Review Article

Oral Chronotherapeutics: Future of Drug Delivery Systems

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Abstract

Chronotherapeutics refers to a treatment method in which *in vivo* drug availability is timed to match rhythms of disease in order to optimize therapeutic outcomes and minimize side effects. it is also known as pulsatile drug delivery system and it focuses on the release of a drug at particular time and at a particular site in order to maintain constant blood levels of a particular drug. They are future of drug delivery systems as these are self programmed oral drug delivery system designed to release a particular drug at a particular rate and at a particular time in order to maintain desired plasma levels by placing these systems in the oral cavity and increasing the patient compliance by avoiding repeated drug administration. The recent advances in oral pulsatile drug delivery technology are CODAS, ACCU-BREAK, SODAS, IPDAS, DMDS Technology.

Keywords: Chronotherapeutics, Drug delivery, Oral drugs, Drug administration routes

INTRODUCTION

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 (Figure 1) in drug therapy, and this has brought a new approach to the development of oral drug delivery systems. Different technologies are being utilized in the development of triggered, pulsatile, controlled and programmed drug delivery devices has intensified in recent years.

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 biochemical, physiological and pathological variations over a 24h period in humans (Figure 2) 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

Figure 1: Chronotheraputics – future of tablets

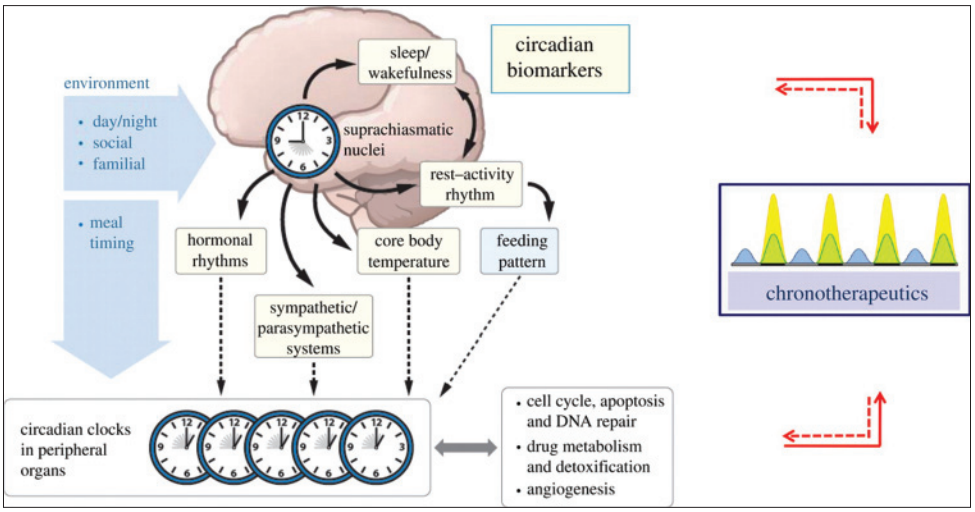

Figure 2: Chronotheraputics – circadian cycle of human body

changes. 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.

Choronotehrapeutic devices currently available control drug delivery by controlling the lag time independent environmental factors such as gastric motility, pH and enzymes. These type of systems can be broadly categorized as multiple and single unit systems. Single unit systems (Figure 3) include various capsular, rupturable coatings, soluble barrier coating and osmosis based systems.

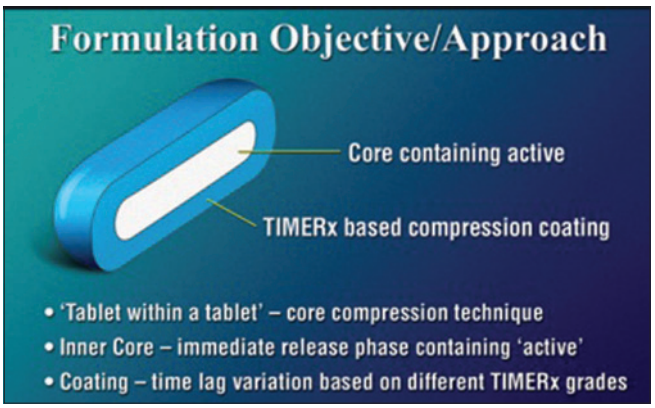

Figure 3: Formulation approach for single unit system

Capsular Systems

It consists of drug formulation inside a plug which is erodible after a predetermined lag phase along with an outer coating of a water insoluble capsule. A swellable hydrogel plug closes the open end of the capsule body. As the capsule comes in contact with fluids the plug swells after the predetermined lag phase and comes out of the capsule leading to the pulsatile release of the drug. The plug is mainly formed by permeable and soluble polymers such as HPMC, agar, pectin and polymetaacrylates. The best example of developed capsular system would be pulsincap system (Figure 4).[1]

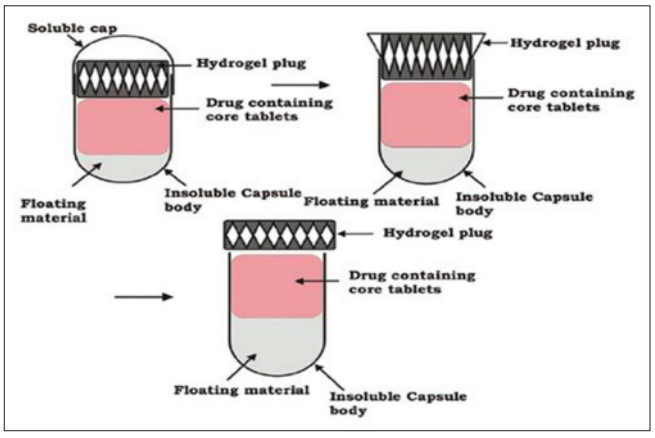

Figure 4: Capsular system

Rupturable Coating Systems

In such kind of systems coating ruptures or disintegrates to release a particular drug. Coating ruptures due to swelling/ osmotic pressure/disintegration/effervescent recipient. The effervescent mixture is generally composed of citric acid and borax which is inserted into the core further coated with ethyl cellulose. Pressure generated due to the formation of the carbon dioxide gas leads to the rupturing of the coating.[2] Increased coating thickness and increased hardness of the core tablet leads to the increase in the lag time. Certain agents such as sodium starch glycollate and low substituted hydroxyl propyl cellulose are used as the swelling agents and they swell upon contact with the GI fluids leading to the complete film rupture and resultant drug release.

Osmosis Based Capsular System (Port System)

It consists of a semi permeable membrane coating a gelatine capsule. Osmotically active agents present in the capsule inside an insoluble plug within the capsule. As this capsule comes in contact with the oral and GI fluids the water diffuses across the semi permeable membrane resulting in increased pressure that results in resultant release of the drug a particular predetermined lag time.[3]

Eg: Ritalin (methyl phenidate): Attention Deficit Hyperactive Disorder

Soluble Barrier Coating System

Here a barrier membrane coats the reservoir of the drug and barrier dissolves after a specific lag time leading to the chronotropic release of the drug.[4] Mainly in the chronotropic system core consists of a coating by HPMC a hydrophilic swellable polymer or cellulose acetate phthalate which results in desired lag phase of the drug release.[5]

Multiparticulate Sytems

They are generally in the form of beads and pellets and they mainly act as reservoirs. All the granules are packed in a capsule after coated the drug over sugar beads. The main advantage of such kind of systems is that it prevents the dose dumping. There are few kinds of multiparticulate system mainly categorized on the basis of pulsatile release by osmotic rupture or rupture of membrane due to other reasons.[6-8]

Major Advances in Oral Pulsatile Drug Delivery:

1. CODAS Technology: CODAS stands for Choronotehraputic Oral Drug Absorption System. It focuses on achieving delay in the drug action. It has been used in manufacturing of verapamil[9] 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.[10]
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 (Figure 5): 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.
4. ACCU-BREAK Technology: They focus on divisible tablets which result in exact smaller dose post division.

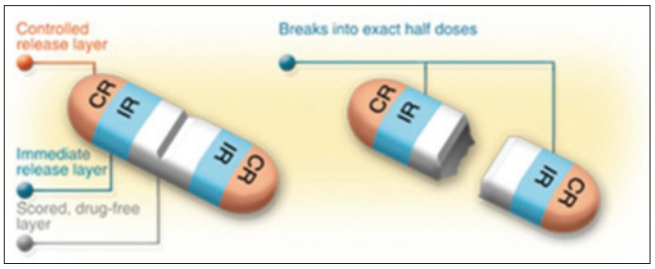

Figure 5: DMDS technology

They contain a controlled release medication separated by drug free break layer.[11]

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.[12]

CONCLUSION

Research in Chronotheraputics 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, Chronotheraputics remains an important area for continuing research. It can be concluded that oral chronotropic drugs help in various drug delivery problems such as extensive first pass metabolism, chronotropic behaviour of the diseases and nocturnal dosing thereby increasing the patient compliance and is the future of the drug delivery systems.

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