Original Article

Chronotherapeutic Challenges In The Pharmaceutical Field For Targeting The Disease At The Optimal Time: An Overview

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Abstract

Chronotherapeutic is a new drug delivery method that gives a pattern of medication input in real-time at various release rates, which may be attained by the supply of Stimulants and pulsative medications. Pulsating formulations become much more interesting as they provide the medication at the appropriate location at the right time and in the appropriate amount at the right area of action. The chronotherapeutic strategy to combat the disease is observed when it is at its height. Some disease activities are based on biological rhythms that are an endogenous self-repressed oscillation.

The dose time relies on the efficacy and pathogenicity of big medicinal products. These Pharmacodynamics and pharmacokinetics of medicines both have an impact on chronopharmacological phenomena. Biochemical are mechanics attributed to a round-the-clock rhythm, physiology and behavioural. Pathophysiological aspects of various disorders like bronchial asthma, arthritis, diabetes, hypertension, stroke etc. revealed the importance of circadian rhythm. The interpretation of changes in drug absorption, distribution, metabolism and excretion depends on time, comprised in chronopharmacokinetics. The right time of a normally designed tablet and a customised Medication concentration can be synchronized with disease activity using a drug delivery system. Modification of biological rhythm is a novel idea for avoiding side effects by adjusting the dose schedule. As a result, the current article examines the therapeutic efficacy and drug safety with its dose time. Consumption of medicines by patients at the right time, in right dosage offers a lot of potential for them.

Keywords: Circadian rhythm, drug delivery system, Chronotherapeutics, Chronopharmacokinetics.

INTRODUCTION:

Due to its simple self-medication, compactness and quick process of creation, an oral route of drug administration is generally accepted (Sastry, Nyshdham and Fix, 2000; Seager, 1998). Nearly 90 percent of medicines are probably used to generate systematic effects via mouth (see Figure 1 and 2). The maximum drugs are administered orally especially solid oral dosage forms (Leon and Herbert, 2009; Hadi and Raghavendra, 2012).

APIs have become the standard for many people all around the world. Almost no one has never used a medicine in their lives. Many people who take medications, on the other hand, place a significant importance on the timing of their administration. Some 60 variety of diseases that includes asthma, arthritis, and cancer, may be treated more successfully with drugs when they are taken at the appropriate intervals of time, which makes treatments more effective. Whereas a faultless therapy is only feasible if the appropriate dosage of this medicine is administered at the appropriate moment. As a consequence, when a drug is not provided when it is not required, numerous unwanted side effects can be eliminated (Hadi and Raghavendra, 2012; Smolensky and Peppar, 2007).

Both biochemistry and physiology of humans do not remain constant throughout a 24-hour of time, but rather change as per the peak and trough timing of the body's circadian rhythm of activities and functions. Throughout the day, several human physiological systems, such as the cardiovascular, hepatic, and renal, pulmonary, perform a range of functions. Clinical and epidemiological research has revealed that the disease activity levels of a variety of illnesses. That include peptic ulcer disease, asthma, arthritis, hypertension, and other diseases have a pattern that is linked to the body's biological clock. When normal biological processes are altered by the time of day, the pathophysiology of illness and its treatment are affected. As a result, he sleep-wake cycle, which is synchronised with the internal biological clock, has an impact on numerous physiological processes in humans (Smolensky and Peppar, 2007; Suresh and Pathak, 2005).

Chronotherapeutics: In the realm of treatment techniques and drug delivery systems, the word "chronotherapeutics" is a new term. Chronotherapeutics is a therapy approach in which medication bioavailabilities in vivo are matched to illness cycles based on their temporal structure, resulting in maximal therapeutic efficacy and minimal adverse effects. Because establishing a person's biological make-up. This method is based on the interdependence of disease Symptoms, risk factors, rhythmic activity, pharmacokinetics, and pharmacologic effect of different APIs from peak to trough. Chronotherapeutics have been shown to offer potential benefits in the treatment of a variety of diseases.

Drug chronotherapy does not need the introduction of new medications, but rather the use of established drugs in a different manner. It may be beneficial if normally designed capsules and tablets are taken at the right time. In the majority of situations, synchronizing medication concentrations to disease activity cycles necessitates the use of specialized drug delivery technology Chronotherapeutic formulations for the treatment of various diseases have as their primary goal the delivery of the maximum concentrations of medication to the targeted areas of the body when they are most needed.

Chronotherapeutics are affected by a number of variables, including pathophysiology or chronopathology of the disease; using the amplitude, period, phase, and level of human circadian time structure, determine the drug distribution pattern, dose, and administration schedule and; drug chronopharmacology, which covers pharmacology, dynamics, toxicity, and aesthetics (Singh, Sharma and Malviya, 2010; Pentewar, Usturge and Rajurkar, 2014; Bjorn, 2007; Kumar, Reddy and Eaga, 2011). Tables 1 and 2 show a few chronotherapeutic medicines that are now on the market, as well as several patents in the field of chronotherapy.

Overview of chronotherapeutic clinical trials:

New challenges were presented to scientists and researchers by Chronotherapeutic. Clinical research on Chronotherapeutic, for example, is needed to include extra characteristics that are not necessary in other clinical trials, according to FDA Sokol.
Additional considerations that must be addressed, according to FDA Sokol, are:

1. Medicament administration time.
2. Seasonal time-related biological variables, such as seasonal diseases (For example seasonal affective disorder).
3. Patients' normal day-to-day habits (For example eating time and sleeping patterns).

According to a 1996 study by the American Medical Association (AMA), chronotherapy would have received greater attention in clinical trials if it had been given more attention. In this study, nearly 75% of the clinicians polled said they would accept additional therapy alternatives if they corresponded to the patients' daily circadian cycles, (Kumar, Kumar and Malviya, 2015) Chronotherapeutic is a field that covers the fundamentals as well as research into chronobiology, chronopathology, chronopharmacology, chronopharmacokinetics, chronopharmacodynamics, chronotoxicology, and chronoesthesy. Chronopharmaceutics etc. all belong to the branch of pharmaceutics that integrates chronobiology with pharmaceutics to a larger extent (Satwara, Patel and Shaikh, 2012).

Chronobiology:

Apart from voluntary control, anatomical & pathophysiological aspects of an individual, body is influenced by natural rhythms like tides, seasons, and the day-night cycle, chronobiology is still a developing field. Health science, on the other hand, has paid little heed to such historical concepts. During the 17th century, Jean Jacques D' Ortous de Mairan, French astronomer, and Carl Linnaeus, Swedish scientist, examined the reaction of various plants to different times of the day. They also noted how the behaviour of the animals altered according on the available amount of light and darkness. However, none of them investigated the concept of a biological clock in the body. However, it became evident in the twentieth century that the biological clock ticks and that the many activities of our lives have underlying links, even inside our own bodies. Finally, researchers discovered that blood pressure naturally varies with the time of day, encouraging them to investigate additional aspects such as work, sleep, and hormone cycles. However, until the 1960s, when scientists' work on chronobiology was recognised as an essential issue for scientific inquiry, chronobiology was not recognised as a prominent field of study. Franz Halberg of the University of Minnesota developed the word "circadian," which refers to a 24-hour period.

From tiny one-celled organisms to humans, the most essential component of life on the planet is biological clocks. Chronobiology is the study of biological clocks that considers the regulation and control of almost all of life's functioning activities. The study of biological organisms' cyclic periodic occurrences and how do they adapt to the solar and lunar cycles is a scientific study.

These episodes of biological periods are of four categories:

- Ultradian cycle is one that lasts less than a day. A neuron, for example, fires in milliseconds, whereas a 90-minute sleep cycle takes milliseconds.
- Circadian cycles are those that persist for more than 24 hours. Awakening and sleeping habits are two examples.
- Infradian cycles are those that last longer than 24 hours. Menstruation, for example, occurs on a monthly basis.
- Seasonal cycles are those types of cycles alter as the seasons change. Seasonal affective disorder, for example, causes depression in a small number of persons throughout the winter months.

In a nutshell, Chronobiology is the study of biological time. This phrase is derived from two ancient Greek words: chronos, which means "time," and biology, which means "knowledge of life." Thus, chronobiology is concerned with the monitoring of all metabolic processes that undergo periodic variations over time and may be measured in seconds to seasons. Chronobiology was first brought into clinical practice in the 1950s as a way to avoid illnesses. Many traditional healers have also stated that therapy must be administered in accordance with numerous internal and external cycles in order to be successful and effective. This research has the potential to aid in the early detection, prevention, and treatment of illnesses, lowering total healthcare expenditures (Ernest, 2005).

Chronopathology: The term "chronopathology" refers to the study of disease progression across time. The study of biological rhythms in disease processes is morbid, even fatal at times.

Chronopharmacology: In the early 1970s, the area of chronopharmacology was identified as a scientific domain worth investigating. It's a research project that looks at how medicines interact with endogenous periodicities and biological timing. It also involves the investigation of pharmacologic agent dosage that is time dependent. Dosing time dependent changes also includes quantifying elements like inherent circadian rhythms and their pharmaceutical effects (CR). Only a few examples include the duration (I), amplitude (A), 24 hr adjusted mean (M), peak-to-trough difference, acrophase, and peak time location on the 24 hr scale. The fundamental goal of chronopharmacology is to comprehend the periodic and hence predictable diurnal variations in pharmacological efficacy (i.e., intended effects) and tolerance (Cardinali and Pandi-Perumal, 2010; Patil, Patil, Salaunkhe and Chaudhari, 2013; Reinberg, 1992).

Chronopharmacokinetics: Chronopharmacokinetic studies have been described for a variety of medications to explain the facts about Chronopharmacology and show that the time of administration affects the outcome on drug pharmacokinetic variation. As a function of delivery time, this concept covers the drug's temporal alterations in absorption, distribution, metabolism, and excretion, known as pharmacokinetic phases that alter in accordance with day time are influenced by several physiological body functions. Pharmacokinetic characteristics, such Cmax (drug peak plasma concentration), Cmax (Tmax) time, demi-life elimination (t1/2), Distribution Value (Vd), Clearance area, AUC area, and protein binding, often considered to be time constant, vary on time. The knowledge of pharmacokinetics of medicinal products may be useful in the clinical environment by altering the entire 24-hour daily dose distribution (Lemmer and Bruguerolle, 1994).

Chronodynamics: The notion of chronodynamics refers to the time of medicine delivery in respect to circadian cycles. Drug effect variations are linked to changes in receptor numbers and conformations related to chemical, drug distributions and fractions, rate limiting step in metabolic pathways, second messenger, and ion channel dynamics. The expected positive benefits as well as the undesirable harmful effects of medicines can be dramatically altered depending on the time of administration (Kumar, Reddy and Eaga, 2011; Lemmer and Bruguerolle, 1994).

Chronoesthesy: The term chronoesthesy refers to a phenomenon in which chronopharmacology investigations may demonstrate more variability despite the fact that the concentration and pharmacokinetics are the identical, in their effects with various biological timings of administration When a biosystem's circadian rhythms alter, it's also known as sensitivity to medication.

Chronotoxicology: Chronotoxicology addresses the interventions related to dose timing and their effects like, variations in rhythm, manifestation, adverse effect severity, and resistance to medications. Chronotoxicology is a branch of chronodynamics that studies the effects of time. Chronotoxicology refers to the fact that certain pharmaceutical classes have a risk of side effects and a limited therapeutic range, resulting in large differences in dose time safety.

The consequences of circadian rhythms: Circadian rhythms are a type of cycles that occurs on a daily basis. Autonomous, daily or 24-hour endogenous oscillations. The circadian clock, which may be located in the hypothalamus suprachiae, is typically synchronised with the circadian cycles. Human physiology and biochemistry are not constant over a 24-hour period, but can rather be modified in a predictable manner, as specified by the maximum and periods of every circadian function and activity of the body. At particular periods during the nocturnal sleep span, the cycles of white blood cells, lymphocytes, prolactin, melatonin, eosinophils, adrenal corticotrophic hormone, follicle stimulating hormone, and luteinizing hormone all come to a head. During the early hours of diurnal activity, serum cortisol, aldosterone, testosterone, platelet adhesiveness, and blood viscosity all reach their highest levels. Afternoons (middle and late), hematocrit and airway calibre are at their highest, but platelet counts and uric acid are at their highest later in the day and evening. As a result, numerous (Smolensky and Peppar, 2007; Suresh and Pathak, 2005).

Diseases currently on target for Chronopharmaceutical formulations (Uhumwangho, Latha, Sunil, Srikanth and Murthy, 2011; Mohapatra, Manohar, Patel, Gupta and Rath, 2021; Tamilanban, Mohamedmajeed and Chitra, 2020). Most of the physiological and many pathological functions of human body are organized with biological rhythms with variable periods. This either proposed an opportunity or challenge in development of delivery systems for drugs to achieve improved therapeutic outcomes. Table 3 provides some examples of specific illnesses. Some diseases currently on target for chronopharmaceutical formulations include:

Asthma: It is well suited for chronotherapy as the studies revealed a progressive increase in airway resistance at night in asthmatics, as well as bronchoconstriction and exacerbation of symptoms vary during the day using drugs like methylxanthine (theophylline), beta 2- agonists (salbutamol) etc. Circadian changes may result in an increase in diurnal resistance causing dyspnea in asthmatics which resulted in 50 to 100 times more occurrence of asthma episodes between 3.0 am and 5.0 am.

Allergic rhinitis: Allergic rhinitis is highly prevalent affecting about 25% and 40% of adults and children in USA respectively. The most common symptoms include sneezing, runny nose, nasal pruritis and nasal congestion that causes nasal congestion and obstruction during the night hours, disrupts sleep. It also results in daytime fatigue, poor work and school performance. In mid 19th century Trousseau was one of first clinical scientists to recognize and emphasize the prominence of day to night pattern in AR symptoms led him to describe AR as "L'asthme dunez", (in English: "asthma of the nose").

Rheumatoid arthritis (RA): RA varies within a day and between days in a rhythmic pattern resulted in daily morning stiffness. It was revealed that in night and early morning, plasma cortisol (anti-inflammatory) is lowest and melatonin (pro-inflammatory) is highest resulting in increased pro-inflammatory cytokine production exhibiting a diurnal rhythmicity. Previously, some workers have shown that some NSAIDs, such as indomethacin and Ketoprofen have better morning absorption with greater rate and/or extent of bioavailability when their controlled release formulations are given in the morning than when they are given in the evening.

Ulcers: It is well postulated that the rhythmic acid secretion leading to pain is highest near the bed-time and early morning. Hence, most ulcer medications are administered at night to enhanced therapeutic effect.

Myocardial Infarction: The onset of myocardial infarction has been shown to be more common in the morning with 35% of events occurring between 6 a.m. and noon. Severe cardiac arrest and transient myocardial ischemia indicate an increase in morning frequency. It may also be important to note that the risk of a heart attack appears to be higher in the morning after waking up. Causes of these findings have been suggested by the release of catecholamines, cortisol, increased platelet aggregation and vascular tone.

Hypertension: The role of chronotherapeutics in controlling high blood pressure is based on the realization that blood pressure is relatively low throughout the day, usually high in the morning and low in the evening. This seems to be related to the high inclination in the morning and a slight inclination after waking up time. Wake propensity is mediated by factors such as elevated body temperature, respiration, cortisol and adrenaline levels. These factors have obvious effects on heart rate and blood pressure. This recorded increase in blood pressure near the time of awakening is responsible for an increased risk of cardiovascular risk in the morning.

The first goal of treating hypertension was to lower blood pressure in equal amounts throughout the day. Chronopharmaceutics addresses this limit by bringing the drug to a different concentration depending on the rhythm of the body's circulation. In this way, it is possible to lower blood pressure at times when patients are at greater risk for cardiovascular events without a significant reduction during low doses. Currently, there are new anti-hypertensive drug products on the market that dispense the drug at an alarming rate from 6 a.m. to noon when medications are given at 10 p.m. Other examples include Innopran XL (Propanolol) and Cardizem LA (Diltiazem) which are manufactured by GlaxoSmithKline USA and Biovail Corporation Mississauga, Canada respectively.

Diabetes: The circadian differences between glucose and insulin in diabetic mellitus have been extensively studied and their clinical significance in converting insulin to type 1 diabetes has been previously discussed. The purpose of insulin therapy is to mimic the normal physiologic pattern of endogenous insulin secretion in healthy individuals, with continuous basal discharge and stimulated food production. Providing basal insulin exogenously in diabetic patients inhibits hepatic glucose production. External administration of dietary doses promotes the absorption of peripheral glucose and reduces the release of glucose from the liver.

Neurological disorders: As an integrated discipline in physiology and medical research, the passage of time enables the discovery of new regulatory processes related to the central mechanisms of epilepsy. Chronophysiological research, which is considered in rhythmic level resolution, suggests several heuristic approaches to the central pathophysiology of epilepsy and to the behavioral classification of epileptic events. Such circadian studies may also lead to some work hypotheses in chronobiology psychophysiology and allow for the development of new theoretical concepts in the field of neurological science. It is also well known that there is a circadian rhythm in the content of NA in the noradrenergic nerve terminals and in the brain region with the highest concentration of noradrenaline (NA). Furthermore, it has been shown that human sleep, its duration and organization depend on its circadian phase. Successful chronological formulation against insomnia that plagues most people represents the entire oscillating cycle of the human sleep process.

Temporal zero order release formulations based on chronotherapy have been developed Chemotherapy, neurological problems, heart disease, asthma, and arthritis are just a few of the ailments that may be treated with it., along with a

regulated release rate from the formulations. Different drugs used to treat such diseases should be administered exclusively at specific times and locations in order to maintain a therapeutic blood level, and drug release behaviour should be managed as a result. Various system and sigmoidal release formulations have been explored for this aim, employing various methods and various polymers or excipients. These methods have the particular feature of releasing a medication from a formulation after a specified lag period as a result; they can be employed in a variety of Chronotherapeutic formulations (Botti and Youan, 2004; Jesy, Vishal and Shital, 2008; Zhang, Zhang and Wu, 2003; Sungthongieen, Puttipipatkhachorn and Paeratakul, 2004; Mohammad and Dashevsky, 2006; Srinivas, 2011).

Merits of Chronotherapeutic formulations:

- Chronotherapy is a drug-free treatment.
- When a person sleeps for a long period of time, chronotherapy is more effective.
- Patients who receive chronotherapy frequently fell asleep; this enhances their health and self-esteem.
- Chronotherapy differs from other therapies in that it has a beginning, middle, and end. As a result, the point at which it will work may be easily predicted.
- It provides you a new routine, such as getting up and going to bed early, which will be strange for a few days but will give you, time to psychologically adjust there is no possibility of dosage dumping (Patel, Patel, Vachhani, Prajapati and Patel, 2010).
- Optimize drug availability at the specific time when disease symptoms are most severe (Smolensky, 1993).
- Optimize drug efficacy by determining the timing and amount of medication.
- By reducing dosing frequency, improved patient compliance and provide a most cost-effective therapy.
- Avoid adverse effects and thus outcomes of toxicity.
- Delivery of drugs exhibiting a chronobiological behavior.
- Demerits of Chronotherapeutic formulations:
- It causes a non-24-hour sleep awakening syndrome when the person sleeps after the therapy or when the person who sleeps for more than a full day (24 hour) during the treatment.
- During chronotherapy, People are becoming less productive, and staying up till the next schedule, which is a little difficult.
- This treatment must be done under medical supervision. There are a lot of process factors.
- Manufacturing necessitates the use of a trained/skilled individual (Wankhade, Rathi, Sapkal and Babhulkar, 2013).

Ideal properties of Chronotherapeutic formulations:

- When used within permissible levels, it should be non-toxic.
- For a certain disease condition, have a precise and real-time triggering biomarker.
- Have a feedback based regulatory system (e.g., self-regulating and adaptive Circadian rhythm capacity, and each patient's ability to discriminate between awake and sleep states).
- It should be biocompatible and biodegradable, especially if it will be given intravenously (Kikuchi and Okano, 2002).

Considering biochemical, physiological, and pathological changes occur in humans over a 24-hour period (Figure 5), chronotherapeutic disorganisation is concerned with the administration of medications based on the disease's intrinsic activity during a certain time period. Medical therapy based on the daily working cycle, which correlates to a person's biological clock on a daily, monthly, seasonal, or annual basis, or to optimise health advantages, is known as chronotherapeutic medicine, while minimising side effects. Chronotherapeutic's major objective is to match treatment time to the inherent timing of disease.

The superchiasmatic nucleus, the body's master circadian clock, regulates the circadian rhythms of the body that exist within human body (Bussemer, Otto and Bodmeier, 2001; Santini, Richard, Scheidt, Cima and Langer, 2000; James *et al.*, 2006). Oral drug delivery systems account for the majority of the worldwide market for dosage forms, as their pattern of medication release is inside the therapeutic window, guaranteeing long-term therapeutic action. When pulsatile medication administration some situations need medication release following a lag time, i.e., a period of no drug release, as shown in Figures 6 and 7. Lag time is required for site-specific medicine transport to the colon, which necessitates avoiding excessive first-pass metabolism in the GIT, as well as drug breakdown in the stomach's gastric acid medium, which leads to bioavailability (Shidhave *et al.*, 2010; Richards, Choi and Tyler, 2003; Santini, Cima and Langer, 1999; Ritschel and Forusz, 1994). Human physiological functions such as metabolism, behaviour, sleep patterns, and hormone synthesis are all governed by circadian rhythms. According to reports, early morning hours, when cortisol levels are high and blood pressure is also high, have a higher risk of heart attacks than later in the night (Lemmer, 1999; Ray and Shahiwala, 2009). Nocturnal asthma causes an increase in reactivity in the early hours of the morning, as well as a rapid increase in stomach acidity in the middle of the night. The necessity of developing time-specific medication administration is highlighted by the fact that cholesterol production is higher at night than day time. Circadian rhythms have a role in all of these occurrences.

PHARMACODYNAMICS AND PHARMACOKINETICS INFLUENCED BY CIRCADIAN RHYTHMS:

Chronopharmacodynamics: The pharmacodynamics of medicines can be affected by biological rhythms at the cellular and subcellular levels that are independent to their pharmacokinetics (Ohdo, 2003; Ohdo, 2007; Ohdo, 2010). The name for this phenomenon is 'chronesthesy.'

Drug absorption: Several orally given medicines have been shown to have circadian variations in absorption in humans. The time of day affects the stomach pH, acid secretion, motility, stomach emptying time, and GI blood flow are all factors to consider (Bloom, Filion, Stunkard, Fox and Stellar, 1970; Belanger, Bruguerolle and Labrecque, 1997). Such alterations may play a role in the time-dependent variation in medication absorption after dose. Circadian variations in pH, for example, may cause medication ionisation to alter according to its physicochemical characteristics.

The physicochemical characteristics of a medication impact the dosing time-dependent variation in drug absorption (lipophilicity or hydrophilicity) (Labrecque and Belanger, 1991). Lipophilic medications show substantial diurnal variations in drug absorption, but hydrophilic drugs show no such changes (Reinberg and Smolensky, 1982). Biological rhythms influence medication absorption via routes other than the oral route (Bruguerolle, 1998; Labrecque and Belanger, 1991).

Distribution of drugs: Body clock Drug distribution is connected to changes in biological fluids and tissues have been found to differ depending on the time of day (Anderson *et al.*, 1999). The sympathetic and parasympathetic nervous systems, whose activity is known to be reliant on the 24-hour clock, with the sympathetic system having a daily effect, are two factors that control blood flow. Thus, a diurnal increase in blood flow and local blood flow in tissues, as well as a potential variation in medication distribution might be explained by a night time reduction in blood flow and local tissue blood flow (Pleschka, Heinrich, Witte and Lemmer, 1996; Feuers and Scheving, 1988).

Substance metabolism: Liver enzyme activity, hepatic blood flow looks to be having an effect on hepatic drug metabolism. Both variables have a circadian time-dependent difference. The brain, kidneys, and liver are just a few of the tissues that be affected. Display a circadian time-dependent variation in enzyme activity (Labrecque and Belanger, 1991; Ohno, 2000). If you're looking for a unique way to express yourself by assessing the chronopharmacokinetics of medicines and their metabolites, several chronopharmacological investigations have looked at temporal variations in hepatic drug metabolism in an indirect way. As a result, there is a circadian time-dependent variation in conjugation, hydrolysis, and oxidation. Circadian fluctuations in the urine 6-hydrocortisol to cortisol ratio in men, for example, reflect changes in cytochrome CYP3A activity (Cambar, Cal and Tranchot, 1992).

Drug elimination: Drug clearance in the kidneys is time-dependent, with higher levels throughout the day due to tubular resorption, glomerular filtration, renal blood flow, urine pH, and tubular resorption are all related to glomerular filtration. The circadian-dependent shift in medication urine excretion might be attributed to these periodic changes in renal functioning. Acidic medicines are eliminated quicker after a night-time dose due to the rhythmicity in urine pH, as evidenced by sodium Salicylate and sulfasylazine (Detli and Spring, 1996).

Techniques Used in Chronotherapeutics:

- The capsule-in-a-capsule concept.
- Technology that allows you to use your tablet as a tablet.
- Capsule-in-a-tablet technology.
- Granules and Tablets-in-a-Capsule technology[Biphasic delivery system]

1. The capsule-in-capsule concept:

Capsule-in-a-capsule technology (CCT) enables a diverse variety of therapeutic applications in single oral capsule dosage units. The inner capsule, which is smaller, may contain a liquid or semi-solid composition, and either or both capsules may be composed of gelatine or HPMC. The inner and outer capsules can be targeted to specific sections of the GI tract using an appropriate coating.

As seen by the recent releases of Combodart TM (GSK) and Vimovo TM, amalgamation treatments are now generating a lot of attention (Pozen, AstraZeneca). Greater regulatory approval, pharmaceutical companies to create life cycle medication that helps patient to accept, comply with their treatment are driving this interest in coalescence therapy. Only the nutraceutical industry has developed this technology into a marketable product at this time. However, various pharmaceutical companies have to design such formulations under development.

Merits of Capsule-in-capsule technology (CCT)

- This technology produced both zero order and multi-phase release.
- In one single oral formulation unit, there are two separate compartments.
- It is possible to obtain patient acceptability and compliance, as well as cost-effective therapy.

- It is possible to produce sustained, pulsed, or delayed release characteristics.
- Drugs can be delivered to two distinct parts of the gastrointestinal system.
- Drugs can be delivered to two distinct parts of the gastrointestinal system.
- It is feasible to achieve a wide range of medicinal applications.

2. Tablet-in-a-tablet technology:

The most common solid dose type is tablets for oral medication delivery. Due to a variety of advantages, one type of tablet formulations has gained significant relevance in pharmacological treatments. The release of these formulations can be regulated or changed (Mangesh Bhad *et al.*, 2010). Even though it has received less favour in recent years, tablet-in-a-tablet technology (see Figure 9, 10) has acquired more attention in producing modified launched goods. This tablet-in-a-tablet technology involves using specifically developed tableting machinery; granular materials are compressed around a prefabricated tablet core. It is a dry technique to apply compression coating. Internal core and surrounding covering components make up this sort of tablet. One turret prepares the core, which is a tiny porous tablet. Following the manufacture of the tablet core, it is moved (in the centre) to a slightly bigger die that is partly loaded with coating powder. Once again, the top of the core is sprayed with coating powder, resulting in a tablet within a tablet. It's a complicated mechanical procedure since the tablet may be slanted when it's moved to the second die chamber. The majority of coating ingredients are water soluble and dissolve quickly after ingesting, allowing for rapid formulation release. The initial dose is released by the outer layer followed by the inner core and hence, the tablet becomes a repeat action tablet. A completely different blood level is achieved when the core rapidly releases the drug, creating a toxicity risk owing to overdose. The first dosage is applied to the outer sugar coating to avoid toxicity, and Enteric polymer is applied to the centre of the tablet.to prevent the medicine from being released in the stomach. Even yet, when producing and delaying the production process, the coating operation needs interpretation. The inner core may be made in a liquid formulation to allow for quick core release when the coat has disintegrated.

Positive points of tablet-in-tablet technology include:

- This is a low-cost, easy-to-use technology.
- It is used to segregate materials that are incompatible (one in core and the other in coat).
- Delayed Release goods, for example, might be created using technology (Release in intestinal or some time release in colon).
- It is not environmentally harmful because it does not require using a large volume of solvents.
- CCT helps to prevent pharmacokinetic drug–interactions while taking multiple medications at the same interval of time by separating their release into the GIT (Latha, Uhumwangho, Sunil, Srikanth and Ramana, 2011; Janugade, Patil, Patil and Lade, 2009; Janugade, Patil, Patil and Lade, 2009a).

3. Capsule-in-a-tablet technology:

Another type of solid oral formulation that has similar therapeutic advantages is controlled release capsules, which frequently contain a number of coated pellets. These are newer combination technologies that combines both controlled release tablets and modified release capsules.

Drugs are often encased in a barrier material made of an erodible or biodegradable polymer in one form or another. By altering the structure of barrier's material, different thicknesses and variable lag times can be produced. Once the barrier material is dissolved, corroded, or destroyed, the drug is released. Filling flexible tablets in a hard capsule may be used to generate a multifunctional and multiple unit system for oral use. Rapid-release mini-tablets, sustained-release mini-tablets, pulsatile mini-tablets, and delayed-onset or sustained-release mini-tablets are all types of mini-tablets may all be made with different lag periods of release. Mini-tablet combinations can be used to generate a multiplied pulsatile drug delivery system (DDS), a site-specific DDS, a slow/quick DDS, and a zero-order DDS, a quick/slow DDS. This method may be utilised to administer medicines selectively at the right moment, which is a chronopharmaceutical strategy for improved disease therapy using circadian rhythms. This new method is referred to as a "tablets in capsule gadget." (See Figure. 11 and 12 for more information). The suggested capsule device comprises of a soluble cover and an impermeable capsule body. The multi-layered tablet formulations are then sealed with a water-soluble cap and placed into the capsule body (Li and Zhu, 2004; Raghavendra, Hadi and Panchal, 2011 Hadi, Raghavendra and Firangi 2012; Patel and Patel, 2011). We can shrink the tablet to the point where it can fit within another capsule, and then use this technology to distribute tablets with different release characteristics inside a single dose form. A fast/slow delivery method might be used to accomplish this technology. The suggested fast/slow delivery devices demonstrate a high degree of modulation flexibility in the delivery programme. To get the required in-vivo profile, the two distinct release phases may be readily changed across a wide range of values for both delivery rate and dosage fraction ratio, based on pharmacokinetics and therapeutic needs (Rao, Hadi, Wahid, Munde, and Ghurghure, 2011). The basic idea behind this method is that the dose is split into many subunits, each of which includes the medicine. As a result, the dosage is equal to the dose's overall functionality is proportional to the total of the drug quantities in each subunit, and the dose's overall functionality is proportionate to the individual subunits (Carla, Jose, Joao, Pinto and Paulo, 2006) Multi-particulate (MP) modified release drug delivery systems outperform single-unit dosage forms in a variety of ways. The medications are freed from the MP once they have been delivered. MP formulations have a more constant in-vivo dissolving capability than single-unit dose formulations, which result in more consistent bioavailability and therapeutic impact (Riis, Bauer-Brandl, Wagner, and Kranz 2007; Dey, Majumdar and Rao, 2008).

Tablet-in-capsule technology has several advantages, including considerable cost savings, a decreased reduced case-fatality ratios and a lower treatment failure rate.

For a single prescription or a mix of prescription and over-the-counter drugs, it offers both regulated and multi-phase release.

- It is possible to obtain patient acceptability, compliance, and cost-effective therapy.
- It is feasible to deliver APIs that are incompatible.
- It is possible to achieve continuous, pulsed, or delayed release characteristics.
- Drugs may be delivered to the two distinct parts of the gastrointestinal system.
- It has a longer colonic residence time, clearer stomach emptying, and so requires less money for long-term treatment-related product development.
- Tablet-in-a-capsule technology has several benefits, including large drug-loading, variable rates of release designs, and meticulous release rate management.
- It has a minimal risk of dose dumping. There is reduced inter- and intra-subject variability, as well as a large degree of dispersion, in the digestive system. All of which reduce the danger of high local drug concentrations.
- It is possible to achieve broad therapeutic applications (Huang, Kao and Wu, 1999).

4. Technology for granules & tablets-in-capsule:

Biphasic delivery methods release drug at variable rates at two separate time periods, such as either quick/slow or vice-versa. A quick/slow-release system gives a preliminary rapid drug release, that is followed by a slow rate of release (ideally) over a predetermined period; otherwise, a slow/quick release system delivers release in the other direction (Lauretta, Evelyn, Maria, and Ubaldo, 1999) (See Figures 13 and 14).

When maximal relief is required rapidly, and to reduce repeated administration, a biphasic release technique can be used, that include sharp initial release followed by a longer release phase. This will work well with peripheral analgesics, antiallergics and antihypertensive drugs (Kuentz, Rothenhäusler, and Röthlisberger, 2006). Traditional zero order release dose formulations, in general, postpone therapeutic levels' release. They don't have a quick start-up time. Instant release granules, on the other hand, give a rapid onset of action, they don't provide a prolonged duration of activity. It is usually better to retain the plasma level relative to keep the concentration of a medication inside the therapeutic window. The fact that the drug diffusion and/or absorption environment varies throughout the GIT is nonetheless problematic, particularly with respect to once-daily dosage formations (Leblanc, Yoon, Kombadjian and Verger, 2000). In accordance with these considerations, we have tablet and granules, which have one part to construct for the quick release of the medication, in the form of a novel oral delivery device (Biphasic), aimed at achieving a high blood level over a brief period of time. The second component is a continuous release matrix, which keeps the plasma level constant for a long time (Moawia and Al-Tabakha, 2010). This method might be used to create a biphasic system for drug delivery that is both rapid and delayed as long as the excipient is filled with powder. Some of the total medication dosage is included in the empty areas between the micro pills. In some medicines, such as analgesic, anti-inflammatory, antimicrobics and antihistamines, this mechanism can cause fast blood levels to increase quickly and then have a lengthy release phase to ensure that repetitions are avoided (Makoto, Kenichi, Minoru and Masao, 2008). Compressed mini-tablet devices are available as a biphasic delivery system. The layer in-between the micro tablets, which fills the vacuum areas, was fabricated to make the drug available within a certain amount of time (rapid release). The fast release part includes many super-disintegrants such as crospovidone and sodium and glycolate etc. carmellose and sodium starch. During mini-tablets, HPMC and Ethyl cellulose are formulated utilising various concentrations. These delivery methods have shown their intended biphasic behaviour through drug release performances (Youan, 2004). The capsule shell is complete with prepared instant release granules and micro tablets. The drug in the speedy release period, the granular substance was dispersed completely in the medication in the mini-tablets was dissolved at a varied pace, depending on the composition, within the first 5 minutes (Verma and Sanjay, 2001).

RECENT TECHNOLOGY AVAILABLE FOR CHRONOPHARMACEUTICALS:

Technology of OROS®: ChronsetTM is an OROS® patented formulation that delivers a bolus medication dosage to the Gastro intestinal tract in a precise time in a targeted manner. It is nothing more than a medication delivery mechanism based on osmosis. The active pharmaceutical medicines are stored in a reservoir system, then encircled by an SPM, a tablet pierced with a delivery hole and laser-formed. The tablet was made up of two layers: one for the medicine and one for the osmotically active component. When this osmotic agent comes into touch with GI fluid, it changes from a non-dispensable to a dispensable viscosity; there by the pump or osmotic pressure differential action, the active medicinal medication is pushed out via the channel. It is commonly utilised in the creation of extended-release tablets.

***CEFORM®*:** Technology produces microphones uniform in size and shape for a medicinal component (Leslie, 1986). The melt spinning method is a blend of temperature, mechanical strengths, thermal degrees, and flow rates for exposure to solid feed (both bio-degradable polymer and bioactive agent combinations). The microspheres manufactured are almost spherical, 150 – 180 metres long and offer a high concentration of medicines. Pills, capsules, suspensions, effervescent tablets, and sachets are just a few of the dosage forms that the microspheres can be utilised in. An enteric coating can be

applied to the microspheres for controlled release or mixed as a fast/slow-release mixture. Cardizem R LA, a one-day diltiazem formulation similar to ChrDDS, was developed using the same technique Arkinstall, 1988).

CONTINR Technology: Molecular coordinated complexes between the non-polar solid aliphatic alcohol and the cellulose polymer, optionally replaced by aliphatic alcohol, are established in this technique by solved polymer with volatiles polar solvent and by the aliphatic alcohol, preferably melting the solved cellulose polymer. This generates a matrix that is bit complex that is used in controlled-release formulations because of its constant porosity (semi-permeable matrices). This method has opened the way for the development of tablets containing sustained-release aminophylline, theophylline, morphine, and for other medications of the dosage form. This technique allows for more precise control of the quantity of medication delivered into the circulation, which helps patients by lowering the number of dosages they must take each day, improving disease management (especially at night), and reducing adverse effects (Youan, 2009; Percel, Vishnupad and Venkatesh, 2001).

DIFFUCAPS® Technology: DIFFUCAPS® technology uses a unit dose form to distribute medicines into the body in a clockwise way. It is a multiparticulate-based technique developed by Reliant Pharmaceuticals LLC for the prolonged release tablet (Innopran®) containing two drugs, Verapamil HCl and Propanolol HCl. The Pulsincap® system is one of the most widely utilised capsule-based pulsatile devices. Diffucaps® is a drug-delivery system created by RP Scherer International Corporation in Michigan, United States. It is therefore made up of one or more drug-delivery particle populations (granules, beads, pellets etc). There is a predefined fast or continued release profile for every bead population with or without a 3-to-5-hour default lag time. The active core of a dosing method can be made by the way of a film-forming formula including API ideally, a water-soluble film compound-forming composition (i.e. HPMC, PVP) that creates a water-soluble/dispersible particle (API). API-containing film-forming formulation can form an accurate metabolism. The active core can be prepared via granulation, fractionation, extrusion, and spheronization of the API-containing polymer composition. A ChrDDS of this type is designed to provide a time-specific plasma concentration profile that is dependent on the physiological needs of the day and is reproducible. This model mimics the Physiological and pathological aspects of a cardiovascular disease according to its pharmacological factors, as well as in vitro/in vivo correlations. The first newly authorised FDA propranolol, including ChrDDS (InnopranRXL), was utilised in hypertension treatment using this technique (Prisant, Devane, and Butler, 2000; Panoz and Geoghegan, 1989).

CHRONOTOPIC® Technology: A membrane system that is erodible, soluble, or breakable is also discussed. It is essentially a medicinal core, covered with a controlled coating for external release. The internal formulation of the medication has been used both for Tablets, capsules, and micro pellets are examples of single and multiple unit dose forms.

EGALET® Technology: A late release shell with two lag plugs that includes an active medication plug in the centre of the unit. The medication is released when the inert plugs erode which determines the lag time. The shells are made up of bioplasticizers (cetostearyl alcohol) and polymers (ethyl cellulose), whereas the plug-matrix is made up of inert polymeric excipients like polyethylene oxides.

CODAS® Technology Chronotherapeutics: This is a multiparticulate device for the oral dosing at night (Conte and Maggi, 1996). A non-enteric coating is added to the drug containing beads in order to delay the drug's release for a period of five hours. A combination of water-insoluble and water-soluble polymers was being used to regulate release. When the polymer of the dosage form interacts with gastro intestinal fluid, it degrades over time, causing holes in the coated layer to appear. The drug diffuses via the holes that arise. The water-insoluble polymer acts as a barrier, allowing Verapamil to be released in a controlled, fashion-like manner (Katstra *et al.,* 2000) pH, posture, and diet have no effect on the rate of release.

GeoClock® Technology: Geomatrix technology is used in the development of the GeoClock® idea (Rowe *et al.*, 2000). For continuous medication release in this technique, a multilayer technology was first proposed. One or both bases are partly covered with the active core or hydrophilic matrix. The core hydration mechanism is adjusted, and the amount of surface area available for medication release has decreased. The barrier layer expands and turns into a gel in the presence of the dissolving liquid. This gelling layer is not degraded; instead, it functions as a regulating membrane that regulates the release process. The dissolving media, on the other hand, gradually removes the erodible surface. With increasing time, more of the active core's planar surface(s) is exposed to the outer world, which increases medication absorption.

PORT® (Programmable Oral Release Technologies) Technology: This produces a coated tablet that may be reprogrammed, encased Technology that allows for numerous medication releases (Monkhouse, Yoo, Sherwood, Cima, and Bornancini, 2003). It has a polymeric core that is covered with a rate-controlling, semipermeable polymer. To achieve a consistent and regulated release from the dosage form, poorly soluble medicines may be coated with solubilizing agents. A semipermeable, rate-controlling polymer coats the gelatine capsule in the capsule form. The active medication is retained inside the capsule shell, along with an osmotic agent. The capsule shell is sealed by a water-insoluble stopper. Depending on the situation, an immediate release compartment can be installed.

Three-dimensional printing® (3DP) technology: This is based on solid freeform manufacturing methods (3DP), a new technology utilised in production of certain oral dose administration medicines. Engineering devices with complex

interior geometries, changing densities, diffusivities, and chemicals is conceivable (Staniforth and Baichwal, 2005). The 3DP technique has been used to make a variety of sophisticated oral drug delivery devices, including pulse release pills, the enteric dual pulsatory tablets (made of single continuous enteric excipient phase), immediate-extended-release pills, breakaway tablets, and dual Diclofenac Sodium printed in two separate spots which gives release of two pulse of drug in an interval of four hours during in vitro testing (Horter and Dressman 2001; Mahev and Bersot, 2001).

TIMERx® Technology: TIMERx® can be utilized for drug release from zero to chronotherapy releases, is a hydrogel-based controlled release technique. Changing molecular interactions can provide a varied kinetic release. In this technique, xanthan and xanthanous bean gums are mostly combined with the addition of dextrose. In the presence of water these components converted to a strong binding gel. The rate at which a substance penetrates the gum matrix of TIMERx by water from the gastrointestinal system, which swells to produce a gel and releases the active therapeutic component, regulates medication releases.

Physicochemical abatement of the API: Physicochemical properties of the active pharmaceutical ingredient, to produce chronopharmaceutical effect, new replacements to the original structure can be made to change solubility, partition coefficient, permeability, crystalline shape, melting temperature, and other properties of the drug (Santini, Cima and Langer, 1999; Santini, Richards, Scheidt, Cima and Langer, 2000). The drug's maximum plasma concentration (Tmax) is dependent on the parent compound's physiochemical alteration (Sershen and West, 2002).

Monitored Microchip: A solid-state silicon microchip is a microfabrication technique that distributes active medication in a pulsatile manner, similar to micrometre-sized pumps, valves, and flow channels (Levi, Zidani and Misset, 1997). It can release single or many chemical compounds in a regulated manner, depending on the situation like filling of tiny reservoir or the electrochemical breakdown of thin anode membranes covering the micro reservoir, which contains chemicals in solid, liquid, or gel form, provides the basis for the release process.

Chronomodulating infusion Pumps: Controlled both outside and inwardly other systems have been carefully investigated both externally and internally, including pre-programmed systems magnetic areas, ultrasound, electrical fields, temperature, light, pH and mechanical stimulation are all examples of modified enzymatic or hydrolyte breakdown systems (Remeling and Hrushesky, 1989). Melodie® (Tzannis, Hrushesky, Wood and Przybycien, 1996), programmable Synchromed® (Jain, Raturi, Jain, Bansal and Singh 2011), Panomat® V5 infusion (Gajanan, Monica, Sameer, and Anuradha, 2009), and Rhythmic® (Nitin, Gajbhiye, Vilasrao, Kisan and Jadhav, 2010) pumps are some of the Chronomodulating infusion pumps on the market. Portable pumps are typically modest in weight (300–500g) to allow for simple mobility and precise medication administration.

PULSATILE/CHRONOTHERAPEUTIC MEDICATION DELIVERY SYSTEM EVALUATION:

Tablet diameter and thickness: Tablet diameter and thickness were critical for Consistency in tablet size Vernier callipers were used to measure thickness and diameter (Parmar *et al.*, 2009; Reddy, Jyothsna, Saleem and Chetty, 2009). This test determines the hardness of a tablet that may chip or break while being kept, transported, or handled. Six tablets were chosen at random for this experiment, and their hardness was assessed using a Hardness tester from Monsanto. A material's hardness is generally measured in KG/CM2 metre (Gazzaniga, Iamartino, Maffione and Sangalli, 1994; Maroni *et al.*, 1999).

Friability: The Roche Friabilator's hardness and stability were tested in real time using the friability test.
The formula (Bhargavi, 2012; Kyatanwar, 2010) was used to determine the percent decrease in weight or friability (F).
F= (1-W/Wo)/100

F=friability, Initial weight (Wo), initial weight (Wo), initial weight (Wo), initial weight (W stands for final weight).

Weight variation: This test is performed to ensure that each pill's weight remains consistent and within the allowed range. This is accomplished by selecting the average weight is obtained by taking a random sample and weighing 20 pills.

Content uniformity: One such test is performed to verify whether the weight of the component in each individual tablet is within the Indian Pharmacopoeia's prescribed range. This test involves picking twenty pills at random, weighing them, and powdering them. In a 100ml volumetric flask, a powdered tablet was dissolved in 0.1 N HCl. It was diluted and the absorbance was measured against a blank of 0.1 N HCl at a certain wave length, yielding an estimate of the percent drug concentration.

Buoyancy determination (In-vitro): Several floating characteristics of the GFDDS are important because they influence the in vivo behaviour of drug delivery systems. However, due to the latter's complexity, no threshold value for the floating system to stay afloat under physiological circumstances appeared to exist.
Floating lag time: Average floating lag time is the time it takes for the tablet to emerge onto the surface of the liquid after being introduced to the dissolving medium Paddle rotation was 50 rpm at pH 1.2 at 37 ± 0.50C.

Total floating time is the time it takes for the tablet to float on the surface of the stomach fluid without pepsin at pH 1.2 at 37 ± 0.50C, and 50 rpm paddle rotation.

Dissolution studies in vitro: The USP XXIV dissolving equipment was used to conduct the tests (paddle rotating method-2). Where necessary, obtained the double beam UV spectrophotometer, samples were diluted with dissolving solution before being tested for the drug (Bhargavi, 2012).

Moisture absorption study: In a medium-filled container put in a horizontal shaker (100 ml of 0.1 N HCl, 37 ± 0.50C, 74 rpm, n=3), the present water absorption of pulsatile release tablets was assessed at specified time intervals. They were then weighed after being cleaned with tissue paper to remove surface wetness, and returned to the medium until the tablet coating broke. The following formula was used to compute.
The percent water uptake update: [(Wt.-Wo/Wo)] = percent water absorption 100,
In which at time t, Wt. weight is the weight of the pill and 'Wo' denotes the actual weight of a dry tablet.
The weight of a dry pill is represented as Wo.

Swelling index: Each pill was precisely weighed and stored in 50 mL of double distilled water. After 60 mins, the pills were correctly removed, measured precisely after wiping away any leftover water with filter paper.
SI= (Wet weight–Dry weight/Dry weight) 100 was used to compute the percentage swelling index (SI) (Kyatanwar, 2010).

Rupture test: A USP paddle device was used to perform a rupture test on coated tablets. All other parameters were identical to those used in the In-Vitro Dissolution Method. The amount of time it takes for the outer layer to dry is known as the lag time to break. The Rupture test was used to determine this (Arora and Ahuja, 2006).

CONCLUSION:

Understanding significance of circadian rhythms in GIT physiology and illness, as well as their impact of daily dosing on the following pharmacodynamics and pharmacokinetic parameters has become more and more recognised over the last three decades. The importance of these day-to-nights changes was not lacking from the point of view of medicine delivery and pharmaceutical researchers demonstrated in order to meet chronotherapeutic principles, significant creativity was used in the creation of delayed drug delivery devices. This results and possible benefits for the above-mentioned technologies in comparison to the traditional dosage forms, such as enhanced patient conformity, convenience, bioavailability, incompatible APIs and rapid start of action. Longer multiple release patterns that can be successfully used in chronotherapy can also be constructed. The Numerous medications' efficacy and toxicity may differ depending on when they're taken in respect to the 24-hour cycles of the circadian-clock biochemical, physiological, and behavioural processes, knowledge of rhythm and evidence of a 24-hour cycle in the risk of illness.

The primary advantage of this technique is that the drug is provided just when necessary. This reduces the possibility of medication resistance in conventional and long-term release formulations. Moreover, certain cancer medications are quite dangerous. These medications present substantial problems in both standard and continuous release therapies. The main objective of these formulations is to detect the circadian rhythm or enough signal to release the medicine. A further problem is the absence of adequate biodegradable, biologically consistent, and rhythmically sensitive rhythmical biomaterials for specific biomarkers. The goal of chronotherapy is to give optimal therapy by directing the medicine at the most appropriate time precisely to a particular place. The distribution of pulsating medicinal products will play a major part in biological cycle correlation by maintaining optimal concentrations in sick countries as required. The time of medication administration in disease therapy has such a major influence on treatment, chronopharmaceutics has emerged as a valuable technique for overcoming drug delivery associated problems and to improve patient compliance.

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CONFLICTS OF INTEREST:

There are no conflicts of interest among the authors.

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Table 1. shows the current market for chronotherapeutic medicines [13]

SI. No.	Disease	Medication	Brand	Manufacturer/Supplier
1	Heart and circulatory Problems	Bisoprolol Fumerate	Bisoprolol PM	Circ Pharma Ltd. Dublin, Ireland
2	Hypertension	Diltiazem HCl	Cardizem LA	Biovail Corporation, Mississauga, Canada.
3	Heart disorders	Famotidine	Pepcid pill (Tablet)	Gen Pharma (int.) Ltd. Maharastra, India.
4	Peptic ulcer	Famotidine	Gaster pill (tablet)	Schwarz Pharma, Monheim, Germany
5	Acute myocardial infarction (AMI)	Isosorbide Mononitrate	IS5MN PM	Circ Pharma Ltd. Dublin, Ireland
6	Hypertension and angina pectoris	Nifedipine	Procardia XL	Pfizer lbs. U. Spharmaceuticals Groups, New York.
7	Hypertension and angina	Nifedipine	ADALAT GITS	Bayer, Roseau, DM
8	Hypertension	Propranolol HCl	Innopran XL	Glaxosmith Kline, USA
9	Hyper lipidemia	Simvastatin	Zocor tablet	Cipla Mumbai
10	Chronic Asthma	Tolbuterol	Hokunalin tape	Manecho Co Ltd.Japan
11	Asthma	Theophylline	Uniphyl extended release tablet	Glenmark Generics Inc.USA
12	Congestive heart failure	Virapamil HCl	Covera HS	G.D.Searle, N.Y, U.S.A
13	Cardiovascular disease	Verapamil HCl	Verelan	Schwarz Phrama, Monhein, Germany

Table 2. In the subject of chronotherapy, there are a number of patents [13, 14]

SI. No.	Patents	Patent No.
1	An injection molded starch capsule for colonic delivery	US6228396
2	Beads	US5439689
3	Drug delivery composition for colonic delivery	US6200602
4	Hydrocolloid gums for colonic delivery	US6555136
5	Implantable electromechanically driven device	US4003379
6	Microchip drug delivery devices	US5797898
7	Oral pulse dose drug delivery system	US6605300
8	One -a-day controlled release Diltiazem HCl formulation	US5834023
9	Pulsatile release histamine H2 antagonist dosage form	US6663888
10	Pulsatile drug delivery of Doxylamine	US4842867
11	Pulsatile particles drug delivery system	US5260069
12	Pulsatile delivery of d-three-methyl phenidate	US6217904
13	Pulsatile delivery of Diltiazem hydrochloride	US6635277
14	Self-powered medication system	US4146029
15	Targeted drug delivery system	CA2305762
16	Unit dosages forms of Diltiazem hydrochloride	CA2215378

Table 3. Clinical manifestations and the circadian rhythm

Sl. No.	Ailment	Circadian Rhythmicity
1	Hay fever	Severe at wake up time (Morning)
2	Nocturnal Asthma	Exacerbation is possible throughout night.
3	Atrophic Arthritis	Evidence most frequent while sleeping.
4	Degenerative Arthritis	Symptoms are most acute in the middle and latter hours of the day.
5	Acute myocardial infarction	Early in the morning, chest discomfort and ECG abnormalities are most prevalent.
6	Congestive heart failure	The frequency is higher in the early hours of the morning.
7	Stroke	Strokes are more common in the morning.
8	Cardiac arrest	After waking up in the morning, the prevalence is greater.
9	Peptic ulcer	Severe throughout the late evening and early morning hours.

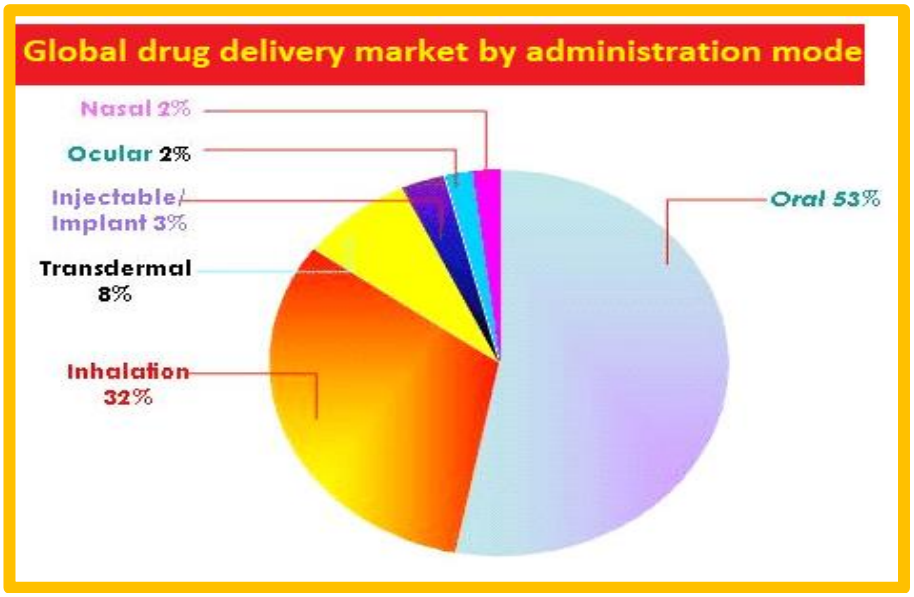

Figure 1. Administrative global medication delivery market.

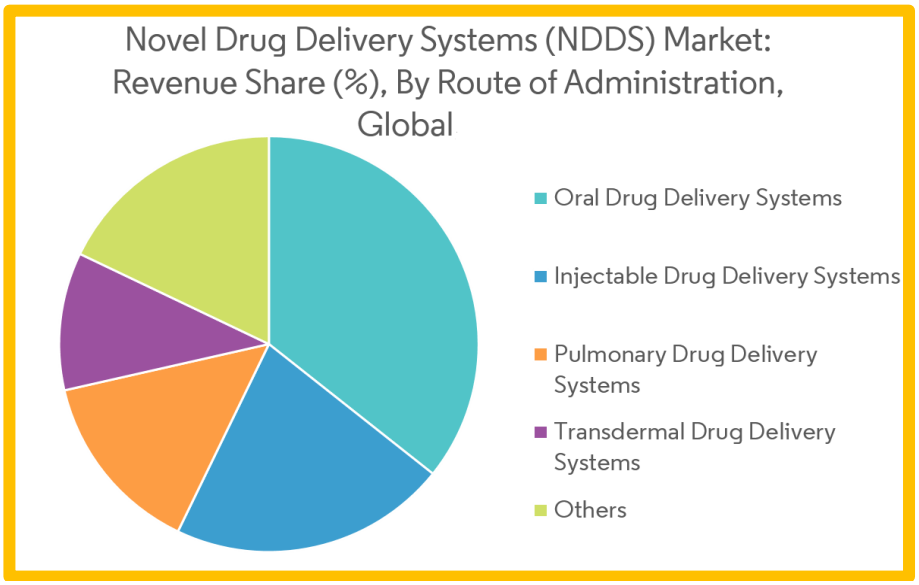

Figure 2. Global Novel Drug delivery market by administration mode.

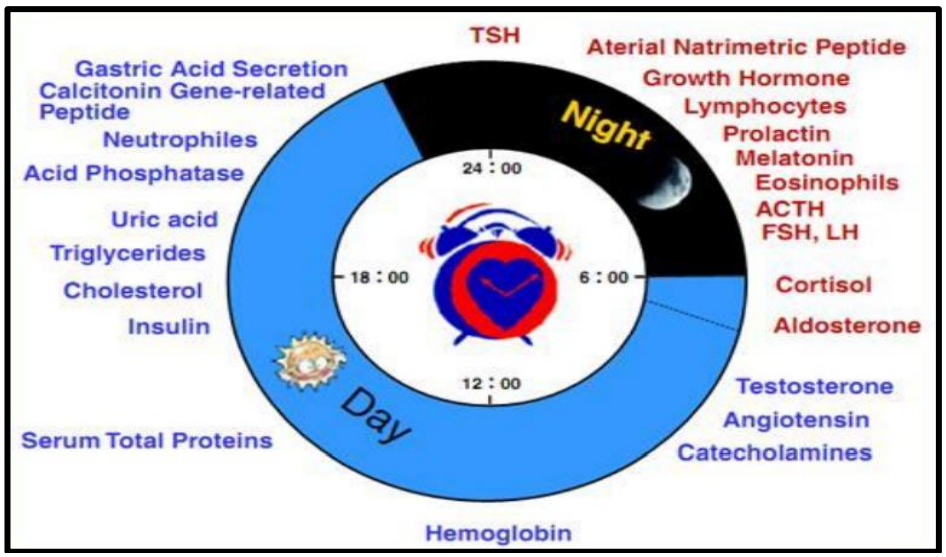

Figure 3. A 24-hour clock graphic depicting the peak time of selected human circadian rhythms is presented in relation to the day-night cycle.

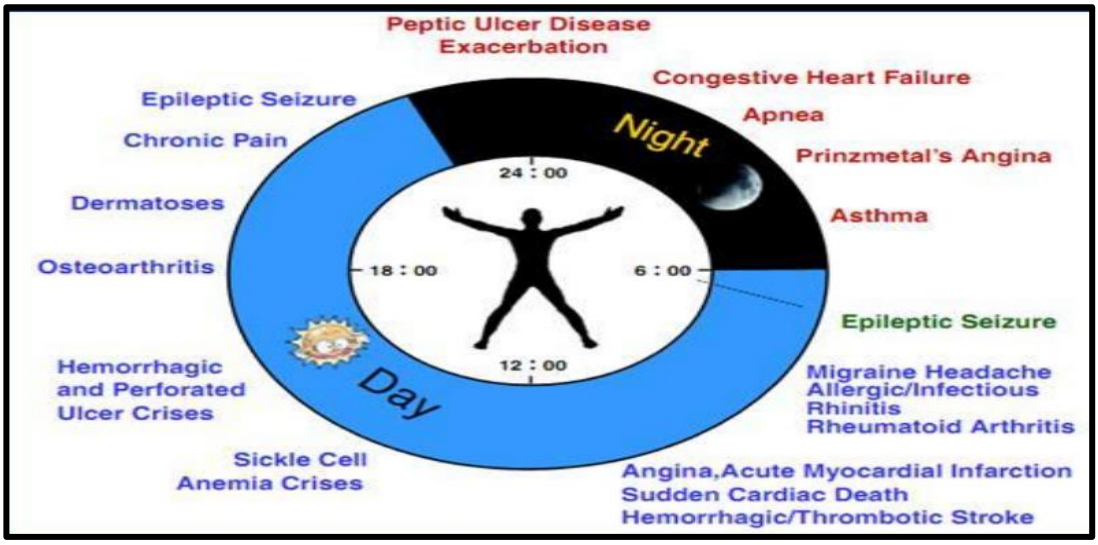

Figure 4. A 24-hour clock graphic depicting the chosen human circadian rhythms' peak time is presented in relation to the day-night cycle.

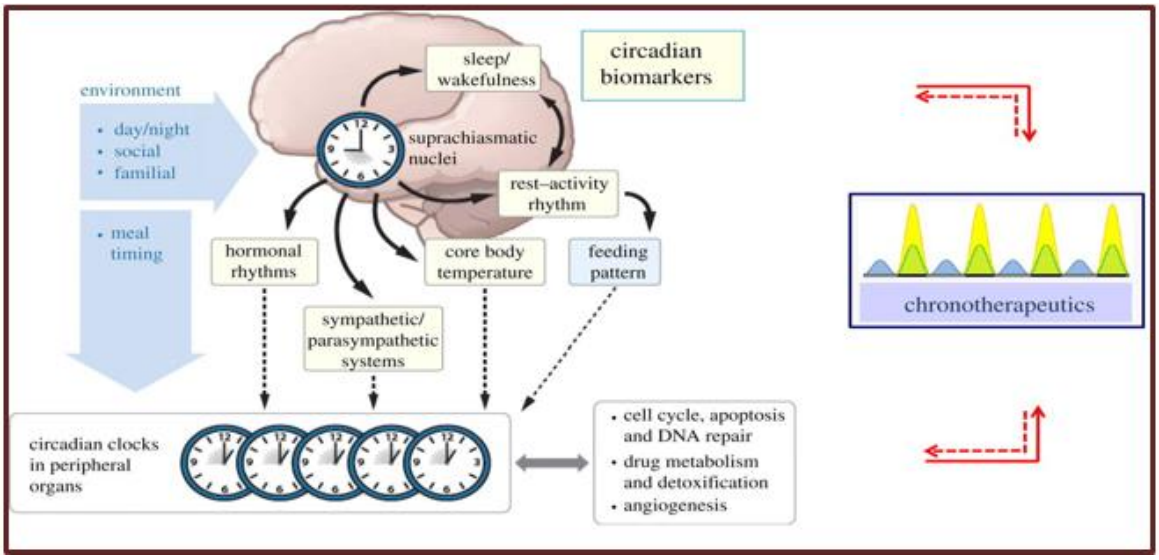

Figure 5. Chronotherapeutic – Circadian cycle of Human body

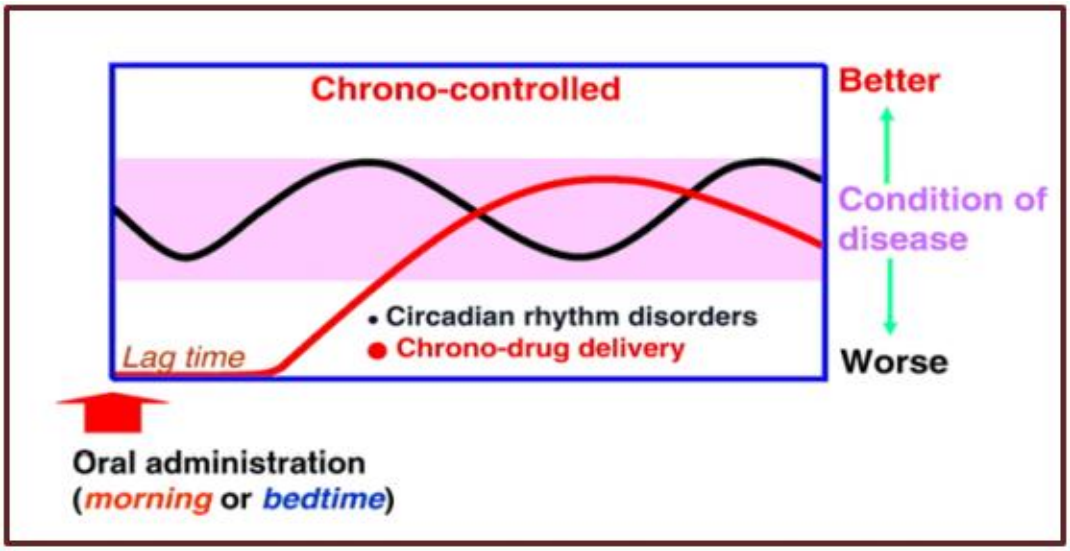

Figure 6. Chronotherapeutic formulations' drug release profiles

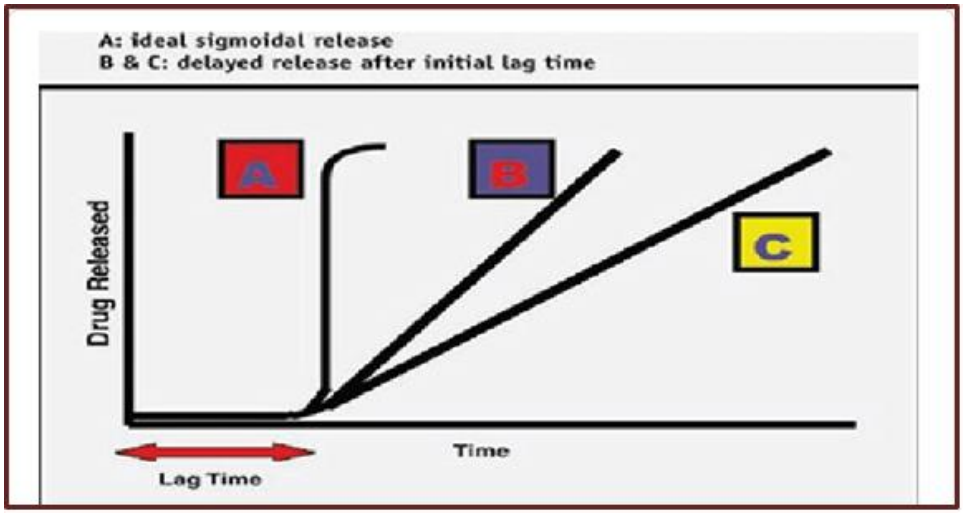

Figure 7. Chronotherapeutic formulations' drug release profile

Figure 8. Capsule-in-capsule technique Filling examples include liquid/liquid, liquid/semisolid, and liquid/beads.

Figure 9. Tablet-in-a-tablet technology

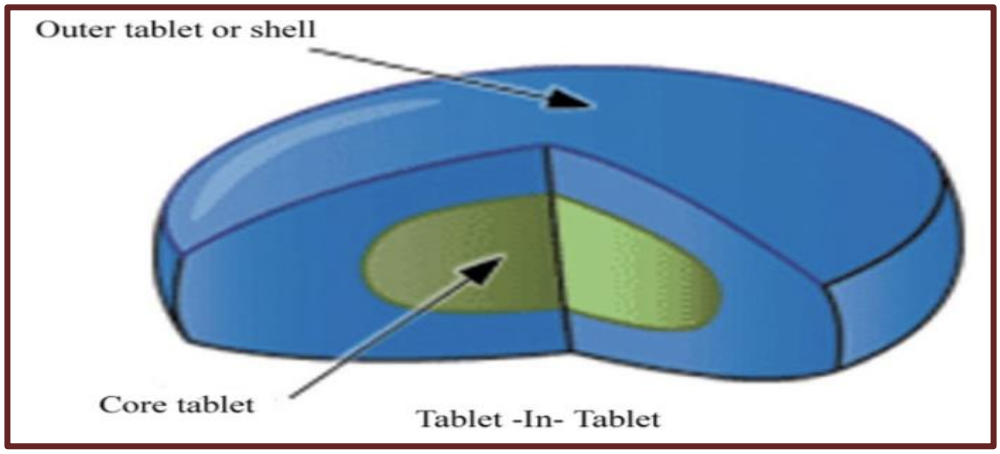

Figure 10. Technology that allows you to use your tablet as a tablet.

Figure 11. Capsule-in-a-tablet technology

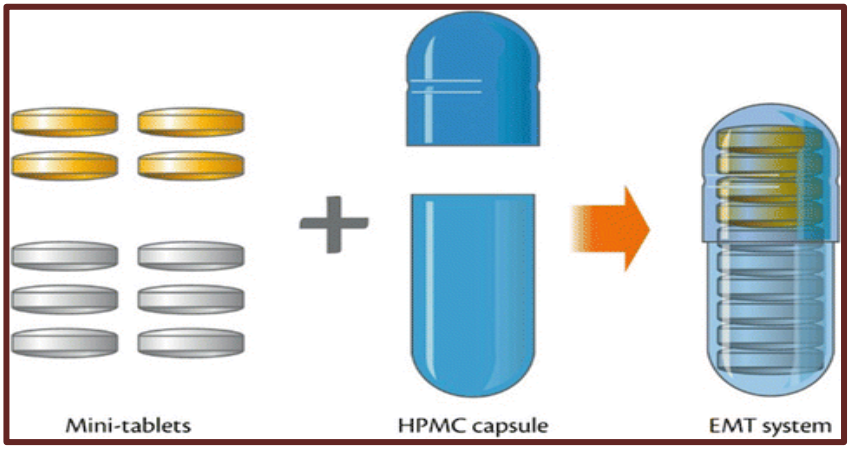

Figure 12. Capsule-in-tablet technology

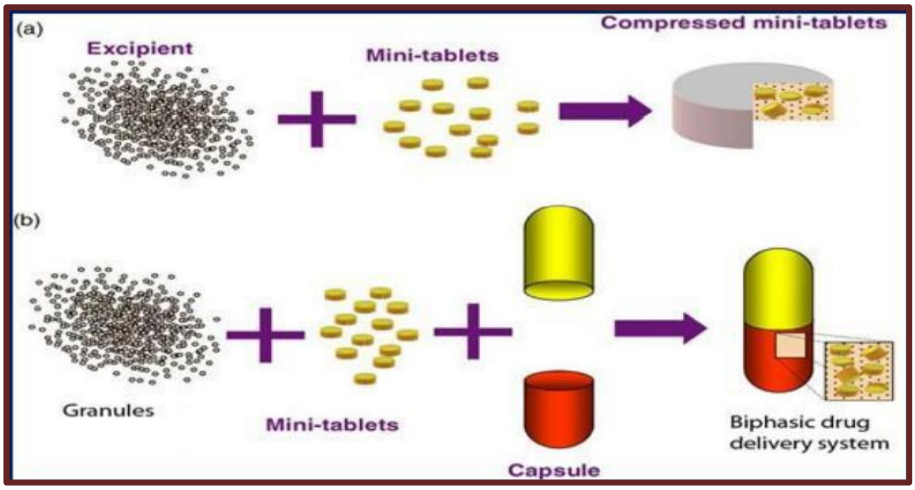

Figure 13. Granules and Tablets-in-a-Capsule Technology

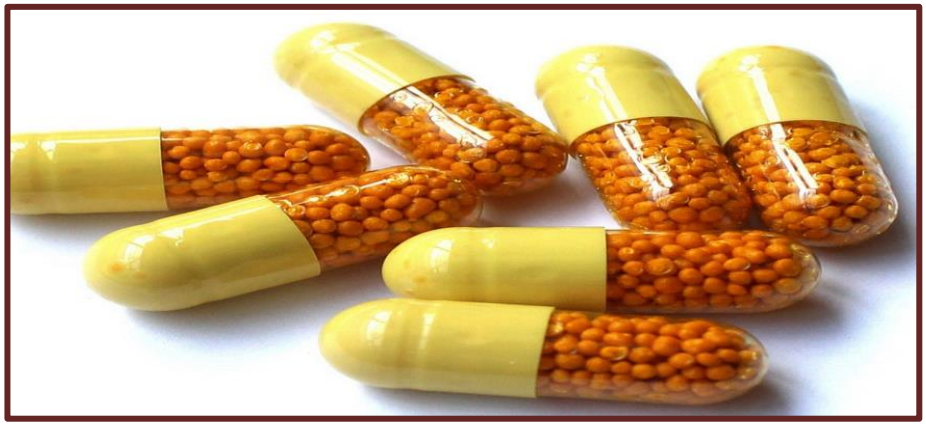

Figure 14. Granules & Tablets-in-capsule technology