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Review on Chronotherapy: A Novel Drug Delivery System

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ABSTRACT:

The goal in drug delivery research is to meet therapeutic needs relating to particular pathological conditions by developing new formulations. Research in the chronopharmacological field has demonstrated the importance of biological rhythms in drug therapy, and this has brought a new approach to the development of oral drug delivery systems. Chronotherapeutics is the discipline concerned with the delivery of drugs according to the intrinsic activities of a disease over a certain period of time because the biochemicals, physiological and pathological variations over a 24 h period in humans have been occurred. Chronotherapeutics deals with the medical treatment according to the human daily working cycle that corresponds to a person's daily, monthly, seasonal or yearly biological clock or in order to maximize the health benefits and minimize the adverse effects. The main goal of chronotherapeutics is to match the timing of treatment with the intrinsic timing of illness. Optimum therapy is given when the right amount of drug is delivered to the correct target organ at the most appropriate time. If symptoms of a disease are varied the circadian rhythms also varied the drug release. In the treatment of many diseases chronotherapeutics drug delivery offers a new approach in the pharmacologic interventions design for the effective treatment in the different types of diseases. The "chronotherapeutics" term is mainly new in the field of drug delivery and in the treatment method. It is defined as the widespread term in which disease follow the circadian rhythm which undergoes the metabolic changes.

KEY WORDS: Chronotherapeutics, biological rhythms, metabolic changes, circadian rhythms

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INTRODUCTION:

Various diseases like asthma, hypertension, ischemic heart disease and arthritis show circadian variation that demand time-scheduled drug release for effective drug action, for example, inflammations associated with morning stiffness, asthma, and heart attack in early hours of the day. Congestive heart failure and myocardial infarction are manifested more frequently during the night or early in the morning. Blood pressure which arises notably just waking up is usually responsible for these attacks. However, for such diseases, conventional drug delivery systems are inappropriate for the delivery of drug, as they cannot be administered just before the symptoms are worsened, because during this time, the patients are asleep. To overcome these problems of conventional dosage forms, the present study attempts to design and evaluate a chronomodulated drug delivery system [1].

Chronomodulated drug delivery system (CHDDS) [2, 3]:

- ✓ Chronotherapeutics is defined as the method in which drug availability is matched with the rhythms of the disease according to the time structure which results in the maximum therapeutic effects and less adverse effects. For understanding concept of chronotherapeutics, it is necessary to understand following concepts:
- ✓ Chronobiology: It is the science concerned with the biological mechanism of the diseases according to a time
- ✓ Chronopharmacology: Chronopharmacology is the science concerned with the variations in the pharmacological actions of various drugs over a period of time.
- ✓ Chronopharmacokinetics: Chronopharmacokinetics involves study of changes in drug absorption, distribution, metabolism and excretion. Pharmacokinetic parameters, which are conventionally considered to be constant in time, are influenced by different physiological functions displaying circadian rhythm. Circadian changes in gastric acids secretion, gastrointestinal motility, gastrointestinal blood flow, drug protein binding, liver enzyme activity, renal blood flow and urinary pH can play role in time dependent variation of drug plasma concentrations.
- ✓ Chronotherapy: Co-ordination of biological rhythms and medical treatment is called chronotherapy.
- ✓ Chronotherapeutics: Chronotherapeutics is the discipline concerned with the delivery of drugs according to inherent activities of a disease over a certain period of time. It is becoming increasingly more evident that the specific time that patients take their medication may be even more significant than was recognized in the past. Chronopharmaceutics consist of two words chronobiology and pharmaceutics. Chronobiology is the study of biological rhythms and their mechanisms.

There are three types of mechanical rhythms in our body.

1. Circadian: This word comes from Latin word circa means about and dies means day.

2. Ultradian: Oscillation of shorter duration is termed as ultradian (more than one cycle per 24h) less than one cycle per day.

3. Infradian: Oscillations that is longer than 24 h (less than one cycle per day).

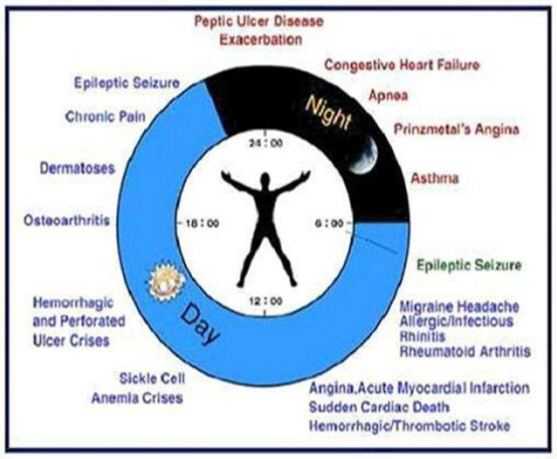

Figure 1: A 24-hrs clock diagram of the peak time selected human circadian rhythms with reference to the day-night cycle

Need of Chronomodulated drug delivery system:

1. Body function that follow circadian rhythms.
2. When circadian rhythm is altered by the hormone such as rennin, aldosterone and cortisol etc. level in blood.
3. When rhythmic variation seen in acid secretion in stomach, gastric emptying, and gastrointestinal blood transfusion.
4. Disease like bronchial asthma, myocardial infarction, angina pectoris, rheumatic disease, ulcer, and hypertension display time dependence.
5. The lag time is essential for the drugs that undergo degradation in gastric acidic medium.
6. It is possible to deliver the drugs to the distal part of GIT like colon targeting with pulsatile drug delivery.
7. Drugs that undergo extensive first-pass metabolism are administered successfully as chronomodulated drug delivery systems.

Advantages of Chronomodulated drug delivery system:

1. Due to its ability to release drug in a burst manner, it increases absorption and bioavailability at target site of absorption.
2. Limit risk of mucosal irritation.
3. Loss of drug by extensive first pass metabolism is prevented.
4. Chronotherapy, programmed delayed release provides optimal treatment of diseases.
5. No risk of dose dumping.
6. Decreases drug interaction due to lower cytochromeP450 iso-enzymes.
7. Avoidance of undesirable side effects.
8. Improved patient compliance.

9. Flexibility in design.

Disadvantage of Chronomodulated drug delivery system:

1. Low drug loading capacity and incomplete release of drug.
2. Higher cost of production.
3. Large number of process variables.
4. Lack of manufacturing reproducibility and efficacy.
5. Batch manufacturing process.
6. Unpredictable IVIVC.
7. Need of advanced technology.

Examples of some of the diseases are shown in Table:

Table 1: Diseases requiring Chronomodulated Drug Delivery

Disease	Chronological behaviour	Drugs used
Peptic ulcer	Acid secretion is high in the afternoon and at night	H_2 blockers
Asthma	Precipitation of attacks during night or at early morning hour	β2agonist, Antihistaminic
Cardiovascular diseases	BP is at its lowest during the sleep cycle and rises steeply during the early morning awakening period	Nitroglycerin calcium channel blockers, ACE inhibitors etc
Arthritis	Pain in the morning and more pain at night	NSAIDs, Glucocorticoids
Diabetes mellitus	Increase in the blood sugar level after meal	Sulfonylurea, Insulin, Biguanide
Attention deficit syndrome	Increase in DOPA level in afternoon deficit syndrome	Methylphenidate
Hyper cholesterolemia	Cholesterol synthesis is generally higher during night than during day time	HMG CoA, reductase inhibitors

Formulation of chronomodulated drug delivery system [4]:

1. **Capsule-based systems:**
   a. Capsular system with a swellable plug
   b. Capsular system based on osmosis
2. **Tablet-based systems:**
   a. System with erodible coatings
   b. System with rupturable barrier coatings

1. Capsule-based systems:

a. Capsular system with a swellable plug:

The system comprises of gelatin capsule body coated with ethyl cellulose or formalin vapours to render it impermeable. The moulded hydrogel plug consisting of insoluble but permeable and swellable polymers (e.g. polymethacrylates) was used to seal the drug contents into the capsule body. In the presence of fluids, the hydrogel plug developed a frustoconical shape and slowly pulled itself out of capsule at a controlled rate independent of nature and pH of the medium giving a rapid bulk release. The lag time was governed by various factors such as length of plug, its insertion distance, and tightness of fit.

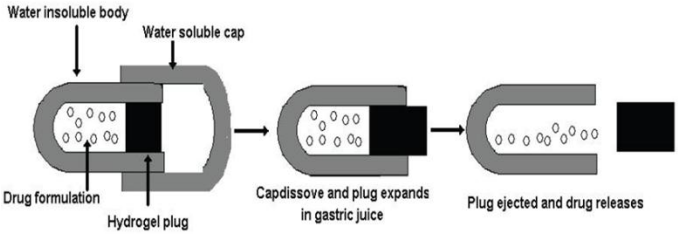

Fig. No. 1: Schematic diagram of Capsule shaped system provided with release controlling plug

b. Capsular system based on osmosis:

Osmotic system is a capsule enclosed with a semipermeable membrane. Inside the capsule are an insoluble plug, osmotically active agent and therapeutically active agent. When this capsule comes in contact with the body fluid, the semipermeable membrane allows the entry of water, which causes the osmotic pressure to develop and the insoluble plug is expelled due to pressure after some lag time. The lag time can be governed by modifying the thickness of the semipermeable layer.

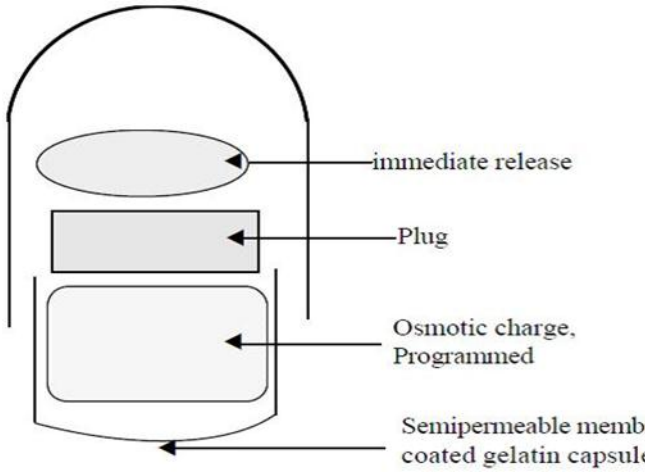

Figure 2: Osmotic Pump

2. Tablet-based systems:

a. System with erodible coatings:

Most of the reservoir devices coated with a barrier layer. This barrier erodes or dissolves after a specific lag period, and the drug is subsequently released. The lag time depends on the thickness of the coating layer. The core tablet is coated with aqueous dispersion of a hydrophobic-surfactant layer. The aqueous dispersion coat is followed by a water soluble coat to improve adhesion to the core coat. As the coated tablet comes in contact with aqueous environment, the film rehydrates and redisperses after a certain time lag proportional to the thickness of coat.

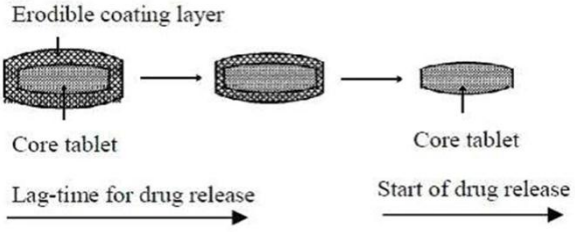

Fig. No. 3: Schematic diagram of Delivery systems with erodible coating layers

b. System with rupturable barrier coatings:

These systems are based upon a reservoir system coated with a rupturable membrane. The outer membrane ruptures due to the pressure developed by effervescent agents or swelling agents. The system consists of a core, swelling agent and a coating film. Coating film dissolves and creates pores. Penetration of water molecules from the surroundings through the pores into the core causes expansion of the swelling agent, bursting the film and releasing the drug with a single pulse. Manipulation of the thickness of coating film can control the lag time.

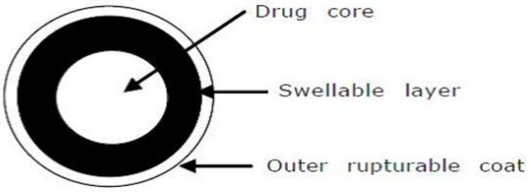

Fig. No. 4: Schematic diagram of Deliver systems with rupturable coating layer

Major Advances in Oral Pulsatile Drug Delivery:

1. CODAS Technology: CODAS stands for Chronotherapeutic Oral Drug Absorption System. It focuses on achieving delay in the drug action. It has been used in manufacturing of Verapamil as this system is so designed to release the drug after a predetermined delay hence helping in the treatment of arrhythmias. Hence once a tablet is taken at night it ensures that plasma level of the drug are maintained at high concentration during early morning when the symptoms of arrhythmias worsen.
2. PRODAS technology: PRODAS stands for Programmable Oral Drug Absorption system. It mainly focuses on uniting the tablet technology within a capsule as a multi particulate system in order to control the drug release.
3. DMDS (Dividable Multiple Action Delivery System) Technology: It mainly focuses improving drug efficacy by allowing the drug tablet to be broken into two halves each being released in order to achieve the same rate profile of that of the whole tablet at different time thereby reducing the side effects and the ease of the adjustment of the dosage.

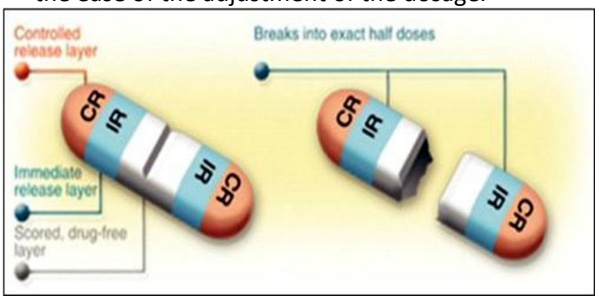

Fig. No. 5: DMDS Technology

4. ACCU-BREAK Technology: They focus on divisible tablets which result in exact smaller dose post division. They contain a controlled release medication separated by drug free break layer.
5. SODAS (Spheroidal Oral Drug Absorption

System) Technology: It is a multi particulate system that enables the drug to be released in pulsatile bursts throughout the day. It mainly has spheroidal beads of 2 mm diameter coated with polymers for controlled release.

Evaluation of chronomodulated drug delivery system:

1. Pre compressional or Pre filling parameters [5]:

a. Angle of repose:

The angle of repose of powder blend can be determined by the funnel method. Accurately weight powder blend were taken in the funnel. The height of the funnel was adjusted in such a way the tip of the funnel just touched the apex of the powder blend. The powder blend was allowed to flow through the funnel freely on to the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation:

$\theta = Tan^{-1} (h/r)$

Where, h and r are the height and radius of the powder cone respectively.

b. Bulk density and tapped density:

Physical mixture from each formula was introduced into a 100 ml measuring cylinder and the initial volume was observed. The cylinder was allowed to fall under its own weight onto a hard surface from the height of 2.5 cm at 2 Sec intervals. The tapping was continued until no further change in volume was noted. The bulk density, and tapped density were calculated using the following formula:

Bulk density = W / V_O

Tapped density = W / V_F

Where, W = weight of the granules

V_O = initial volume of the granules,

V_F = final volume of the granules.

c. Hausner's ratio:

It indicates the flow properties of the powder and is measured by the ratio of tapped density to the bulk density:

Hausner's Ratio = Tapped density/Bulk density

d. Compressibility index (Carr's index):

Compressibility index is an important measure that can be obtained from the bulk and tapped densities. In theory, the less compressible a material the more flowable it is. A material having values of less than 20% has good flow property

CI = tapped density - bulk density/ tapped density x 100

2. Evaluation of Plug [6]:

a. Thickness:

Thickness of the plug is important for uniformity of size. Thickness was measured using Vernier Calipers. It was determined by checking the thickness of ten plug of each formulation.

b. Hardness:

The hardness of each plug was checked by using Monsanto hardness tester. The hardness was measured in terms of kg/cm^2. 3 plugs were chosen randomly and tested for hardness. The average hardness of 3 determinations was recorded.

3. Evaluation of formaldehyde treated empty capsules [7]:

a. Physical Tests:

i. Identification Attributes:

After treating with formaldehyde, the body of the capsule was tested for hardness and stickiness when touched with wet hands.

ii. Visual Defects:

The capsules bodies were tested whether it got shrunk or distorted into different shapes due to the complete loss of moisture

iii. Solubility Test for Formaldehyde Treated Capsules:

The empty hard gelatin capsule was stirred vigorously in 100ml of dissolution medium taken in 250 ml beaker, with magnetic stirrer. The dissolution medium used was water, 1.2 pH, 7.4 pH and 6.8 pH phosphate buffer. The time at which the capsule dissolves or forms a soft mass was noted.

iv. Dimensions:

Variation in dimensions between formaldehyde treated and untreated capsules were studied. The length and diameter of capsules were measured before and after formaldehyde treatment, using vernier caliper due to loss of water vapour from capsules.

b. Chemical Test (Qualitative Test for Free Formaldehyde):

To 1 mL of sample solution in a test tube, add 4 mL of water and 5 mL of acetyl acetone solution, place the test tube in a water bath at 40 ^{0}C for 40 min, at the same time reference solution is placed in the same manner using 1 mL of standard formaldehyde

solution. The sample solution is not more intensely colored than the standard solution inferring that less than 20 µg/ml of free formaldehyde is present in 25 capsules body.

4. Evaluation of Modified Capsules [8]:

a. Thickness of the coating:
Thickness of the cellulose coating was measured by using vernier callipers. It was expressed in mm.

b. Weight variation:
10 capsules were selected randomly from each formulation and weighed individually for weight variation. The test requirements are met if none of the individual weights are less than or more than ±10% of the average.

c. Lag time [9]:
Lag time is the total time period after which the plug is ejected out of the capsule body and the drug releases immediately. Lag time was determined visually using buffers. For lag time determinations USP rotating basket apparatus was used. Capsules were placed in the basket; temperature was maintained at 37°C at 50 rpm.

d. Drug content uniformity:
From each batch, ten capsules were randomly selected and the contents were removed and powdered. From this sample 100 mg powder was accurately transferred into a 100 ml volumetric flask. To this 10 ml of buffer was added to dissolve drugs. The solution was made up to volume with buffer. The resulted solution was filtered through 0.45 µm filter paper and suitably diluted and the drug content was estimated spectrophotometrically.

e. *In-vitro* dissolution studies:
In-vitro dissolution profile of each formulation was determined by employing dissolution apparatus by rotating basket method. The dissolution media was maintained at a temperature 37±5^{0}C at a speed of 100 rpm. Modified capsule was placed in a basket in each dissolution vessel. 5 ml of the samples were withdrawn from dissolution media at suitable intervals and the same amount was replaced with same fresh buffer. The absorbance was measured using UV-Visible spectrophotometer.

5. Evaluation of tablets [6]:

a. Weight variation:
The weight of the tablet being made was routinely determined to ensure that a tablet contains the proper amount of drug. The USP weight variation test is done by weighing 20 tablets individually, calculating the average weight and comparing the individual weights to the average. The tablets met the USP specification that not more than 2 tablets are outside the percentage limits and no tablet differs by more than 2 times the percentage limit.

b. Tablet thickness:
Thickness of the tablet is important for uniformity of tablet size. Thickness was measured using vernier calipers. It was determined by checking the thickness of ten tablets of each formulation.

c. Tablet hardness:
The hardness of each batch of tablet was checked by using Monsanto hardness tester. The hardness was measured in terms of kg/cm^2. 3 tablets were chosen randomly and tested for hardness. The average hardness of 3 determinations was recorded.

d. Friability:
20 tablets were weighed and the initial weight of these tablets was recorded and placed in Roche friabilator and rotated at the speed of 25 rpm for 100 revolutions. Then tablets were removed from the friabilator, dusted off the fines and again weighed and the weight was recorded.
% friability = ((initial weight of tablet – final weight of tablet) / initial weight of tablet) ×100

e. Disintegration time:
The test for disintegration was carried out using USP disintegration test apparatus. To test the disintegration time of tablets, one tablet was placed in each tube and the basket rack was positioned in a 1 litre beaker containing buffer solution at 37°C ± 1°C such that the tablet remains 2.5cm below the surface of the liquid. The time taken for the complete disintegration of the tablets was noted.

f. Water uptake test:
The % water uptake capacity of tablets was determined in the containers filled with 100 ml of buffer placed in a biological shaker at 37°C. Speed of shaker was adjusted to 75 rpm. Tablets were removed from containers at predetermined regular intervals, blotted with tissue paper, weighed and again placed in medium till the outer coating of tablet started to rupture. The % water uptake was calculated using the formula:
% Water uptake = ((Wt -Wo)/Wo) ×100
Where, Wt is weight of wet tablet at time t and Wo is weight of dry tablet.

g. Rupture Test:
The Rupture test on coated tablets was carried out using USP paddle apparatus at 75 rpm and various buffers were used as the dissolution medium. The

time at which the outer coating layer starts to rupture was noted.

h. Lag time [10]:
Lag time was evaluated in buffer. Formulated coated tablets were placed in 900 ml of buffer, agitated at 75 rpm maintained at 37±0.5°C. The time taken for outer coating to rupture was monitored and reported as lag time.

i. Drug content:
The tablets were tested for their drug content uniformity. At random 20 tablets were weighed and powdered. The powder equivalent was weighed accurately and dissolved in 100ml of buffer. The solution was shaken thoroughly. The undissolved matter was removed by filtration through whattman's filter paper No.41. Then the serial dilutions were carried out. The absorbance of the diluted solutions was measured. The concentration of the drug was computed from the standard curve.

j. *In-vitro* Dissolution studies:
In-vitro dissolution profile of each formulation was determined by employing dissolution apparatus by rotating paddle method in different media. The dissolution media was maintained at a temperature 37±5^{0}C at a speed of 100 rpm. Tablets were placed in each dissolution vessel. 5 ml of the samples were withdrawn from dissolution media at suitable intervals and the same amount was replaced with same fresh buffer. The absorbance was measured using UV-Visible spectrophotometer.

6. *In-vivo* release studies [11]:
The prepared formulation is tested for an *in-vivo* study to check the passage of the dosage form throughout the GIT. In this study, drug granules are replaced with barium sulphate. The dosage form is prepared in the similar manner as optimized formulation. The volunteer with overnight fasting is taken for the study. The laxative is given to the volunteer before 12 h of the study to completely empty the GIT content. The X-ray study is performed at 2-h, 3-h, 5-h, and 8-h interval.

7. Kinetics of drug release [12]:
The dissolution profile of all batches are fitted to various models such as zero order, first order, Higuchi, Hixon Crowell, Korsmeyer and Peppas to ascertain the kinetic of drug release.

8. Stability studies:
Stability studies were carried out as per ICH guidelines.

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