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Review Article

A Chronotherapeutics Approach to the Management of Hypertension: A Review

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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 outcome sand/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 methylprednisolone. 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. Herein, we focus on the chronotherapy of hypertension; however, as necessary background we first present the major concepts and mechanisms of biologic timekeeping.

INTRODUCTION

Many functions of the human body vary considerably in a day. These variations cause changes both in disease state and in plasma drug concentrations. Human circadian rhythm is based on sleep-activity cycle, is influenced by our genetic makeup and hence, affects the body's functions day and night (24-hour period) [1].The dependence of bodily functions in certain disease states on circadian rhythm is well known. 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] .Diseases, such as hypertension, asthma, peptic ulcer, arthritis, etc; follow the body's circadian rhythm. For example, osteoarthritis worsens during the day and is most bothersome in the evenings but for people with rheumatoid arthritis, the pain usually peaks in the morning and decreases as the day progresses.

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Cardiovascular diseases such as hypertension and angina, and chest pain, also 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. Optimal clinical outcomes cannot be achieved if drug plasma concentrations are constant. 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. The term, 'Chronopharmaceutic drug delivery system', is used to describe a kind of drug formulation which can cause circadian variation in drug plasma levels [6,7].

CHRONOTHERAPEUTICS

The term "chrono" basically refers to the observation that every metabolic event undergoes rhythmic changes in time. Researchers have concluded that all living organisms are composites of rhythms with varying frequencies that may range from seconds to seasons. Perhaps the best known and studied chronobiologic frequency is the circadian rhythm which approximates the earth's 24-hour rotation around the sun. Researchers have recently concluded that both disease states and drug therapy are affected by a multitude of rhythmic changes that occur within the human body [3]. Chronotherapeutics refers to a treatment method in which *in vivo* drug availability is timed to match rhythms of disease in order to optimize therapeutic outcomes and minimize side effects. It is based on the observation that there is an interdependent relationship between the peak-to-trough rhythmic activity in disease symptoms and risk factors, pharmacologic sensitivity, and pharmacokinetics of many drugs [8]. As more continues to be learned about chronobiology and chronotherapeutics, it is becoming increasingly more evident that the specific time that patients take their medication may be even more significant than was recognized in the past. The tradition of prescribing medication at evenly spaced time intervals throughout the day, in an attempt to maintain constant drug levels throughout a 24-hour period, may be changing as researchers' report that some medications may work better if their administration is coordinated with day-night patterns and biological rhythms.

Chronobiology

Chronobiology is the technical study of biologic rhythms and their fundamental mechanisms. So it is the formal study of biological temporal rhythms like tidal, annual, seasonal, weekly and daily rhythms. 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 conjunction with and often in response to periodic changes in environmental condition [9].

Biological rhythm within a single day is termed as circadian rhythm. Here, the oscillation time is 24 hours. Term *Circadian* is derived from the Latin term *circa* meaning "about" and *dies* which is derived from "a day" (Lamberg, 1991).

Table 1: Types of Biological Rhythms

Period (τ)	Major rhythmic components
Short (τ <0.5h)	0.1s< τ <1 s τ≈min pulsatiles
Intermediate (0.5h <τ <6 days)	Ultradian (0.5h <τ <20h) Circadian (20h <τ <28h) Infradian (28 h <τ <6 days)
Long (τ >6 days)	Circasepatan (τ≈ 7 days) Circamensual (τ≈ 30 days) Circannual (τ≈ 1 year)

Human Circadian Time Structure:

The human circadian time structure is always peak for 24hrs as shown in figure. This figure also shows that the peak time of human circadian rhythm in the synchronization with the routine sleep in the darkness from 10:.30pm to 6:30am and activities during light of the day between 6:30am and 10.30pm. [10,11] as shown in Fig1.

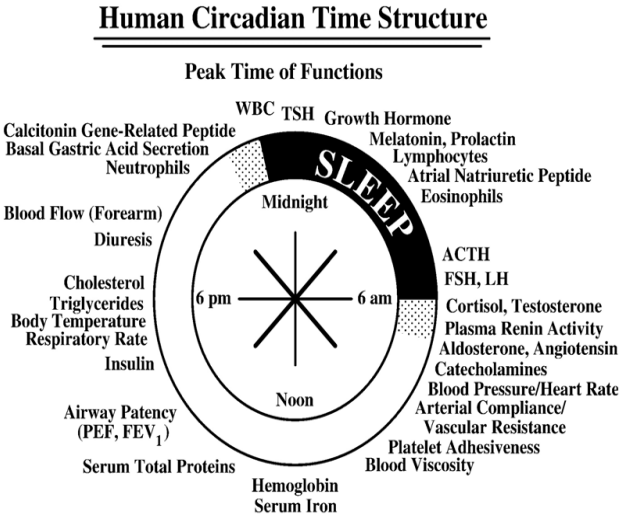

Figure 1: Human Circadian Time Structure

These rhythms are help in defining the temporal organization of the human beings. The human circadian structure is to depict the peak time of 24hr rhythms.

Disease and Chronotherapeutics

Up to now, design of drug delivery has been governed by the homeostatic theory. This theory is based on the assumption of biological functions that display constancy over time. However, chronobiological studies have established circadian rhythm for almost all body functions, e.g., heart rate, blood pressure, body temperature, plasma concentration of various hormones, gastric pH and renal function. It has become apparent that rhythmic processes are indispensable for the treatment of human diseases. Just as physiological functions vary over time, pathological states of disease have circadian rhythms. Epidemiological studies have documented the elevated risk of disease symptoms during the 24-hour cycle.

The potential benefits of chronotherapeutics have been demonstrated in the management of a number of diseases. In particular there is a great deal of interest in how chronotherapy can particularly benefit patients suffering from allergic rhinitis, rheumatoid arthritis and related disorders, asthma, cancer, cardiovascular diseases, and peptic ulcer disease.

Various diseases where chronotherapeutics applies are-

Anti-inflammatory Therapy

In the case of individuals who suffer from rheumatoid arthritis and related painful joint disorders, the non-steroidal anti-inflammatory agents (NSAIDs) such as ibuprofen may be more effective at relieving pain, if the drug is administered at least 4 to 6 hours before the pain reaches its peak. It will be more helpful if arthritis patients take the NSAIDs before bed time if they experience a particularly high level of discomfort in the morning.

Anti-asthma Therapy

It has been estimated that symptoms of asthma occur 50 to 100 times more often at night than during the day. Many circadian-dependent factors appear to contribute to the worsening of nocturnal asthmatic symptoms. For example, cortisol (an anti-inflammatory substance) levels were highest at the time of awakening and lowest in the middle of the night, and histamine (a mediator of bronchoconstriction) concentrations peaked at a level that coincided with the greatest degree of bronchoconstriction at 4:00 am. A research finding also reveals that theophylline absorption is slower at night .The enhanced understanding of the chronobiological impact upon the pathology of asthma, and the pharmacology and pharmacokinetics of the drugs used in its management, have led to new approaches to disease management and enhanced patient care [12].

Chemotherapy

Antineoplastic drugs cause cytotoxic effects on healthy and diseased tissues. As would be expected, the biological rhythms of both healthy and tumor cells may influence the susceptibility of normal and malignant cells to these agents. It has been demonstrated that "susceptibility rhythms" to drugs may differ between healthy tissue and cancerous tissue. Therefore, the "correct" timing of drug treatment may reduce host toxicity, increase maximum drug tolerance, and ultimately result in better tumor management. The pharmacologic and pharmacokinetic properties of the drug, rhythmic changes in DNA and RNA synthesis, RNA translational activity and mitotic activity may influence tumor cell susceptibility. It appears that the timing of drug administration in the treatment of cancer can have a significant impact upon treatment success.

Cardiovascular Therapy

The differences in patterns of illness between day and night for cardiovascular disorders such as hypertension, angina, heart attack, sudden cardiac death and stroke have been documented. Medications have been formulated, and dosing schedules established, in an attempt to provide appropriate concentration of a drug in the target area of the body when the drug is most needed. For example, it has often been found that the blood pressure of a hypertensive patient increases rapidly in the morning after awakening, typically peaks in the middle to late time of the day, decreases in the evening, and is lowest while the patient sleeps at night. It may also be important to recognize that the risk of heart attack appears to be greatest during the early morning hours after awakening. Currently, there are antihypertensive products in the market that are chronotherapeutic medications with novel drug delivery systems, releasing drug during the vulnerable period of 6 am to noon upon administration of medications at 10 pm.

Anti-ulcer Therapy

It is well established that patients with peptic ulcer disease often experience the greatest degree of pain near the time that they go to bed, as the rate of stomach acid secretion is highest at

night. The timing of administration of ulcer medications has a significant impact on their therapeutic effect.

Chronotherapeutics in Hypertension

Patients with hypertension have a characteristic circadian pattern of blood pressure (BP) variability in a 24-h period, characterized by a wide range while awake and active, and a narrower range during sleep and inactivity. Blood pressure in the untreated hypertensive individual declines by approximately 10% to 20% during sleep compared with the mean awake BP values. Early in the morning (assuming a typical day night activity cycle), the BP rises sharply on awakening, when physical and mental activities increase. Antihypertensive therapy has been traditionally dosed in the morning after awakening, and in recent years most of the newly developed antihypertensive agents have been once-daily, long-acting preparations. However, theoretically, this pattern of drug dosing may be suboptimal since pharmacodynamic activity is attenuated at the end of the dosing period, when a large rise in BP may occur. Presently, only a few studies have been performed to evaluate the effects of nocturnal dosing of standard long-acting drugs. Consequently, we undertook an assessment of the effects of a new formulation of verapamil controlled onset extended release verapamil HC1 (COER-24)—that is dosed nocturnally and has a controlled onset of delivery (4 to 5 h post dose) and an extended release for the remainder of the dosing period. Through ambulatory BP monitoring, evaluation revealed that this verapamil formulation produced changes in BP that followed the circadian rhythm of BP: lower reductions during sleep, when the BP is intrinsically lowest, and appropriately larger reductions during the early morning and daytime hours, when ambulatory BP values accelerate and plateau to their highest levels. These data demonstrate that it is possible to design antihypertensive therapy for once-nightly dosing, thereby providing a chronotherapeutic regimen for patients with hypertension. Am J Hypertens 1996; 9: 29S–33S

A major objective of a chronotherapy for cardiovascular diseases would be to deliver the drug in higher concentrations during time of greatest need (e.g., the early morning post-awakening period) and in lesser concentrations when the need is less (e.g., during the middle of the sleep cycle). At present, there are not enough data to know whether altering the dosing time of a conventional antihypertensive or anti-anginal therapy would achieve these objectives. Recently, the effects of the timing of the dose of a conventional antihypertensive agent on circadian blood pressure patterns, for example, morning vs. evening dosing of a once-daily agent have been evaluated in only a few studies with somewhat inconsistent results [13, 14].

In a study examining chronopharmacology, an ACE inhibitor was dosed either in the early morning or at bedtime in 18 moderately hypertensive patients. Palatini et al demonstrated that nocturnal dosing of the drug resulted in a substantially greater effect on nocturnal pressure than morning dosing. There was no significant difference in daytime blood pressure between the two groups. Measurement of ACE activity showed that nocturnal dosing induced a more sustained decline in plasma ACE. A recent review of the effects of ACE inhibitors on circadian rhythm of blood pressure discusses this subject in detail. The greater decline in nocturnal pressures (i.e., an increase in "dipping"), although not formally proven as such, may be detrimental in the elderly or in subjects who have already had a cerebro vascular event.

In contrast to the study of the ACE inhibitor quinapril, studies with ß blocker atenolol, the dihydropyridine calcium channel blockers nifedipine-GITS or amlodipine, showed no differential effects on blood pressure when these drugs were dosed in the morning vs. the evening. Blood pressures were controlled for the better part of the 24-hour time interval after medication dosing. Like many studies in this area, relatively small sample sizes were studied; thus, these studies were underpowered for their designated task, that is, to demonstrate equivalence of the effect of dosing times on 24-hour, awake, or sleep blood pressure. Lemmer recently provided a review on the impact of dosing time on the response to antihypertensive therapy in which he observed that circadian patterns were generally unchanged when comparing morning vs. evening administration of a variety of antihypertensive agents. In this review, as expected, nocturnal medication dosing generally reduced asleep blood pressure more than morning dosing of the same medication. Similarly, nocturnal medication dosing was accompanied by a waning of effect at the end of the dosing interval. In reviewing this issue it is obvious that drug class, formulation, and dose amount have an important influence on the observed findings [15].

The first chronotherapeutic therapy for hypertension and angina pectoris has recently been developed and marketed. This mode of therapy matches drug delivery to both the circadian pattern of blood pressure as well as conforming to the rhythm of myocardial ischemia. The cardiovascular drug verapamil has been employed in this delivery system that has a delay in release for approximately 4-5 hours after dosing and then has an extended release for approximately 18 hours. When taken at bedtime, the delivery system provides optimal drug concentrations between 4 a.m. and noon, a period of time when both blood pressure and heart rate rise in association with awakening and increased physical activity. Thus, hemodynamic parameters, such as blood pressure and heart rate, are modified during the early morning hours. This delivery system allows the drug to remain clinically effective during the daytime, whereas when asleep -- a time when blood pressure naturally is lower and cardiovascular demands are less so -- the drug is minimally active. Although this mode of drug delivery is novel it is not unique in its ability to control morning blood pressure. Other long acting medications, administered in the morning, such as long acting ß blockers or calcium channel blockers, have been shown to have a relevant residual effect 18-24 hours out after dosing. The impact of nocturnally administered medication in reducing asleep blood pressure is very much formulation-dependent. For example, antihypertensive medications -- such as ß blockers or calcium channel blockers -- with conventional delivery systems can increase nighttime ischemic episodes when given to patients exhibiting so-called nocturnal "extreme dipping." Alternatively, doxazosin, which has a slow rate of absorption, does not excessively reduce asleep blood pressures when administered at bedtime while still controlling early morning peak.

Data from recent studies demonstrate that antihypertensive and/or antianginal therapy can be designed to provide reductions in blood pressure or myocardial ischemia those closely mimic circadian rhythms. The verapamil formulation was developed for bedtime administration, because it has a delay in drug release so that appearance of the drug occurs before early morning awakening. The implications of this type of therapy may be important since a number of studies have shown that cardiovascular events occur frequently in the early morning hours, in association with increases in blood pressure, heart rate, cardiac ischemia, enhanced platelet aggregability, and increases in plasma catecholamines [16].

Chronotherapy links the biologic effects of a disease associated with time and the timing of drug delivery. Future research in the area of the chronotherapeutics of cardiovascular diseases will evaluate whether timing of drug delivery has an effect on outcomes, including heart attack and stroke. In the meantime, comparative clinical trials are needed that evaluate the effects of chronotherapeutic vs. homeostatic antihypertensive therapies on clinical end points, including improvement in blood pressures, quality of life, silent ischemia, and cardiac function.

It is suggested that targeted antihypertensive therapy, which optimizes blood pressure and pulse rate control, may be associated with a positive cardiovascular outcome. In addition, it is believed that a chronotherapeutic approach for hypertension therapy (wherein blood pressure and pulse rate are more precisely controlled according to circadian patterns) may offer distinctive hemodynamic advantages in comparison with a homeostatic approach (wherein medication delivery rates achieves a constant effect independent of circadian variation on blood pressure or heart rate) to the treatment of hypertension.

Chronotherapeutics, or delivery of a medication in concentrations that vary according to the specific physiologic need at different times during the dosing period, is a relatively new practice in clinical medicine. Epidemiologic studies document that the incidence of many cardiovascular diseases, including myocardial infarction and stroke, vary predictably in time over 24 hours (the circadian period). Advanced diagnostic technologies using ambulatory monitoring of blood pressure and ECGs have further demonstrated that there are marked diurnal variability in the level of pressure in hypertensive patients and the degree of myocardial ischemia in patients with coronary disease. These diagnostic techniques are also of sufficient sensitivity so as to allow us to study the effects of varying the timing of dosing, or delivery of a concentration of a drug on end points, such as changes in blood pressure, heart rate, or intensity of angina. The first chronotherapeutic agent for hypertension and angina pectoris, COER®- verapamil, has recently

been developed and released. The theoretical advantage of this formulation is that delivery of the active drug verapamil has been tailored to the typical circadian rhythm of blood pressure and heart rate. Thus, patients with hypertension and angina are better covered in the early morning hours when cardiovascular need appears to be the greatest and the effects of traditional medications seem to wane. There are no data available as of yet to ensure the question of long term benefit of this approach as therapy. A multi-national study (CONVINCE) that evaluates primary prevention of cardiovascular events with this chronotherapeutic approach vs. standard of care with diuretics and/or ß blockers is currently underway. This study is anticipated to be completed sometime in the next two years [17, 18].

Techniques of Preparation

Controlled release formulations can be divided into subgroups of rate-controlled release, delayed-release and pulsed-release formulations. Delayed-release formulations include time-controlled release and site specific dosage forms. When constant drug plasma levels need to be avoided, as in chronotherapy, time-controlled or pulsed-release formulations are preferable, especially in the treatment of early morning symptoms. By timing drug administration, plasma peak is obtained at an optimal time and the number of doses per day can be reduced. Saturable first-pass metabolism and tolerance development can also be avoided. Various technologies to develop time controlled peroral drug delivery systems have been extensively studied in recent decades. Some of these systems are discussed in the following subsections.

Enteric Coated System

This system has traditionally been used to prevent the release of a drug in the stomach (see Fig 2). Enteric coatings are pH sensitive and drug is released when pH is raised above 5 in the intestinal fluid. These formulations can be utilized in time-controlled drug administration when a lag time is needed. Because of the unpredictability of gastric residence, such systems cannot be the first choice when a time-controlled release is required. In the treatment of nocturnal asthma, a salbutamol formulation containing a barrier coating which is dissolved in intestinal pH level above about 6,has been successfully used . The system contains a core which is film coated with two polymers, first with HPMC and then with a gastro-resistant polymer (Eudragit® L30D). In this system the duration of the lag phase in absorption can be controlled by the thickness of the HPMC layer.

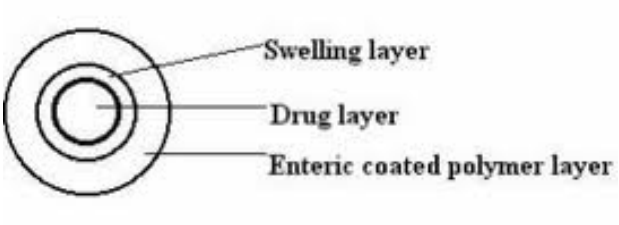

Figure 2: Enteric coated system.

Layered Systems

These are one or two impermeable or semipermeable polymeric coatings (films or compressed) applied on both sides of the core. To allow biphasic drug release, a three-layer tablet system was developed. The two layers both contain a drug dose. The outer drug layer contains the immediately available dose of drug. An intermediate layer, made of swell able polymers, separates the drug layers. A film of an impermeable polymer coats the layer containing the other dose of drug. The first layer may also incorporate a drug-free hydrophilic polymer barrier providing delayed (5 h) drug absorption. Conte *et al* has also studied a multi-layer tablet system (Geomatrix®). It consists of a hydrophilic matrix core containing the drug dose. This kind of three layer device has been used in the treatment of Parkinsonian patients using L—dopa / benserazide. Night-time problems and early-morning symptoms of Parkinsonism can be avoided by using a dual-release Geomatrix@ formulation, which allows daily doses of drug to be reduced and leads to extent of bioavailability 40 % greater than when a traditional controlled release formulation is employed.

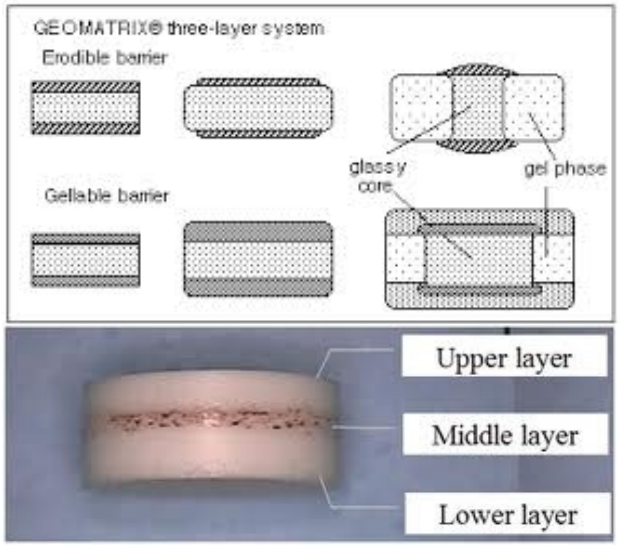

Figure 3: Layered System

Time-controlled Explosion Systems (TES)
These systems have been developed for both single and multiple unit dosage forms. In both cases, the core contains the drug, an inert osmotic agent and suitable disintegrants. Individual units can be coated with a protective layer and then with a semipermeable layer, which is the rate controlling membrane for the influx of water into the osmotic core. As water reaches the core, osmotic pressure is built up. The core ultimately explodes, with immediate release of the drug. The explosion of the formulation can also be achieved through the use of swelling agents. Lag time is controllable by varying the thickness of the outer polymer coating [19-21].

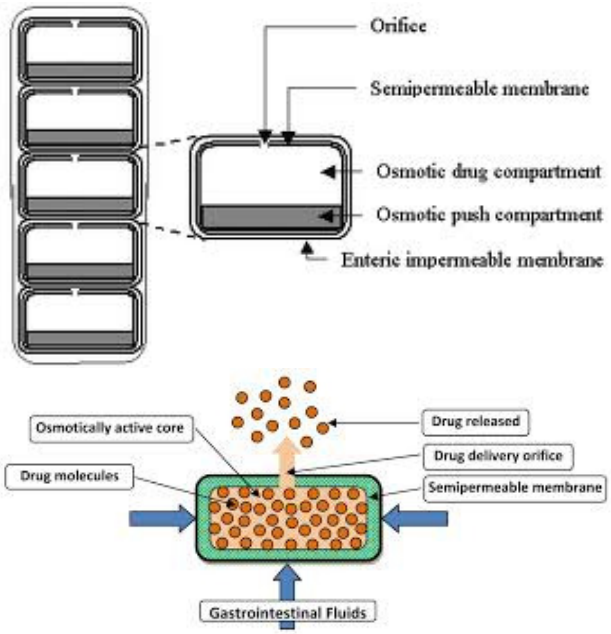

Figure 4: Time Explosion System

Sigmoidal Release Systems (SRS)
For the pellet-type multiple unit preparations, SRS containing an osmotically active organic acid have been coated with insoluble polymer to achieve different lag-times. By applying different coating thicknesses, lag times *in vivo* of up to 5 hours can be achieved. Release rates from SRS, beyond the lag time, has been found to be independent of coating thickness.

Press-coated Systems
Delayed-release and intermittent-release formulations can be achieved by press-coating. Press-coating, also known as compression coating, is relatively simple and cheap, and may involve direct compression of both the core and the coat, obviating the need for a separate coating process and the use of coating solutions. Materials such as hydrophilic cellulose derivatives can be used and compression is easy on a laboratory scale. On the other hand, for large-scale manufacture, special equipment is needed.

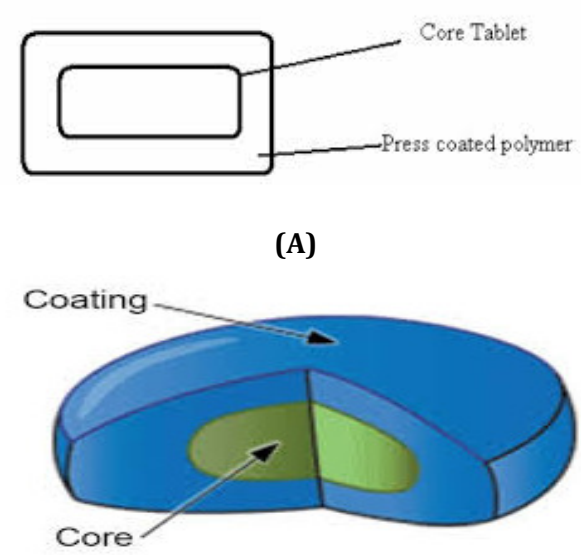

Figure 5: (A) Schematic representation of a Press Coated System **(**B**)** Press Coated System

Advantages
- Avoids degradation of in upper gastrointestinal tract.
- Drug targeting to specific site like colon, cancer.
- Protection of gastric mucosa from irritating drugs.
- Improved patient compliance.
- Drug loss is prevented by extensive first pass metabolism.
- Extended release of drug in pulsatile manner.
- Biological rhythms are taken into consideration.
- Right timing and the amount of medication optimizes the drug's desired effect and minimizes the other ones.
- More effective use of already existing drugs.
- Reduction of dose requirement.
- Reduced dosage frequency.
- Lower daily cost of patient due to fewer dosage units required by the patient in therapy.

Disadvantages
- Not suitable for patients who do shift work (alternate day and night) for whom chronotherapy may be too complicated.

- Gastrointestinal transit times vary not only from patient to patient but also within patients as a result of food intake, stress and illness.
- Drug layering or core making for multiple unit systems is a time consuming and hard-to- optimize process.
- Major drawbacks of existing oral chronotherapeutic systems are their dependence human action to trigger the drug release.

CONCLUSION

Circadian rhythm of the body is an important concept for understanding the optimum need of drug in the body. Chronotherapeutic drug delivery system is one such system that , by delivering drug at the right time , right place and in right amounts , holds good promises to benefit the patients suffering from chronic problems like arthritis , asthma ,hypertension etc.

Thus designing of proper pulsatile drug delivery will enhances patient compliance, drug delivery to the target site and minimizes the undesired effects.

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