

A REVIEW ON IMPACT OF CHRONOPHARMACEUTICS ON THE TREATMENT OF DISEASE

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ABSTRACT

A major objective of chronopharmaceutical science in the treatment of several diseases is to deliver the drug in higher concentration during the time of greatest need according to the circadian onset of the disease or syndrome. The physiology and biochemistry of a human being is not constant during the 24 hours, but it shows some variability in a predictable manner as defined by the timing of peak and trough of each of the body circadian processes and functions in relation to the time. There are quite a few approaches are in progress to control the drug to the desired degree to the clinical physiology of diseases with the aid of single unit and multiparticulate systems. The chronotherapy of a medication may be accomplished by the judicious timing of conventionally formulated tablets and capsules are of current interest.

Keywords: Chronotherapy; Circadian rhythm; Chronobiology; Chronotherapeutics.

INTRODUCTION[1-2]

The treatment of the disease to the fullest not only depends on the medicine but it also depends on the time and month of administration. The action of body defence system depends on the various factors like age, gender, genetics etc. Some people of the medical community recently studied about the role of biological rhythms against diseases. These rhythms of our body clocks are called as biological clocks.

Which change with the environment these biological clocks are also controlled by our genetic makeup these clocks are responsible for the changes in our body throughout the day like blood pressure, blood coagulation, blood flow and other functions of the body.

Circadian Rhythms[3,4,5]

As mentioned above human body consist of a 24 hour in-built cycle, these are called Circadian rhythms. Researchers had found out that these circadian rhythms are useful for the treatment of various patho-physiological conditions of human body.

There are some other rhythms 3, 4, 5 which affect our body such as

Ultradian: these are the cycles shorter than a day. Ex: 90 minutes sleep cycle

Circadian: This lasts for over 24 hours. Ex: sleeping and waking patterns.

Infradian: cycles longer than 24 hours. Ex: monthly menstruation

Seasonal: such as *seasonal affective disorder (SAD)*, this causes depression during the short days of winter in susceptible people.

Chronotherapy[6]

Chronotherapy refers to the treatment of biological rhythms coordination. It deals with Chronobiology. As nature has its seasons which changes rhythmatically, likewise every person's body has its own rhythms which are governed either by genetics or by the environmental changes. By determining these biological rhythms of a person one can increase or decrease the dose of the drug thereby avoiding the unwanted effects of the particular drug.

Chronobiology

Chronobiology is the science concerned with the biological mechanism of the diseases according to a time structure. "*Chrono*" pertains to time and "*biology*" pertains to the study, or science, of life.

Chronopharmacology

Chronopharmacology is the study of the manner & extent to which the kinetics & dynamics of medication directly affected by endogenous biological rhythm & also how the dosing time of medications affects biological timekeeping & features (period, level, amplitude & phase) of biological rhythms. Chronopharmacology includes chronopharmacotherapy, Chronopharmacokinetics & Chronotoxicity.

It is the investigative science that elucidates the biological rhythm dependencies of medication. It is useful to solve problems of drug optimization i.e. to enhance the desired efficiency or to reduce its undesired effects. So Chronopharmacological approaches involve a lesser risk of errors and or false information than the conventional homeostatic approach.

Drug Chronotherapy

It is not the usage of the novel medication but it's the use of the old drugs in a different way. The main aim of this drug chronotherapy is to use the old drug differently which gains more results. It includes either revising the drugs profile and reformulating it in such a way that it got the delayed release into the blood stream or using the additional pumps which help in the delayed release. Such changes are made to get the enormous benefits.

Ref:-Bar-Shalom D., Wilson, CG., Washington N., 2009. Chronotherapy using EgaletTM technology. In: Youan, B.-B.C. (Ed.), Chronopharmaceutics. John Wiley & Sons, New Jersey, pp. 165-173.

"Sensitivity to chemotherapeutic agents depends on the specific molecular state of the circadian clock"

Advantages of Chronotherapy[7]

- Chronotherapy is drug-free
- Chronotherapy is more effective when a person sleeps for several hours.
- While Chronotherapy patients often fall asleep this improves their condition and confidence as well.
- Chronotherapy is different from other treatments because it got the beginning, middle, and an end. So one can predict easily the point at which it will work.
- It gives you a new schedule like getting up and sleeping early which will be quite unusual for some days but it will give u a period to adjust psychologically.

Rf 7. Staels B., when the clock stops ticking, metabolic syndrome explodes, Nat. Med. 12: 54-55 (2006)

Disadvantages of Chronotherapy[8]

- It develops a non 24 hours sleep wake syndrome after the treatment as the person sleeps for over 24 hours during the treatment. It's not quite common but the degree of risk is not known.
- Person may also be sleep deprived sometimes.
- Person become less productive during chronotherapy and staying awake till the other schedule will be bit uncomfortable.
- You will have to take some time off from your busy normal schedule as its time taking therapy.
- Medical supervision is mandatory for this therapy. And regular consulting of sleep speacitists is recommended.
- One has to keep himself awake till the next sleep schedule. so he have to get himself busy so that he stay awake till the other schedule.
- Person going through the therapy may feel unusually hot or cold sometimes. have to consult the doctor regularly to avoid side effects

Ref 8. Smolensky MH., D'Alonzo GE. Medicalchronobiology: concepts and applications. Am Rev Respir Dis, 147(6 Pt 2): S2-19 (1993)

Diseases and Chronotherapeutics

The potential benefits of chronotherapeutics have been demonstrated in the management of a number of diseases (Fig:1). 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.

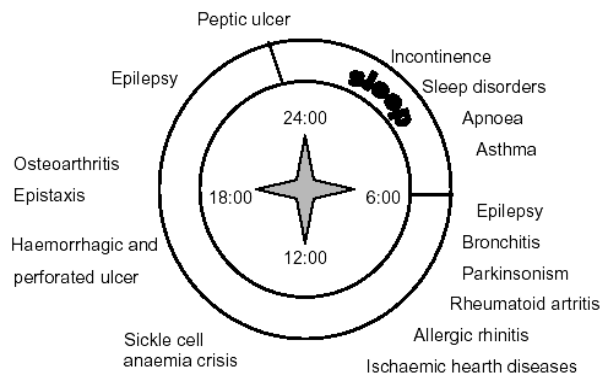


Fig. 1: Diseases known to display circadian rhythm

Circadian rhythms and their implications[9-10]

Circadian rhythms are self-sustaining, endogenous oscillation, exhibiting periodicities of about one day or 24 hrs. Normally, circadian rhythms are synchronized according to the body's pacemaker clock, located in the suprachiasmic nucleus of the hypothalamus. The physiology and biochemistry of human being is not constant during the 24 hrs, but variable in a predictable manner as defined by the timing of the peak and through of each of the body's circadian processes and functions. The peak in the rhythms of basal gastric and secretion, white blood cells (WBC), lymphocytes, prolactin, melatonin, eosinophils, adrenal corticotrophic hormone (ACTH), follicle stimulating hormone (FSH), and leuteinizing hormone (LH), is manifested at specific times during the nocturnal sleep span. The peak in serum cortisol, aldosterone, testosterone plus platelet adhesiveness and blood viscosity follows later during the initial hours of diurnal activity. Hematocrit is the greatest and airway caliber the best around the middle and afternoon hours, platelet numbers and uric acid peak(Fig:2 and 3)

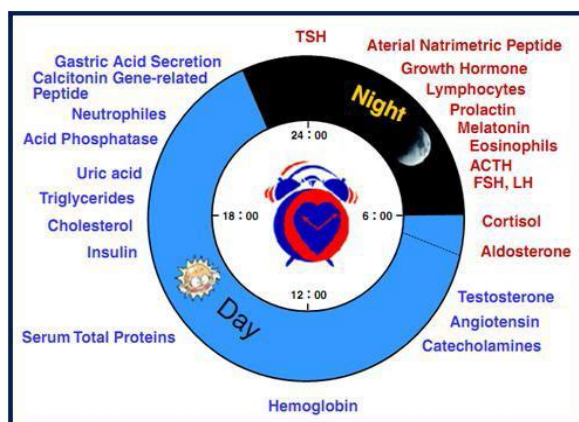


Fig. 2: A 24-hrs clock diagram of the peak time of selected human circadian rhythms with reference to the day-night cycle

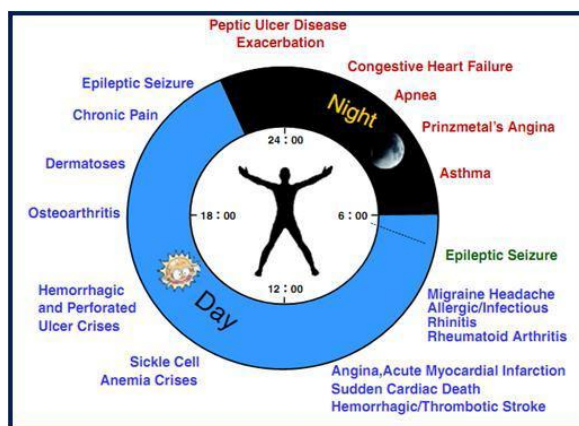


Fig. 3: A 24-hrs clock diagram of the peak time of selected human circadian rhythms with reference to the day-night cycle

Table 1: Disease Influenced by Chronotherapy

| S. No. | Selected Diseases | Influenced by Chronotherapy |
|--------|-------------------|---|
| 1 | Cardiovascular | Hypertension, angina, myocardial infarction |
| 2 | Inflammatory | Rheumatoid arthritis, related disorders |
| 3 | Neoplastic | Various forms of cancer |
| 4 | Gastrointestinal | Peptic ulcer disease |
| 5 | Respiratory | Allergic rhinitis, asthma |

Pulsatile drug delivery systems[11-12]

It is the one type of drug delivery system, where the delivery device is capable of releasing drug after predetermined time delay (i.e. lag time) known as pulsatile drug delivery system (Fig:5). Pulsatile drug delivery systems are gaining lot of interest and attention these days.

These systems have a peculiar mechanism of delivering the drug rapidly and completely after a "lag time" i.e., a period of "no drug release." Though most delivery systems are designed for constant drug release over a prolonged period of time, pulsatile delivery systems are characterized by a programmed drug release, as constant blood levels of a drug may not always be desirable.

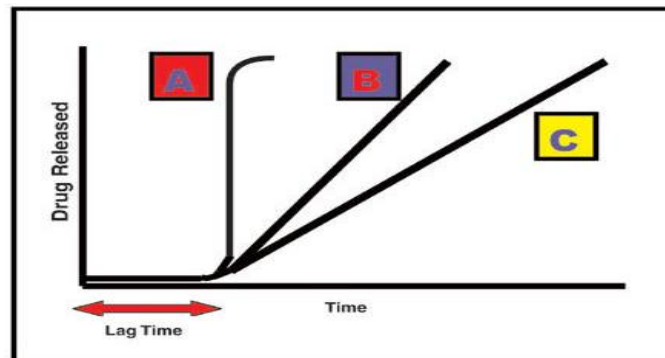


Fig. 5: Drug release profiles from pulsatile drug delivery system

A = Release of drug as a "pulse" after a lag time, B = Delivering the drug rapidly and completely after a "lag time" and C = Constant drug release over a prolonged period of time after a "lag time".

Classification of Pulsatile Drug Delivery Systems

Pulsatile drug delivery system can be broadly classified into three classes;

- I. Time controlled pulsatile drug delivery
- II. Stimuli induced pulsatile drug delivery
- III. Externally regulated pulsatile drug delivery

I. Time controlled pulsatile drug delivery

A. Single unit pulsatile systems

1. Capsule based systems E.g. Pulisincap system

2. Capsular system based on Osmosis

- a. 'PORT' System
- b. System based on expandable orifice
- c. Delivery by series of stops.
- d. Pulsatile delivery by solubility modulation

3. Pulsatile system with Erodible or soluble barrier coatings

- a. The chronotropic system
- b. 'TIME CLOCK' System
- c. Compressed tablets
- d. Multilayered Tablets

4. Pulsatile system with rupturable coating

B. Multiparticulate / Multiple unit systems

1. Pulsatile system with rupturable coating

E.g. Time -controlled Explosion system (TCES)

2. Osmotic based rupturable coating system

E.g. Permeability controlled system

3. Pulsatile delivery by change in membrane permeability

Types of Modified release drug delivery systems

Extended release dosage forms: A dosage that allows at least a twofold reduction in dosage frequency as compared to that drug presented as an immediate release form.

Example: Control release, sustained release.

Sustained release: It includes any drug delivery system that achieves slow release of drugs over an extended period of time not particularly at a predetermined rate. Sustained release dosage forms to complement the pharmaceutical activity of the medicament in order to achieve better selectivity and longer duration of action. Sustained release products are helpful to reduce the dose frequency and side effects of drugs and improve patient convenience.

Controlled release: It includes any drug delivery system from which the drug is delivered at a pre-determined rate over a long period.

Delayed release dosage forms: A dosage form releases a discrete portion of drug at a time or times other than promptly after administration although one portion may be released immediately after administration. Ex. Enteric coated dosage forms.

Targeted release dosage forms: A Dosage forms that release drug at /or near the intended physiological site of action. Targeted release dosage forms may have extended release characteristics.

Repeat action dosage forms

It is a type of modified release drug product that is designed to release one dose or drug initially followed by a second dose of drug at a later time.

Prolonged action dosage forms

It is designed to release drug slowly to provide a continuous supply of drug over an extended period.

Various group of drugs and its Chronotherapies

Cardiovascular functions such as heart rate and blood pressure show 24 h variation. The incidence of cardiovascular disease such as acute myocardial infarction, strokes and arrhythmia also exhibits clear diurnal oscillation since most of these disorders can induce fatal or severe outcomes. It is important to elucidate the precise mechanism of the onset of these diseases [14]. The dependence of our body functions in the certain diseased state depends on the circadian rhythm [13].

| Class of drug | Examples |
|--|---|
| Cardiovascular drugs | Verapamil, Propranolol, Diltiazem, Nifedipine, Enalapril |
| Antiasthmatic drugs | Methylprednisolone, Prednisolone, Albuterol, Terbutaline, Theophylline |
| Anticancer drugs | Cisplatin, Oxaliplatin, Doxorubicin, 5-Fluorouracil, Folinic acid, Methotrexate, Mercaptopurine |
| Non-steroidal anti-inflammatory Agents | Ibuprofen, Ketoprofen, Indomethacin, Tenoxicam, Acetylsalicylic acid |
| Anti-ulcer agents | Cimetidine, Ranitidine, Famotidine, Pirenzepine, Omeprazole |
| Anticholesterolemic agents | Simvastatin, Lovastatin |
| Others | Vitamin D3, Diazepam, Haloperidol |

Common onset time of cardiovascular system

| Disease | Common onset of action |
|--------------------------------------|------------------------|
| Atrial fibrillation | Morning/ night |
| Ventricular tachycardia/fibrillation | Morning |
| Acute coronary syndrome | Early Morning |
| Pulmonary embolism | Early Morning |
| Cerebral infraction | Morning |
| Subarachnoid haemorrhage | Day time |

Marketed Technologies

There are various types of pharmaceutical technologies used for the preparation of drugs for chronotherapy [15,16,17].

Technologies used for the parenteral route in chronotherapy include the use of chrono modulating infusion pumps (Panomat™) and controlled release microchip strategies. And technologies used for oral administration are Ceform™. There are other methods like three dimensional printing (3dp) which includes usage of erodible polymers for the controlled release and changing the physicochemical properties of the drug. The most recent was the floating pulsatile system using high internal phase emulsion based porous material for Chronotherapy.

Low density floating multiparticulate pulsed release dosage forms are also available [18]. The desired release of ranitidine hydrochloride from the tablet with a coating successfully explains the combined principles of floating and pulsatile used in chronotherapy [19]. Many marketed products in the form of transdermal drug delivery system having chronopharmaceutical applications are available [20]; some of them are ChronoDose™, crystal reservoir [21] and thermo responsive membrane systems [22].

For rectal route-aminophylline delivery system was reported and many novel chronopharmaceuticals has been used for this purpose [23].

Chronotherapy in various Diseases [24]

Like our body has an inbuilt 24 hour cycle in the same way some diseases will also follow the circadian patterns, chronotherapy is very useful in treating such type of diseases by adjusting the dose and the time of drug administration according to the circadian

rhythms. The following is the list of some diseases which can be more significantly cured by chronotherapy

- Hypertension
- Bronchial asthma
- Peptic ulcers
- Myocardial infraction
- Arthritis
- Cerebrovascular accidents
- Hypercholesterolemia

Hypertension

Heart rate and blood pressure will be high at the time we wake up in the morning i.e. A.M and it will begin to decrease in the afternoon and it reaches to the minimum at midnight [24,25]. But the blood pressure is comparatively high in case of hypertension patients upon awakening. This physiological condition is described as morning surge or A.M. surge [26]. The systolic blood pressure rises up to 3mmHg/hour for 4-6 hours after getting up called post-awakening and the diastolic myocardial ischemia takes the lead as well in the morning [27,28].

Cerebrovascular accidents

Cerebrovascular accidents are more common in the morning hours between 10A.M to 12 noon and it will decrease considerably from noon to midnight. The main aim of chronotherapy in these conditions is to deliver the drug in the higher doses in morning and little lower dose at noon and in midnight times. Various ACE inhibitors like Atenolol, Nifedipine and amlodipine are more effective when administered during night [29].

Bronchial asthma

Asthma have the more circadian variations when compared to the other diseases. so various chronotherapy studies have been undertaken and one of the study shows that the intake of the time released theophylline i.e. theo24 at 3 P.M achieved a therapeutic dose at night and the toxic levels during the day was avoided [30].

Arthritis

According to the chronotherapeutic studies the more desirable results has been achieved for rheumatoid arthritis when the dose was given in the evening. Blood pressure also rises up to 2mmHg/hour [31].

Myocardial Infarction

The release of the catecholamine's, cortisol, increase in platelet aggregation and the vascular tone will be high in the morning. These are the main reasons for the outburst of the myocardial infarction in the morning with 34% events taking place from 6 A.M till noon. Acute cardiac arrest and transient Cyclooxygenase inhibitor-2 will relieve the pain effectively when taken in the morning [32]

Peptic Ulcer Disease

A histamine antagonist when given at night shows the better result unlike when given at regular intervals around the clock. This is because the more acid secretion, more pain and perforation of gastric and duodenal ulcers are more subjective at night rather than in day time [33].

Hypercholesterolemia

The morning doses were recommended at first for HMG CO-A inhibitors but after the discovery of circadian rhythms the profile was re-evaluated and the evening doses were recommended as the cholesterol intake and cholesterol biosynthesis is more in the evening hours even in fasting state [34]

Regulatory Concern

Although the chronopharmaceutical products are more useful over the normal products they are some regulatory problems, this is

because the MR formulations have a unique challenges from the normal formulations and manufacturing. They require a more precise drug profile and characterization for the controlled release delivery[35]

Chronotherapeutic Drug Delivery Systems

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[36-38]. 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[39]. Various technologies to develop timecontrolled peroral drug delivery systems have been extensively studied in recent decades. Some of these systems are discussed in the following subsections.

Enteric-coated systems[40]:

Enteric coatings have traditionally been used to prevent the release of a drug in the stomach (see Fig 6). Enteric coatings are pH sensitive and drug is released when pH is raised above 5 in the intestinal fluid. These formulations can be utilised 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.

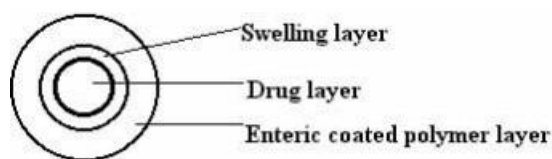


Fig. 6: Schematic representation of enteric coated system

Layered systems[41-42]

These are one or two impermeable or semi permeable polymeric coatings (films or compressed) applied on both sides of the core. To allow biphasic drug release, a three-layer tablet system was developed[36].

The two layers both contain a drug dose. The outer drug layer contains the immediately available dose of drug. An intermediate layer, made of swellable 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[42]. 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.

Time-controlled explosion systems (TES)[43-44]

These 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 semi permeable 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.

Sigmoidal release systems (SRS)[45-46]

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[47]

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 (Fig:7).

The major drawbacks of the technique are that relatively large amounts of coating materials are needed and it is difficult to position the cores correctly for the coating process.

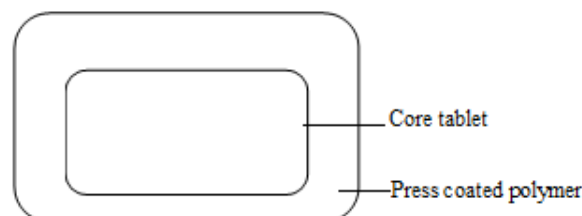


Fig. 7: Schematic representation of a press-coated system

In recent years, various controlled release, especially time-controlled release, drug delivery systems based on compression coating technology have been studied. Most of such formulations release drug after a lag phase, followed by a rapid dissolution of the core. Conte *et al* have developed a press-coated device in which the inner core contains the drug and the outer coat is made of different types of polymers. The outer barrier, which controls drug release, can be either swellable or erodible. Lag times can be varied by changing the barrier formulation or the coating thickness Matsuo *et al* have developed a diltiazem hydrochloride formulation intended for use in the treatment of time-related symptoms of ischemic heart disease and hypertension [48]. The tablet consists of a core, which contains the drug, and a coat formed by compressing hydroxyethylcellulose. Diltiazem is rapidly released after a delay of several hours. Marvola *et al* have developed a press-coated tablet formulation in which most of the total amount of drug is in the tablet core [49]. Hydrophilic polymers such as hydroxypropyl methylcellulose and sodium alginate have been used in the coat to control drug release as illustrated in (Fig. 7). The extent of bioavailability of furosemide, ibuprofen and salbutamol sulphate from the system developed has been found to be satisfactory[50-53].

Other systems[54-58]

Elementary osmotic pumps can be useful for delivering drugs based on chronotherapeutic requirements. One type of elementary osmotic pump can deliver salbutamol, initially at a constant delivery rate, then as a final pulse dose [54]. Such a system could deliver a dose during a nocturnal asthma attack. The first chronotherapeutic system for the treatment of hypertension and angina pectoris, a controlled onset extended-release (COER-24) verapamil formulation, was developed and registered in USA [55,56].

This formulation was tailored to the circadian rhythm of blood pressure and heart rate to better cover early morning symptoms of cardiovascular diseases. COER-24 is an osmotically controlled single unit system. Around the device, which consists of a drug layer and a push layer, are two membranes.

The first is a semi-permeable insoluble membrane while the second is a release delaying hydrophilic polymer coat.

Gastrointestinal fluid penetrates the semi-permeable membrane, and as it enters the drug layer and push layer via the hydrated coat (within 4 to 5 hours), the push layer expands, pressing against the drug layer and causing drug release at a constant rate for 18 hours. If taken at bedtime, the system provides optimal drug concentration when the patient wakes up and during day time. Pulsinocapo is a delivery system which releases drug contents at a predetermined time or at a specific site within the gastrointestinal tract[57]. Each capsule is composed of a water insoluble body and a water soluble cap, and also contains the drug dose which is sealed with a hydrogel plug. At a predetermined time after ingestion, the swollen plug is ejected from the capsule and the drug is then released into the small intestine or colon. The dimension of the plug and its position in the capsule can be varied and the system delivers drug at exactly the programmed time, 1 to 10 hours after drug administration, to various regions of the gut[58].

CONCLUSION

In order to achieve the development of chronopharmaceutical dosage forms, currently, the site specific and time controlled release preparation with a designated initial lag time phase without drug release followed by a rapid and sustained phase release system of the diseased condition is wide important phenomenon to consider.

Drugs used for ideal treatment of disease should be administered only at the required time to maintain the therapeutic blood levels. Hence such a design can be used as a drug delivery system for chronopharmacotherapy. Success of the In vitro drug release studies recommends the product for further in vivo studies, which may improve patient compliance to the greater extent.

Research in chronopharmacology has demonstrated the importance of biological rhythms in drug therapy and this has led to a new approach to the development of drug delivery systems. Optimal clinical outcome cannot be achieved if drug plasma concentrations are constant. If symptoms of a disease display circadian variation, drug release should also vary over time. Different technologies have been applied to develop time-controlled, pulsed, triggered and programmed drug delivery devices in recent years. Since it is seems that timing of drug administration in disease therapy has significant impact upon treatment success, chronotherapeutic remains an important area for continuing research.

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