns. This gave rise to time sensitive drug delivery systems which promised to deliver the drug at a particular time of the day, as per the need of the regimen. The situation demanded release of drug as a "pulse", after a time lag, such that the design gives complete and rapid drug release followed by the intentional lag time. Such systems came to be known as pulsatile drug delivery systems (PDDS), time-controlled systems, or sigmoidal release systems. Time controlled systems have been developed in close association with emerging chrono therapeutic delivery ideas, after it was confirmed by many clinical studies that the symptoms of several pathophysiological conditions, as well as the pharmacokinetic and pharmacodynamic profiles of most drugs, are subject to rhythmic or circadian variation patterns.

Section 1: Chronopharmacology: Basis of Chronotherapeutics and time programmed drug delivery

Biological processes and functions are anatomically and physically present into three dimensional spaces and the biological time structure is synchronised with spatial time[2]. This biological time structure is described as the biological rhythm and is characterized by short, intermediate, and long period oscillations [2]. The biological rhythms occur endogenously and are self sustainable in nature and are predominantly characterised by period, level, amplitude, and phase. ultradian (20 hr), circadian (24 hr), and infradian (28 hr) rhythms define the periodicity of the biological rhythms[2]. Among these periodic rhythms, the 24 hr cycle i. e the circadian pattern is most important for the practice of medicinal pharmacotherapy of patients owing to its parallel nature with the clock time cycle. Numerous biological rhythm studies have helped delineate the temporal organization of humans and human circadian time structure can be best portrayed by synchronising it with 24-hr rhythms on a time line as shown in figure 1[2].

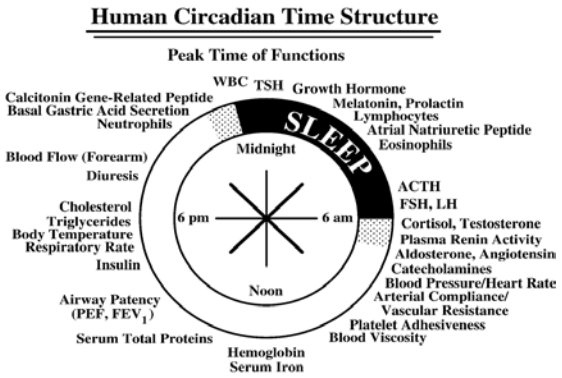

Fig. 1: Human circadian time structure showing the evidence of synchronization between certain selected biological variables with the 24 hour clock.

Clinical evidence supports the fact that Circadian rhythms influence mammalian physiology. The prime function of the circadian rhythm is to optimize cellular processes along with optimization and coordination of various metabolic processes and human behaviour regarding its sleep wake cycle. The Circadian Time System is hierarchically structured along the master pacemaker located in the superchiasmatic nucleus of the hypothalamus[3,4]. This master pacemaker located in hypothalamus controls and coordinate with the others peripheral clocks located in different tissues and cells[3].

Playing a key role in normal physiology and behaviour is not the only function of the circadian clock, but according to many reported clinical studies, it has been found that abnormalities in the circadian rhythm are associated with the pathophysiology of various diseases including asthma, cardiovascular diseases, diabetes, cancer, autoimmune disorders and various psychological conditions[5]. Many molecular targets and biochemical signals inside the cells are expressed in sync with the circadian rhythm which can affect the bioavailability, potency and efficacy of many drugs[6]. A considerable number of genes, drug receptors and metabolizing enzymes are expressed in circadian manner, leading to a significant lag in their efficacy related to the time of the day at which they are administered, which gives sufficient evidence of circadian rhythm playing an important role in the biochemical action of the drug.

Chronotherapeutics is the purposeful delivery of medications in unequal amounts over time[2]. Chronotherapeutics takes into account rhythm determinants in (i) disease pathophysiology (chrono pathology), (ii)chronopharmacology (chronokinetics, chronodynamics, chronesthesy, and chronotoxicology) of medications, and (iii)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 and/orminimize adverse effects[1]. Figure 2[3] signifies the relative function of chrono reception center in the human brain to the activities that it coordinates.

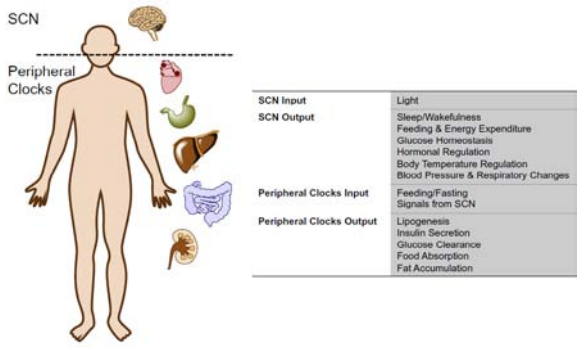

Fig. 2: Chronobiology of Super Chiasmatic Nuclei (SCN), the centre for chrono reception

Chronotherapeutics is a treatment process in which bioavailability of the drug administered, will depend upon the time at which it is administered, with regards to the rhythmic activity of the symptoms of the disease condition for which the drug is administered, in order to maximize its health benefits and minimize the side effects. Whether a disease, symptom or condition can be treated with Chronotherapy, will depend upon the fact that whether there is any co- dependence between the peak-to-trough rhythmic activity in disease symptoms and associated risk factors, and pharmacokinetics of the drug[5]. As more about the subject of chronobiology and chronotherapy is being understood, the fashion in which a dosage regimen is designed and the time prescribed at which the Patient shall take the medication, is a matter of concern today more than what it was in the past[5,7]. The custom of prescribing medication several times a day in order to maintain its even concentration in blood, seems to be changing now as researchers are coming in agreement with the fact that certain medications can work better if taken in synchrony with the coordinated day night cycle and respective biological rhythms[8].

The potential benefits of chronotherapeutics till now has been reported in the management of a number of diseases like cancer, cardiovascular diseases, allergic rhinitis, rheumatoid, asthma, cancer and peptic ulcer[9]. Among them the most noticeable is the chronotherapeutics of cardiovascular system owing to their visible rhythmicity(blood pressure, heart rate, pulse) with time and space[2,5].

This review will cover the potential, scope and emergence of chronotherapeutic drug delivery in cardiovascular diseases and the candidate drug delivery systems suitable to realise the required interventions.

Cardiovascular system and Chronotherapy: The association

The cardiovascular system is highly organised in time; blood pressure (BP), heart rate (HR), peripheral resistance, or activities of vasodilating hormones, all display pronounced circadian variations[8]. Pathophysiological events like sudden cardiac death, stroke, ventricular arrhythmias, arterial embolism, and symptoms of coronary heart disease such as myocardial infarction and ischemia, angina attacks in case of stable angina or variant angina or even in silent ischemia, do not occur arbitrarily, instead they have been found to show circadian phase dependency at the time of dose administration[9]. Beta-blockers, calcium channel blockers, oral nitrates and ACE inhibitors, all show a time dependent efficacy patterns[9]. In a clinical study by lemmar et al, it was shown that beta adrenoreceptor blockers, oral nitrates and calcium channel blockers display action depending upon the time of the day at which they were administered[5]. In the case of hypertension, the pharmacology behind that could be the increased levels of nor epinephrine at night which leads to the morning rise in BP as the concerned receptors of norepinephrine are expressed in a high concentration at that time of the day. This rise in epinephrine at night is a case of disturbed circadian rhythm[10].

Rhythms of the cardiovascular system: foundation of chronotherapy

Heart rate was among the first physiological function which was reported to have irregularity in pattern through the sleep wake cycle[8,9]. Variation in pulse rate and its hasty increase in early mornings, also called as the morning surge, were reported as earlyas in the starting of the 17th century[9,10]. In the 18th and 19th centuries general observations as well as detailed data on daily variations in pulse rate and pulse quality were reported[9,10]. Though the Rhythms of HR and BP are the most studied periodic functions in the cardiovascular system, there are other cardiac measurements that have been shown to exhibit circadian variations as well, for example, peripheral resistance, stroke volume, cardiac output, blood flow, ECG demonstrations in the plasma concentrations of pressor hormones such as norepinephrine, angiotensin, rennin, aldosterone, plasma cAMP concentration in blood viscosity and aggregability, and atrial natriuretic hormone[9].

A clinical survey of 7731 patients, who were initially being treated for Thrombolysis in Myocardial Ischemia, also produced the evidence for a circadian variation in the onset of pain with a maximum between 6:00 hr and 12:00 hr and it was observed both in patients with unstable angina and patients with evolving non-Q-wave acute MI[2].

Section 2: Candidate drug delivery systems suitable for the realization of chronotherapeutic goals

If time programming is concerned then the paramount available delivery system would be pulsatile. PDDS are being better recognized in pharmaceutical technology as they deliver the right dose at the desired time at a desired site[11-13]. The disease conditions for which PDDS is proving to be promising are duodenal ulcer, cardiovascular diseases, arthritis, asthma, diabetes, neurological disorder, cancer, hypertension and hypercholesterolemia[11,14,15]. The classification of PDDS includes, time controlled systems where the release is solely controlled by the delivery system, stimuli induced systems, in which the release is controlled by the internal or external stimuli, like PH induced or inflammation induced or enzyme induced[11,14,16]. In case of

chemically induced systems, stimuli can be electrochemical signals, magnetic impulse, ultrasound or irradiation[11,15].

Time controlled pulsatile release system

These time-controlled systems can be classified as singular (tablet or capsule)systems or multiple systems.

Singular systems

Pulse-in-cap system [11, 17]

Different PDDS single-unit systems have been developed so far. The design of this kind of system includes an insoluble capsule body containing a drug and a plug[11,17]. The role of the plug is to create a lag time, which is pre-programmed, and remove itself later either by dissolution, swelling or erosion[11,17]. Illustration of single unit system is The Pulsincap® system, in which the capsule body is water insoluble due to formaldehyde induced cross linking, and is filled with drug formulation[11,16]. Capsule body in these systems stay sealed where the plug opens. As the capsule body comes in contact with dissolution medium or gastro-intestinal fluids, the plug starts swelling which creates pressure on the capsule shell, and it bursts after the predetermined lag time, releasing the drug in the gastric or intestinal medium[11,14]. The time lag in these systems is controllable. By changing the size and position of the plug, the lag time can be modified[11,14]. Nagaraja G et al in 2013 have worked on the preparation of pulse in cap formulation of Losartan Potassium which is a first line antihypertensive drug, for the preparation of its chronotherapeutic drug delivery system[18].

Porous port systems

The port system is called so because it creates porous opening for the entry of extracellular fluid or water. It contains an osmotically active agent in a gelatine shell capsule, which is coated with a semi permeable membrane and also contains an insoluble plug along with the drug formulation[11,16]. As water diffuses across the semi permeable membrane or as the capsule comes in contact with the aqueous medium, the osmotically active agent prevents the exit of water from the capsule shell[11]. This creates an internal pressure inside the capsule that eventually ejects the plug, after a predetermined lag time. As a general rule, more will be the thickness of semi permeable membrane, more will the time lag. The advantage of this system is its high degree of correlation with the in vivo experiments[11].

Modified solubility systems

These systems contain a solubility modulator which is responsible for the pulse in the delivery system. The solubility modulator prevents the solubility at a particular pH or any other kind of stimulus induced solubility[11,14]. The system consists of a drug along with a modulating agent and also sodium chloride which acts as an Osmogen. The quantity of NaCl in the system is adjusted in such a way that saturation of the delivery system does not take place as it contacts the aqueous medium[11,14]. The solubility of the drug will depend upon the amount of solubility modulator added in the system, which in turn is responsible for the pulse in the delivery system[11]. The advantage of the system is that it is not restricted to a certain class of drug but in fact can be used for a large number of drugs.

Reservoir delivery systems

Mostly pulsatile drug delivery systems are reservoir systems. A certain coating of polymer is done to prevent the drug from bursting before time and this coating layer can be called as a plug layer. This plug tends to dissolve or wear out after a certain programmed lag time which leads to rapid drug release. The lag time is proportional to the thickness of the plug layer.

The Time Clock® system[11]which is a reservoir system comprises of a solid drug on which there is a lipid coat of carnauba wax, bees wax and surfactants[11]. The lipid layer prevents the release of drug in a hydrophobic environment and the surfactant used, such as polyoxyethylene sorbitanmonooleate will help the rapid release of the drug in the desired environment [11]. The emulsification of the coat takes place in the aqueous environment. This will lead to the dispersion of the core in the aqueous environment. Time taken for the coat layer to dissolve in the aqueous environment will depend upon the thickness of the film. Easy manufacturing without the use of any sophisticated instrumentation is an advantage of this type of delivery system.

Another classic example of reservoir delivery system is *The Chronotropic® system*[11] which consists of a drug trapped in a core which is further coated with a release retardant and swellable polymer such as hydroxypropylmethyl cellulose (HPMC), which retards the onset of drug release by offering a desired lag time[11,14]. Lag time offered by the delivery system will depends upon the thickness and the viscosity grade of HPMC used[11]. Formulation of all types of solid dosage forms can be achieved by this system.

Multiple systems

Multiple drug delivery systems mainly consist of small discrete units in which the drug is trapped. The small discrete units are independent in nature and more than a single active ingredient can be incorporated in them. They are useful for the combination drugs which are incompatible with each other. The advantages of multiple systems include multiple drug administration, small size, reduction in dose, and accuracy in transit time in different subjects, better stability and finally reduced side effects due to minimum drug interaction used together in formulation. The loopholes in the system include non reproducible results in manufacturing capacity, several formulation steps, use of specialised instruments and high cost of production.

Pulsatile delivery by change in membrane permeability

Membrane permeability is a common method to modify release in many delivery systems. In case of polymers containing quaternary ammonium compounds, membrane permeability can be brought about by addition of counter ions in the polymer[11,14]. hydrochloride counter-ions are coupled with polymers containing quaternary ammonium compounds to manipulate their membrane [11,14]. The ammonium group in the acrylic polymer is hydrophilic in nature so it assists the polymer to interact with water and change its permeability so that it permeates the underlying core[11,14]. Example of acrylic polymer containing quaternary side chain is Eudragit 30D and is reportedly the most widely used polymer to construct this delivery system.

Sigmoidal release system [13]

Sigmoidal release systems have been developed to achieve time controlled drug delivery in the intestine. It utilises pellets of succinic acid coated with ammonio-methacrylate copolymer which when released in intestine gives a typical sigmoidal release curve[11]. The velocity at which water enters the delivery system controls the lag time to be achieved by the system. Water dissolves the acid and the drug inside the delivery system and thus this solution formed increases the permeability of the polymeric coating[11]. The different types of acids that can be used in the formulation of sigmoidal release system are succinic acid, glutaric acid, acetic acid, citric acid, tartaric acid and malic acid[11,14].

Burst coat pulsatile delivery system

Non-pareil sugar seeds are coated with an erodible and swellable polymer followed by a coat of insoluble polymer[11]. The swelling agents used aresodium starch glycollate, sodium carboxymethyl cellulose, L-hydroxypropyl cellulose, etc[11]. As water enters, the swellable layer starts expanding, which result in the burst of the film followed by rapid drug release, which is independent of medium pH and drug solubility.

Time controlled expulsion system [11]

The formulation contains the drug, a low bulk density diluent, mineral oil and disintegrant, and is further coated by an enteric polymer for example cellulose acetate[11,14]. As the dosage form is immersed in an aqueous medium, water starts penetrating the core and displacing the lipid material. As the lipid material gets

completely out of the delivery system, internal pressure in the dosage form raises enough to generate stress, resulting in the breakage of the coating material and release of drug from the system[11,14,16].

Apart from time controlled pulsatile delivery systems, there are many other variations to pulsatile delivery system which are advantageous in making modified release dosage forms. These include the following.

Stimuli induced pulsatile release system

During environmental changes like change in solvent composition, temperature, ionic strength and electric fields, some of the polymers undergo phase transition and display swelling de-swelling effects. Such environmental changes act as internal stimulus for the release of the dosage form. In case of gels, these stimuli, that is, the environmental changes, bring drug release as a response which may swell-deswell or rupture as a response to the stimuli. As the fluid phase gets saturated inside the gel, it forces the drug out of it and this is a possible mechanism of action of drug release from this delivery system[11].

Chemical stimuli induced pulsatile systems

Hydrogels[11,14,2]

There are many bioactive compounds within the body. Certain Novel gels have been introduced whichact in proportion to the concentration of the bioactive compounds in the body to modify their swelling and de swelling behaviour[11,14]. Gels forming cross linkage units by antigen anti body complexation should be given special mention in the category of novel gels since this type of cross linking is very specific in nature. Both polymerized antibodies and naturally derived antibodies have affinity towards specific antigens in the body, but the specific swelling and de swelling behaviour is attributable to the difference in their association constant [11,14].

PH sensitive drug delivery system [11,14,16]

This PDDS acts at a specific site which has an accepted pH range, and has two components merged in a single system. The first part consists of an immediate release section and the other contains a pulsed release section[11]. The pulsed release section releases the drug in response to change in pH as it's a pH sensitive delivery system. pH dependency can be minimized by manipulating the system by coating with resistance polymers which resist release at a specific pH range[11,14]. Use of pH dependent polymers will ease the formulation of this type of delivery system.

Specialized technology in pulsatile drug delivery system

Chronotherapeutic Oral Drug Absorption System (CODAS) [8,10,11]

Release its drug component after a prolonged period of time, after administration, is the primary aim of this technology. Verelan® which is a chrono therapeutic anti-hypertensive Virapamil formulation is an example of CODAS [8].[10,11]. The drug release is approximately four to five hours after ingestion. The system consists of drug loaded beads which are coated with release controlling polymers. The amount of release-controlling polymer determines the total lag time. The polymer used in CODAS for controlling the release consist of two components, viz water soluble component and water insoluble component. As the fluid from the gastrointestinal tract comes in contact with the polymer coated beads, the water-soluble polymer starts dissolving slowly as the system encounters the fluids in gastro intestinal tract, to let the drug diffuse, while the water insoluble polymer poses as a barrier layer to control the release and prevent burst effects. This controlled onset extended release delivery system provides peak plasma concentration in the morning hours, after a bed time administration, minimizing the morning surge in BP.

Spheroidal Oral Drug Absorption System (SODAS)[11,16]

This technology is based on the production of controlled release beads which are inherently flexible to accommodate different drugs due to its inherent flexibility, for the production of customized dosage forms[11,16]. This gives SODAS an edge to provide a number of tailored drug release profiles, including immediate release, extended release, sustained release and controlled release. The reverse can also be achieved by this technology i. e. the release can be delayed for a long number of hours which gives it a good scope for chronotherapy.

The Intestinal Protective Drug Absorption System (IPDAS) [11,16,18]

Masking of gastrointestinal irritant compounds is the primary aim of this high density multiparticulate tablet technology. High density controlled release beads compressed into a tablet form constitutes the basic structure of this delivery system. The tablet made with IPDAS® technology rapidly disintegrates and disperses its beads in the stomach. These beads pass gradually, in a controlled manner in the duodenum and the intestinal tract. The passage of beads from the stomach is independent of the feeding state.

EURAND's pulsatile and chrono release System [19,11,16]

This system can be used where ever more than one pulse at predetermined lag time is required, as per the disease condition. This effect of the EURAND system can improve efficacy and minimize side-effects of a drug substance. The example of successful use of this technology, is in the formulation of circadian rhythm controlled release dosage form of propanalol hydrochloride, having a four-hour lag time before release after oral administration[19,11]. After bedtime administration, it shows a zero release phase of several hour sand is released in the early morning hours after initial delay in release, to achieve peak plasma concentration.

Section 3: Challenges in formulation of cardiovascular chrotherapeutic dosage form

The delivery system

Cardiovascular diseases running in sync with the circadian rhythm often show an increase in symptoms in the early morning hours. This requires the formulation of a dosage form that can provide sufficient lag time after bedtime administration. Formulation of a dosage form that can successfully provide the long lag time without sinking or passing through gastric cavity before time, into the intestinal tract will give the desired effects expected out of the delivery system. This calls for the delivery system to float in the gastric media, which is quite a challenging task[20]. Moreover it requires specialized technology to achieve the desired effects in the dosage form. This may take an initial investment of capital in order to fulfil the goals of chrono therapeutic delivery dosage form.

The active pharmaceutical ingredient

Modification in the API is also an option to manipulate the time at which peak plasma concentration takes place. Classic example of the use of this approach can be of statins (HMG-CoA reductase inhibitors), which are anti hyper lipidimics[16]. Modification of the chemical structure of lovastatin by adding a methyl group makes simvastatin, which has a higher solubility than lovastatin[16]. Physiochemical modification of these compounds affects the time to reach the peak plasma concentration which is an indicator of the onset of action of the drug and its bioavailability. Other drugs used in cardiovascular diseases can be modified to deliver a time lag in their effect which is another method of formulating chrono therapeutic dosage forms but the task stays challenging.

Section 4: Present chronomedication for cardiovasular diseases

Chronotherapy of ischemic heart disease [21]

Controlled-Onset, Extended-Release (COER)-Verapamil (USA: Covera HS™; other markets: Chronovera™)[21] is the first significant drug-delivery tablet for ischemic heart disease and hypertension chronotherapy. It got the approval from the United States Food and Drug Administration (FDA) in 1999 for marketing by the Searle Pharmaceutical Company. The technology used in this delivery system, delays the release of verapamil for approximately 4–5 h following the recommended bedtime ingestion[21,2]. Medication is released after this lag

time so that the highest blood concentration is achieved in the morning between 6 and 10 a. m., followed by an elevated drug level maintained throughout diurnal activity. The half-life of Verapamil governed by its active metabolite leads to a progressive decline of drug level in the evening and nocturnal phase, minimizing the concentration during the first half of nighttime sleep, when the risk of myocardial ischemia is low.

Graded-Release Long-Acting Diltiazem[21,22]

(Cardizem LA, Biovail Pharmaceuticals): This dosage form was approved by the United States FDA in 2003 for once-daily dosing at either time of the day. Multiple-dose studies of diltiazem has shown that the ingestion of the 360 mg dose of Cardizem LA at around 10 p. m during bedtime, results in a kinetic profile which is suitable for the chronotherapy of hypertension and IHD. The blood concentration level stays depressed during middle of the night, and then rises to achieve a maximum in the morning. An elevated drug level is maintained during the afternoon and early evening. multi-centre trial on Cardizem LA reported that bedtime administration of up to 540 mg/day is significantly more effective in controlling morning BP and HR than the ACE inhibitor ramipril taken at bedtime in doses of up to 20 mg/day. Cardizem LA has been found to have a good safety profile, and the occurrence of adverse events was in a dose-independent manner and comparable to the placebo treated group. The most common side effects were headache in around 11.7% subjects which was reportedly independent of dose followed by upper-respiratory infection in 5.6%, and lower-limb edema[4].

Chronotherapy of hypertension and arrhthymia

The β-antagonist propranolol chronotherapy (Innopran XL™, Reliant Pharmaceuticals) [22,19] was approved by the united states FDA in the year 2003. This capsular dosage form results in trough drug blood concentration toward the midnight hours of night time sleep around 4.00 am and elevated plateau of drug concentration in the afternoon and early evening as reported by a multiple dose study[22,19]. Recent findings from 24-hour trials have documented potent chronotherapeutic systolic and diastolic BP reduction ability of this β-antagonist in the morning, with persistent BP-lowering activity throughout the entire 24-hour dosing interval.

CONCLUSION

Ace inhibitors, calcium channel blockers oral nitrates and beta adereno receptor blockers remain the key treatment options for the therapy of cardio vascular disorders. Multi centre clinical trials had revealed that COER Virapamil is therapeutic in both dipper and non dipper hypertension in a dose dependent manner and has a more desirable and efficacious release profile then the conventional Virapamil formulations[3]. Same goes for other marketed chronotherapeutic formulations of cardiovascular disorders. Though there are evidences for certain drugs in each of the above mentioned category to show no response in morning and evening dosing that can supposedly be seen as a negative response towards chrono therapeutic drug delivery, still first line treatment drugs (ACE inhibitors and ARBs) of major cardiovascular disorders like hypertension and myocardial infarction had shown tremendous response to the chrono therapeutic drug delivery. This calls for the need to improve the delivery systems for the existent drugs into modified chrono therapeutic delivery systems, in order to improve the overall treatment regimen of CVS disorders. Oral drug delivery remains the most popular and convenient mode of drug delivery. Treatment with modified chronotherapetic delivery system is equivalent in cost to the conventional once but has improved patient compliance due to decreased dosing intervals. PDDS offers a number of technologies to convert conventional DDS into chronotherapeutic systems. They should be utilized effectively in order to provide maximum benefit to the end consumer weather for cardio vascular diseases or any other diseases which can be treated chrono therapeutically for that matter.

Abbreviations

GI-gastro-intestinal, hr- hour, SCN- super chiasmatic nuclei, IHD-ischemic heart disease, ACE- angiotensin converting enzyme, ARB-angiotensin receptor blocker, FDA- food and drug administration

CONFLICT OF INTERESTS

Declared None

REFERENCES

1. Hoffman AS. The origins and evolution of "controlled" drug delivery systems. J Control Rel 2008;132(3):153-63.
2. MH Smolensky, NA Peppas. Chronobiology, drug delivery and chronotherapeutics. Adv Drug Deliv Rev 2007;59(9-10):828-51.
3. K Griffett, T P Burris. The mammalian clock and chronopharmacology. Bioorg Med Chem Lett 2013;23:1929–34.
4. Jean-Paul Comet. Simplified models for the mammalian circadian clock. Procedia Computer Sci 2012;11:127–38.
5. Reddy Akhilesh B, O'Neill John S. Healthy clocks, healthy body, healthy Mind. Trends Cell Biol 2010;20(1):36–44.
6. Lamberg L. Chronotherapeutics: implications for drug therapy. Am Pharm 1991;11:796-9.
7. Dubal Ashwini *et al*. Chronotherapy: A novel drug delivery system. IJRAP 2011;2(6):1692-700.
8. Ramón C Hermida, Diana E Ayala, Carlos Calvo, Francesco Portaluppi, Michael H Smolensky. Chronotherapy of hypertension: Administration-time-dependent effects of treatment on the circadian pattern of blood pressure. Adv Drug Deliv Rev 2007;59(9-10):923–39.
9. Ramón C Hermida, Diana E Ayala, Francesco Portaluppi. Circadian variation of blood pressure: The basis for the chronotherapy of hypertension. Adv Drug Deliv Rev 2007;59(9-10):904–22.
10. B Lemmer. The importance of circadian rhythms on drug response in hypertension and coronary heart disease—from mice and man. Pharmacol Ther 2006;111:629–51.
11. Sharma GS, SrikanthMV, Uhumwangho MU, Phani Kumar KS, Ramana Murthy KV. Recent trends in pulsatile drug delivery systems-A review. Int J Drug Delivery 2010;2:200-12.
12. Yui N, Okano T, Sakurai Y. Inflammation responsive degradation of cross-linked hyaluronic-acid gels. J Control Rel 1992;22:105-16.
13. Xiaoling Li, Bhaskara R Jasti. Design of controlled release drug delivery systems. The mcgraw-Hill Companies Inc; 2006.
14. Devdhawala Mehul G, Seth Avinash K. Current status of chronotherapeutic drug delivery system: An overview. J Chem Pharm Res 2010;2(3):312-28.
15. Sokar MS, Hanafy AS, El-Kamel AH, El-Gamal SS. Pulsatile core-in-cup valsartan tablet formulations: *In vitro* Evaluation. Asian J Pharm Sci 2013;8:234-43
16. P Roy, A Shahiwala. Multiparticulate formulation approach to pulsatile drug delivery: Current perspectives. J Control Rel 2009;134(2):74-80.
17. Vinupama S, Szzhwetha S, Kamath K, TS Keerthi, Senthilkumar SK. Pulsatile drug delivery system: A review. Int Bull Drug Res 2011;1(1):19-31.
18. Nagaraja G. Design and evaluation of time programmed pulse incap system for chronotherapeutic delivery of losartan potassium. J Chem Pharm Res 2013;5(6):76-87.
19. Viskin S, Golovner M, Malov N, Fish R, Alroy I, Vila Y, *et al*. Circadian variation of symptomatic paroxysmal atrial fibrillation. Eur Heart J 1999;20(19):1429-34.
20. Shakya Rajani, Thapa Panna, Saha Ranendra N. *In vitro* and *in vivo* evaluation of gastroretentive floating drug delivery system of ofloxacin. Asian J Pharm Sci 2013;8:191-8.
21. F Portaluppi, B Lemmer. Chronobiology and chronotherapy of ischemic heart disease. Adv Drug Deliv Rev 2007;59(9-10):952–65.
22. F Portaluppi, RC Hermida. Circadian rhythms in cardiac arrhythmias and opportunities for their chronotherapy. Adv Drug Deliv Rev 2007;59(9-10):940–51.