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CHRONOTHERAPEUTIC DRUG DELIVERY SYSTEM: A RATIONAL APPROACH FOR MANAGEMENT OF HYPERTENSION

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ABSTRACT

Chronotherapeutics is the purposeful timing of medications, with or without the utilization of special drug-release technology, to proportion serum and tissue concentrations in synchrony with known circadian rhythms in disease processes and symptoms as a means of enhancing beneficial outcomes and/or attenuating or averting adverse effects. The concept of chronotherapeutics, although relatively new to hypertension and cardiovascular medicine, was first introduced and proven worthy in clinical medicine in the 1960s;the morning alternate-day corticosteroid tablet dosing schedule was introduced as a convenient means of minimizing the adverse effects of such anti inflammatory medications as prednisolone and methyl prednisolone. The chronotherapy of hypertension takes into account the clinically relevant features of the 24-hour pattern of blood pressure (BP) (i.e., the accelerated morning rise at the commencement of diurnal activity and the extent of decline during nighttime sleep) plus potential administration-time (circadian rhythm) determinants of the pharmacokinetics and dynamics of individual antihypertensive medications. Hypertension occurs in over 90% of all patients with cardiovascular disease (CVD) in the world and it is a major risk factor for end-organ damage, CVD and death. Studies over the last decade have revealed that blood pressure (BP) and CVD are influenced by our behaviour such as what we eat and even conditioned by the time of day. Also, the ability of the night: day ratio of systolic BP predicts the risk for cardiovascular events more accurately compared with office BP measured only at once. This article reviews the chronobiology of hypertension, and the design of various chronotherapeutic drug delivery systems developed for its management.

INTRODUCTION

Many functions of the human body vary considerably in a day. These variations cause changes both in diseased state and in plasma drug concentrations. The dependence of bodily functions in certain disease's state on circadian rhythm is well known[1]. A number of hormones are released by the brain in the morning, while others are released during sleep. Blood pressure and heart rate are highest during the hours of 6.00 a.m. to 12.00 noon[2]. Cardiovascular diseases such as hypertension, angina and chest pain follow a definite circadian rhythm. Epidemiologic studies have documented the heightened morning-time risk of angina, myocardial infarction and stroke[3-4]. The goal in drug delivery research is to develop formulations to meet therapeutic needs relating to particular pathological conditions. Research in the chronopharmacological field has demonstrated the importance of biological rhythms in drug therapy, and this has brought a new approach to the development of drug delivery systems. In certain diseases, optimal clinical outcomes cannot be achieved if drug plasma concentrations are kept constant throughtout. If symptoms of a disease display circadian variation, drug release should also vary with time. Utilization of different technologies in the development of time-controlled, pulsed triggered and programmed drug delivery devices has intensified in recent years. Another issue that has emerged from circadian variation of physiological function is that drug pharmacokinetics can be time dependent (i.e.chronopharmacokinetics)[5]. Therefore, variation in disease state and drug plasma concentration need to be taken into consideration in the development of drug delivery systems intended for the treatment of diseases with adequate dose at the appropriate time[6-7].

CHRONOPHARMACEUTICS

Chronopharmaceutics is branch of pharmaceutics that deals with the design and evaluation of drug delivery systems that release bioactive agent at a rhythm that ideally matches in real time the biological requirement for a given disease therapy. Ideal chronopharmaceutical drug delivery system (ChrDDS) should:

- Be non-toxic with in approved limit of use.
- Have a real time and specific triggering biomarker for a given disease state.
- Have a feed- back control system (i.e self- regulated and adaptive capability to circadian rhythm and individual patient to differentiate between awake –sleep status).
- Be compatible with the body fluids and biodegradable.

- Be easy to manufacture at economic cost.
- Be easy to administer to patient and enhances compliance to dosage regimen[8].

BIORHYTHMS

Human body has been found to follow biological rhythm. Several physiological processes in human vary in a rhythmic manner in synchrony with the internal biological clock. It gives an overview of most serious diseases displaying significant daily variation. The scientific study of biological rhythm clearly reveals that biological function and processes are not static rather than they are dynamic and variable in a predictable manner as rhythm of defined period. Chronobiology deals with the study of three types of biorhythms affecting human body. These are as follow:

- **Ultradian Rhythms:** Oscillations of shorter duration are termed ultradian rhythms (more than one cycle per 24hours).e.g.90 minutes sleep cycle.
- **Infradian Rhythms:** Oscillations that are longer than 24 hours are termed as infradian rhythms (less than one cycle per 24 hours).e.g. Monthly menstruation.
- **Circadian Rhythms:** Circadian rhythms are self-sustaining, endogenous oscillations that occur with a periodicity of about 24 hours. Normally, circadian rhythms are synchronized according to internal biologic clocks related to the sleep-wake cycle[9-10].

CIRCADIAN TIME FRAMEWORK

The human circadian time structure is always peak for 24hr as shown in figure. This figure also shows that the peak time of human circadian rhythm in the synchronization with the routine-sleep in darkness from 10:30 pm to 6:30 am and activities during the light of the day between 6:30 am and 10:30 pm. These rhythms are help in defining the temporal organization of the human beings. The human circadian time structure is to depict the peak time of 24hr rhythms on a clock basal gastric acid secretion, white blood cell count (WBC), Calcitonin a gene-related protein and arterial natriuretic peptide occurs late at night or early sleep. Growth and thyroid stimulating hormone(TSH),blood lymphocyte and eosinophil number and plasma melatonin and prolactin crest during sleep as the adrenocorticotropic (ACTH),Follicle stimulating hormone and luteinizing hormone (LH) and plasma cortisol, renin activity, angiotensin and aldosterone are peak in the morning. The circadian clock can act as an instrument for the estimation of the day and night length and for seasonal phenomena it also act as clock for changing the day and night length which can regulated appropriately[11].

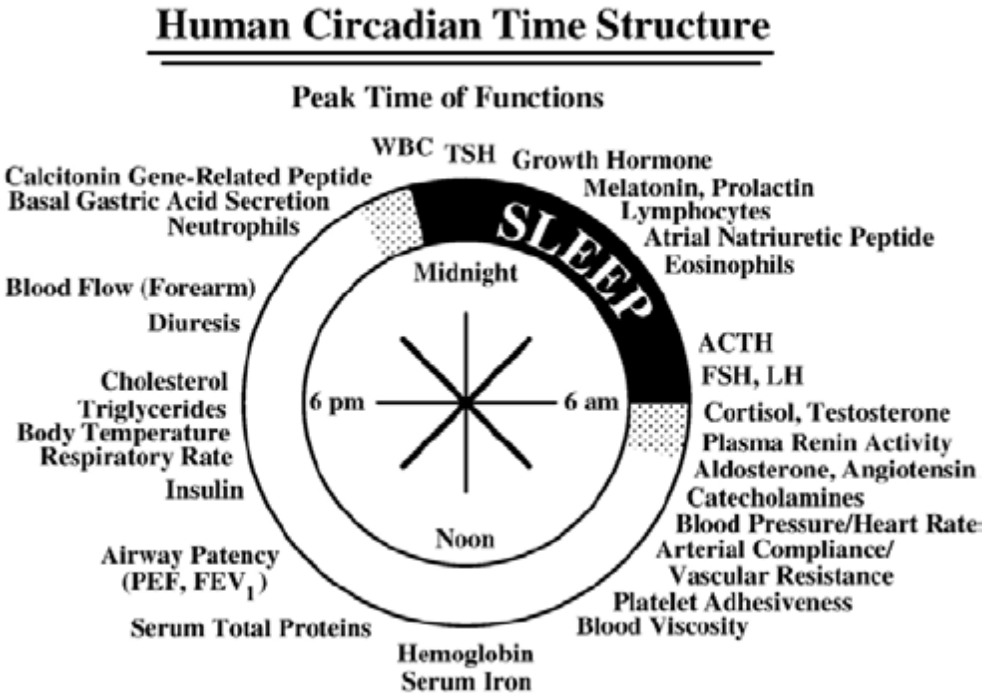

Fig.1 Diagram Showing Human Circadian Time Structure

APPLICABILITIES OF CHRONOPHARMACOTHERAPY

1. Drugs having High First Pass Metabolism: Some drugs, such as beta blockers and salicylamide undergo extensive first pass metabolism and require fast drug input to saturate metabolizing enzymes in order to minimize pre-systemic metabolism. Thus, a constant/ sustained oral method of delivery would result in reduced oral bioavailability[12].

2. Biological Tolerance: Drugs that produce biological tolerance demand a system that will prevent their continuous presence at the biophase, as this tends to reduce their therapeutic effect. The lag time is essential for drugs that undergo degradation in gastric acidic medium (e.g., peptide drug) and irritate the gastric mucosa or induce nausea and vomiting. Targeting a drug to a distal organ of gastrointestinal tract (GIT) like the colon, requires that the release is prevented in the two-third portion of the GIT[13-14].

3. Special Chronopharmacological Needs: Circadian rhythms in certain physiological functions are well established. It has been recognized that many symptoms and onset of disease occur during specific time periods of the 24 hour day e.g., Hypertension and angina pectoris attacks are most frequently in the morning hours[15].

4. Local Therapeutic Needs: For the treatment of local disorders such as inflammatory bowel disease, the delivery of compounds to the site of inflammation with no loss due to absorption in the small intestine is highly desirable to achieve the therapeutic effect and to minimize side effects[16].

5. Drug Absorption Differences in Various Gastrointestinal Segments: In general, drug absorption is moderately slow in the stomach, rapid in the small intestine, and sharply declining in the large intestine. Compensation for changing absorption characteristics in the gastrointestinal tract may be important for some drugs[17].

HYPERTENSION

Hypertension is a chronic medical condition in which the systemic arterial blood pressure (BP) remains elevated. It is present in over 90% of all patients with cardiovascular disease (CVD) and affects nearly 74 million individuals in the world. This condition is a major risk factor for stroke, myocardial infarction, heart failure, arterial aneurysm and chronic kidney failure. The chronic elevation of BP is a silent disorder in that its progression occurs largely asymptomatically. However, its impact is deafening causing CVD and end-organ damage, which eventually leads to shortened life expectancy. Simple relationship between high BP and CVD that is heavily influenced by our behavior and what we eat is also conditioned by the time of day. Hence, circadian rhythm is a significant input into the regulation of BP[18-20].

CHRONOBIOLOGY OF HYPERTENSION

Analysis of large, population-based studies has shown that many cardiovascular events-including myocardial infarction (MI), stroke and sudden cardiac death-cluster during the initial hours of morning activity, between 6.00 a.m. and 12 noon[21-23]. In the Framingham Heart Study, the time of day of sudden cardiac death was analyzed among >5,000 patients in the original cohort over a follow- up period of 38 years. The risk of sudden cardiac death was greatest at 6 a.m. and 12 noon than other times during the day[21]. Furthermore, a meta- analysis of 30 studies including >66,000 patients demonstrated that the incidence of MI is highest between 6 a.m. and 12 noon (approximately 40% greater than at other times)[22]. Finally, a meta –analysis of 31 studies including almost 12,000 patients showed that stroke occurs in a very similar pattern with a 49% increase during the hours between 6 a.m. and 12 noon[23]. Research studies over the last few decades have revealed some important findings regarding the typical 24-hour BP profile. One of the strongest among these findings is the ability of the night: day ratio of systolic BP to

more accurately predict risk for cardiovascular events compared with office BP[24]. Heart rate (HR) and BP have distinct circadian rhythms in both normotensive and hypertensive persons. The BP and HR in both normotensive and hypertensive patients are higher during the morning hours (4:00-6:00hr) than any other time of the day due to a decrease in sympathetic output occurring at night while the individual is asleep[25-28]. Upon waking, the systolic blood pressure (SBP) rises rapidly by 20-25 mmHg and diastolic blood pressure (DBP) by 10-15 mmHg. A schematic representation of the change in BP during a 24hr period is shown in Figure 2.

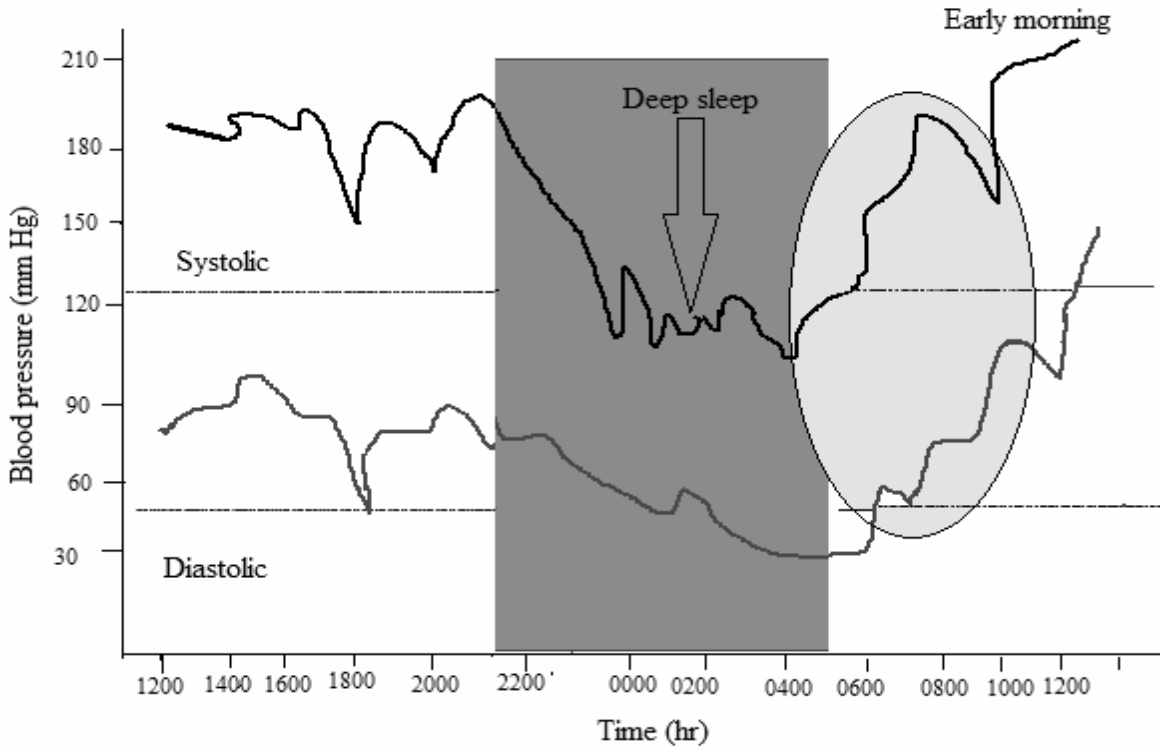

Fig.2 Schematic representation of changes in BP in a patient with untreated hypertension, Dotted lines represent the normal limit for ambulatory systolic and diastolic BP.

However, different forms of hypertension may exhibit different circadian patterns. In normotension as well as in hypertension, there is a general night drop in BP, whereas in secondary hypertension caused by any of the following conditions such as renal disease, gestation, cushing's disease, the rhythm in BP is abolished or even reversed with highest values at night in about 70% of the cases. Ghergel et al[29-32] represented the extent of the drop in BP during the night in the region of 10-20%. Approximately two-thirds of the world's population present with BP drop of this magnitude during the night and they are known as dippers.

DRUGS TO TREAT HYPERTENSION

The treatment of hypertension includes various types of drugs such as diuretics, β and α adrenoceptor blocking drugs, calcium channel blockers, converting enzyme inhibitors, and others that differ in their sites of action[33].

Table. 1 ANTIHYPERTENSIVE DRUGS

Direct Vasodilators	**Centrally Acting Sympatholytics**	**Alpha -Blockers**	**Angiotensin II Antagonist**
	Clonidine Methyldopa Guanfacine	Doxazosin Prazosin Terazosin	Losartan potassium Olmesartan Candesartan
Diuretics	**ACE Inhibitors**	**Beta –Blocker**	**Calcium Channel Blockers**
Hydrochlorohtiazide Spironolactone Triamterene Bumetanide	Captopril Benazepril Enalapril Fosinopril Ramipril	Atenolol Labetalol Metoprolol Propranolol Timolol	Amlodipine Diltiazem Felodipine Nicardipine Nisoldipine Verapamil

β-Adrenoceptor Antagonists

Beta-blockers antagonise the effects of sympathetic nerve stimulation or circulating catecholamines at beta-adrenoceptors which are widely distributed throughout body systems. In general, however, there is a tendency for β-adrenoceptor antagonists to predominately reduce daytime BP levels and not to greatly affect nighttime values, being less/not effective in reducing the early morning rise in BP[34-35]. Consistently, decreases in HR by β-adrenoceptor antagonists are more pronounced during daytime hours. In healthy subjects, a cross-over study with Propranolol similarly showed a more pronounced decrease in HR and BP during daytime hours than at night[36].

Calcium Channel Blockers

In primary hypertension, three times daily dosing of non retarded verapamil did not greatly change the BP profile, however, less effective at night[37]. A single morning dose of a sustained-release verapamil showed a good 24-hour BP control Dihydropyridine derivatives(DHP) differing in pharmacokinetics, seem to reduce BP to a varying degree during day and night, drug formulation and dosing interval may play an additional role. In eight studies in essential hypertensives using a cross-over design, DHP did not differently affect the 24-hour BP profile after once morning or once evening dosing. Some studies have shown that different cardiovascular active compounds such as propanolol oral nitrates and nifedipine showed higher peak drug concentration (C_{max}) and/ or a shorter time-to-peak concentration (t_{max}) after morning than evening oral drug dosing, at least when non-retarded formulations were used[38-41].

Angiotensin-Converting Enzyme Inhibitors

Angiotensin-converting enzyme inhibitors (ACEI) clinical studies demonstrated a different effect of the ACEI enalapril, perindopril, trandolapril, quinapril, ramipril when dosed in the morning vs evening. Kuroda et al[42] investigated the effects of the long-acting lipophilic ACEI trandolapril when ingested just before going to bed or in the morning in 30 hypertensive patients. Bed time administration of the medication was found to be safe and effective means of controlling morning BP in hypertensive patients without the induction of excessive BP reduction nocturnally. The fixed combination of captopril and hydrochlorothiazide was slightly more effective in reducing nocturnal BP when administered in the evening[43]. More recently, Hermida et al[44]investigated the administration-time-dependent efficacy of spirapril, an ACEI recommended for once-daily administration because of its extended duration of action due to its long elimination half-life of about 40hr. Morning administration of spirapril, was significantly more effective than bed time administration in reducing the diurnal BP mean and is significantly less effective in controlling nocturnal BP. Accordingly, the diurnal/nocturnal BP ration was significantly reduced with spirapril ingestion on awakening and significantly increased with spirapril ingestion at bedtime.

α – Adrenoceptor Antagonist

α –adrenoceptor antagonist's effectively reduces peripheral resistance in the early hours in the morning than at other times of the day and night. Indeed, a single night time 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[45].

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[46].

MARKETED TECHNOLOGIES OF CHRONOTHERAPEUTIC DRUG DELIVERY SYSTEM FOR HYPERTENSION

Different marketed technologies has been developed for Chronotherapeutic drug delivery ,such as Pulsincap™, DIFFUCAPS,CODAS®, OROS®, PROCARDIA, CEFORM. Some of them are discussed below.

PULSINCAP™ TECHNOLOGY

Pulsincap was developed by R.R. Scherer International Corporation (Michigan). This device consists of a non-disintegrating half capsule body sealed at the open end with a hydrogel plug that is covered by a water-soluble cap. The whole unit is coated with an enteric polymer to avoid the problem of variable gastric emptying. When this capsule comes in contact with the dissolution fluid, it swells and after a lag time, the plug pushes itself outside the capsule and rapidly releases the drug.

Another formulation approach was in the form of a bead or granule with a four-layered spherical structure which consists of a core, a drug, swelling agent (e.g., sodium starch glycolate or carboxy methyl cellulose sodium) and an outer membrane of water-insoluble polymer (e.g., ethyl cellulose, Eudragit® RL). The penetration of GI fluids through the outer membrane causes the expansion of the swelling agent. The resulting stress due to swelling force leads to the destruction of the membrane and subsequent rapid drug release. Polymers used for designing the hydrogel plug were various viscosity grades of hydroxyl propyl methyl cellulose, polymethyl methacrylates, polyvinyl acetate and poly ethylene oxide.

Another new approach was enteric-coated, timed-release, press-coated tablets (ETP tablets). These tablets were developed by coating enteric polymer on timed-released, press-coated tablets composed of an outer shell of hydroxyl propyl cellulose and core tablets containing diltiazem hydrochloride as a model drug[47-48].

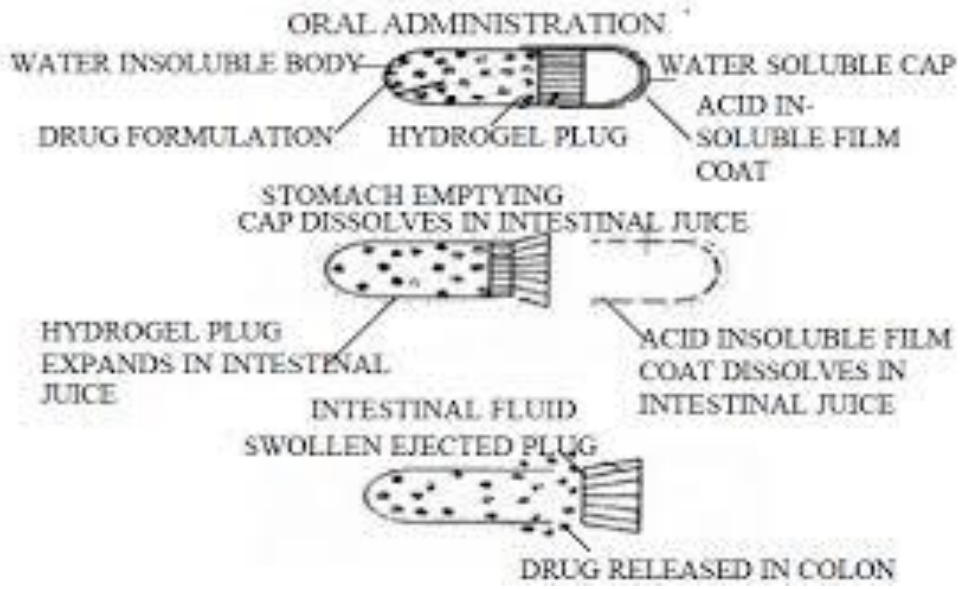

Fig.3 Pulsincap Technology

DIFFUCAPS® TECHNOLOGY

DIFFUCAPS technology is the most popular and versatile approach for chronotherapy for delivering drugs into the body in a circadian release manner. It is made up of multiparticulate one or more populations of drug-containing particles. Diffucaps® technology in its simplistic form involves the preparation of:

(1) Drug-containing cores by drug-layering on inert particles.

(2) Customized release (CR) beads by coating immediate release (IR) particles with one or more functional dissolution rate controlling polymers or waxes.

(3) Combining one or more functional polymer coated Diffucaps® bead populations into hard gelatin or Hydroxypropyl Methylcellulose (HPMC) capsules.

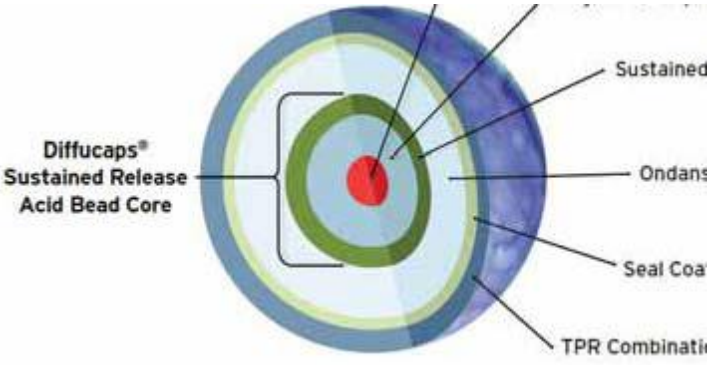

Fig.4 Diffucap Technology

Diffucap is type of multiparticulate bead system containing several layers of drug, excipients, and release-controlling polymers. The beads contain a layer of organic acid or alkaline buffer to direct the solubility of a drug by creating an optimal pH microenvironment for drugs showing poor solubility in intestinal pH, in environments with pH greater than 8.0, or in physiological fluids. On the other hand, the beads consist of a solid-solution of drug and crystallization inhibitor in respect to improve bioavailability by maintaining the drug in its amorphous state. The active core may be produced by granulating and milling and/or by extrusion and spheronization of API. Such a chronotropic drug delivery system is intended to provide a plasma concentration–time profile, which changes according to physiological need during the day, i.e. mimicking the circadian rhythm and severity/manifestation of a cardiovascular disease, predicted based on pharmacokinetic and pharmacodynamic considerations and in vitro / in vivo correlations. This type technology has been used to prepare the first and recently FDA approved propranolol containing chronotropic system (***InnopranR XL***) for the management of hypertension.

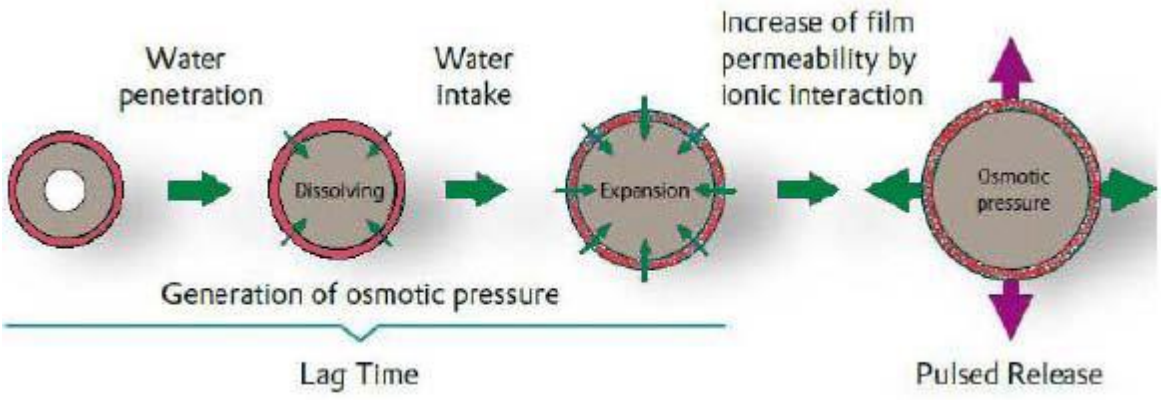

Fig.5 Drug Release Mechanism in Diffucaps Technology

Diffucaps technology is particularly suitable for drugs that conventionally need multiple daily doses or drugs require customized release formulations. Every Diffucaps bead has an inert core enclosed by drug as well as coated with a functional polymer membrane to control the rate of drug release. Diffucaps can also be combined with other proprietary Aptalis Pharmaceutical Technologies to optimize drug delivery. Diffucaps beads are less than 1.5mm in diameter and can be filled into capsules or compressed into orally disintegrating tablets[49].

CODAS (Chronotherapeutic oral drug absorption system)

Elan Drug Technology developed CODAS® technology to compliment circadian pattern, controlled onset, an extended release delivery system, rate of release essentially independent of pH, posture and food. Verelan® PM uses the proprietary CODAS™ technology, which is designed for bedtime dosing, incorporating a 4- to 5 h delay in drug delivery. The controlled-onset delivery system results in a maximum plasma concentration (C_{max}) of verapamil in the morning hours. These pellet-filled capsules provide for extended release of the drug in the gastrointestinal tract. The Verelan® PM formulation has been designed to initiate the release of verapamil 4–5 h after ingestion. This delay is introduced by the level of non-enteric release-controlling polymer applied to drug-loaded beads. The release-controlling polymer is a combination of water soluble and water insoluble polymers. As water from the gastrointestinal tract comes into contact with the polymer-coated beads, the water soluble polymer slowly dissolves, and the drug diffuses through the resulting pores in the coating. The water insoluble polymer continues to act as a barrier, maintaining the controlled release of the drug. The rate of release is essentially independent of pH, posture and food. Multiparticulate systems, such as Verelan® PM, have been shown to be independent of gastrointestinal motility[50].

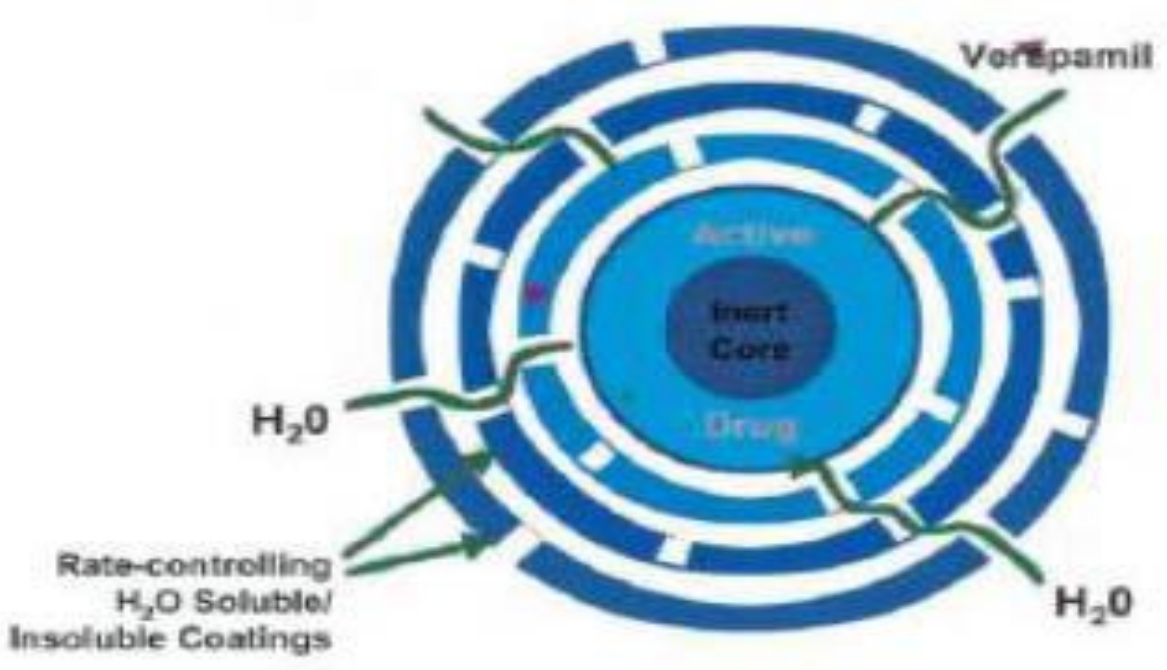

Fig.6 Chronotherapeutic Oral Drug Absorption System

OROS TECHNOLOGY

OROS delivery systems were adopted for poorly water soluble drugs. The push-pull system is comprised of a bilayer or trilayer tablet core consisting of one push layer and one or more drug layers. The drug layer contains the poorly soluble drugs, osmotic agents and a suspending agent. The push layer contains among other things, an osmotic agent and water swellable polymers. A semipermeable membrane surrounds the tablet core. A variety of OROS® systems (ALZA Corp.) have been developed: Procardia XL®, Ditropan XL® and Concerta® are notable examples.

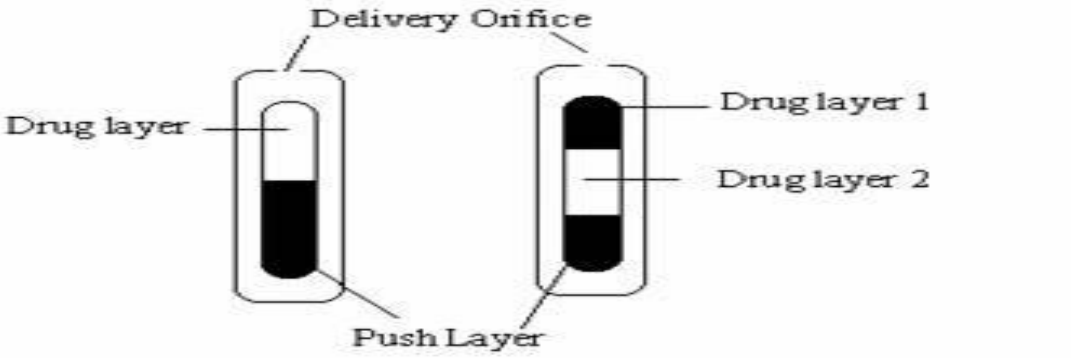

Fig. 7 Push-pull system

The recently developed L-OROS® SOFTCAP™ delivery system combines the features of a controlled-release and bioavailability-enhanced delivery system to enhance compliance and therapeutic effect[51]. L-OROS™ technology was developed by Alza to overcome the drug solubility issue. These formulations include self-emulsifying liquid carrier formulations (SEF) that allow a drug to be more readily absorbed through the gastrointestinal membrane and blood stream. The SEF in L-OROS systems consists of drugs in non-aqueous liquid carriers formulated to give either a solution or a nanosuspension. As a drug in solution is released in the GI tract, it forms very small droplets (< 100 nm), increasing the drugs solubility, thereby enhancing bioavailability. As the drug in a nanosuspension is released, the drug nanoparticles are dispersed, and aggregation is prevented[52-54].

Table.2 MARKETED CHRONOTHERAPEUTIC DRUG DELIVERY TECHNOLOGIES

Technology Employed	Proprietory Name	Dosage Form	Drug Delivery Mechanism	Active Ingredient	Indication
OROS®	Covera-HS®; XL	Tablet	Osmotic Mechanism	Verapamil Hydrochloride	Hypertension
PULSYS	Moxatag	Tablet	Multiple pellet types of varying release profiles	Amoxicillin	Infection
PULSINCAP™	Pulsincap™	Capsule	Rupturable system	Dofetilide	Hypertension
RITALINA®	Ritalin®	Tablet	Osmotically regulated system	Methyl Phenidate	ADH
DIFFUCAP®	Innopran®; XL	Tablets	Multiparticulate system	Verapamil Hydrochloride Propranolol	Hypertension
UNIPHYL®	Uniphyl	Tablet	Externally regulated system	Theophylline	Asthma
CODAS®	Verelan® PM;	Extended Release capsule	pH dependent system	Verapamil Hydrochloride	Hypertension

CONCLUSION

Rapid advancement and newer developments in the field of drug delivery have led to the formulation of the pulsatile drug delivery system, which, on one hand, can be formulated with ease and, on the other hand, provides a significant amount of therapeutic benefits. These systems deliver the drug at right time, place and amount in the patient's body. The circadian disorders generally require chronopharmacotherapy, which can be easily accomplished by pulsatile drug delivery system in a very organized manner. During the last two decades, pharmaceutical technology has grown leaps and bounds and, with the advent of pulsatile drug delivery, one can remain assured of accomplishment of goal for safe and effective therapy. There are a number of ailments that require the drug/bioactive be delivered in a specific way. The same cannot be either achieved or the benefits are partial when it comes to conventional dosage forms. Significant modification and designing of the conventional delivery systems in the form of pulsatile delivery systems ensures the time-controlled pulsatile release of bioactive compounds, which is prerequisite in the treatment of such disorders. Different technologies have been applied to

develop time-controlled, pulsed, triggered and programmed drug delivery devices in recent years. Since it is seems that timing of drug administration in disease therapy has significant impact upon treatment success, chronotherapeutics remains an important area for continuing research.

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