



Review Article

CHRONOPHARMACEUTICAL DRUG DELIVERY SYSTEM-A GUIDED THERAPY

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Abstract: The purpose of this review is to portray the basic concepts and advances in chrono-optimized preparations. Chronopharmaceutics is an emerging discipline combining the traditional goal of pharmaceutics with recent knowledge in different disciplines derived from advances in chronobiology. It is basically concerned with the delivery of drugs according to inherent activities of a disease over a certain period of time. The chronotherapy of a medication may be accomplished by the appropriate timing of conventionally formulated tablets and capsules and the special drug delivery system to synchronize drug concentrations to rhythms in disease activity. The present article gives an overview of various types of chronomodulated drug delivery systems and also tries to highlights some of the recent advances being done in chronopharmaceutical drug delivery system
Keywords: Chronopharmaceutics, Time Dependent Pharmacokinetics, Circadian rhythm, Chronotropic.

Introduction

Pharmaceutics is an area of biomedical and pharmaceutical sciences that deals with the design and evaluation of pharmaceutical dosage form. Chronopharmaceutics is a branch of pharmaceutics devoted to the design and evaluation of drug delivery system that release a bioactive agent at a rhythm that ideally matches in real time the biological requirement of a given disease therapy or

prevention¹. Chronopharmaceutical drug delivery system (ChrDDSs) elevated to a new concept that is the ability to deliver the therapeutic agent to a patient in a staggered profile and should embody time controlled as well as site specific drug delivery systems regardless of the route of administration². ChrDDSs can be demonstrated better in fig. 1³.

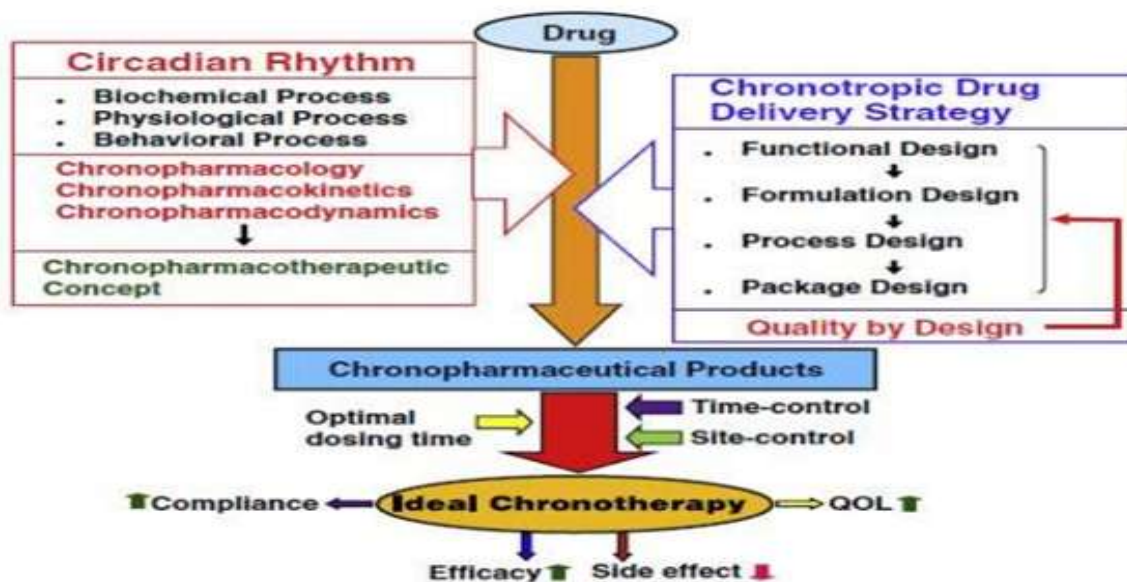


Fig 1: Design and development of new Chronopharmaceutical DDS in accordance with circadian rhythm of human body

Circadian rhythms are the human biological functions which are represented on a 24 hour clock and can also alter the

sleep-wake cycle. Diseases that undergo these temporal variations are shown in fig. 2⁴.

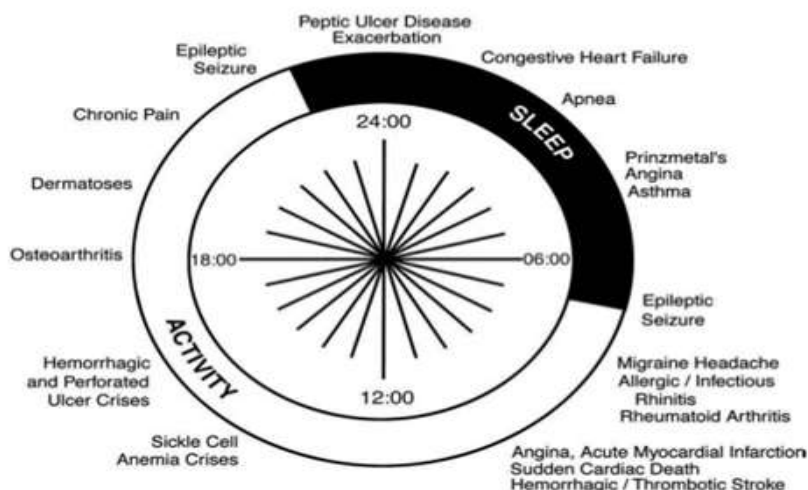


Fig 2: Disease with established circadian rhythm.

Different modeling approaches have been established for above disease out of which some are discussed below⁵⁻⁶:

1. *Modeling cardiovascular diseases-*

$$\frac{dn_{mi}}{dt} = 29.3 - 6.74 \cos\left(\frac{2\pi \times t}{24}\right) + 5.03 \sin\left(\frac{2\pi \times t}{24}\right) + 0.78 \cos\left(\frac{4\pi \times t}{24}\right) - 3.55 \sin\left(\frac{4\pi \times t}{24}\right) \text{ eq.1}$$

Where,

$\frac{dn_{mi}}{dt}$ = Number of myocardial infarctions per hour.
 t= time of day in hour.

2. *Modeling cancer chemotherapy-*

Lumped parameter (e.g. Gompertz Model) and cell cycle models are applied to describe tumor growth as well as its behavior respectively. Differential equations of each cell cycle are provided in eq. 2-6.

$$X_{G0} = - (T_{G0} + d_{G0})X_{G0}(t) + 2rT_M X_M(t) \text{eq. 2}$$

$$X_{G1} = - (T_{G1} + d_{G1})X_{G1}(t) + 2(1-r)T_M X_M(t) \text{eq. 3}$$

$$X_s = - (T_s + d_s)X_s(t) + T_{G1}X_{G1}(t) \text{eq. 4}$$

$$X_{G2} = - (T_{G2} + d_{G2})X_{G2}(t) + T_s X_s(t) \text{eq. 5}$$

$$X_M = - (T_M + d_M)X_M(t) + T_{G2}X_{G2}(t) \text{eq. 6}$$

Where,

X_i = number of cells in a particular stage.
 T_i = transition rate between stages.
 d_i = death rate for cells in a particular stage.
 r = enter the resting stage.
 (1-r) = return to the RNA/protein synthesis stage.

3. *Modeling glucose insulin interaction-*

Low order structured and physiological based model are used to estimate glucose and insulin as depicted in eq. 7-9.

$$\frac{dG(t)}{dt} = (P_1 - X(t))G(t) - P_1 G_b \text{eq. 7}$$

$$\frac{dX(t)}{dt} = P_2 X(t) + P_3 I(t) \text{eq. 8}$$

$$\frac{dI(t)}{dt} = E(t) - nI(t) \text{eq. 9}$$

Where,

G(t) = plasma glucose

Harmonic regression equations (eq. 1) are used to describe this modeling e.g. in case of frequency of onset of myocardial infarction according to creatine -kinase MB (CK-MB) activity.

I(t) = Plasma insulin
 X(t) = insulin concentration in a remote compartment
 E(t) = exogenous insulin
 P_i = parameters
 G_b = Basal glucose concentration.

4. *Modeling other diseases-*

Equations (eq. 10) are developed for biochemical markers require for other diseases.

$$f(t) = M + A \cos(\omega t + \phi) + e_i \text{eq. 10}$$

Where,

$f(t)$ = pharmacokinetic/pharmacodynamic (PK/PD)
 M = mesor (midline value about which oscillation occur)
 A = amplitude (half the differences between the highest and lowest values)
 ω = the angular frequency.

Need for chronotropic DDS:⁷

The conditions or the instances in which this system is required are:

- When possible daily variations in pharmacokinetic may be responsible for time dependent variations in drug effects (e.g. some antimicrobial agents are more effective at a specific time of day).
- When drugs have a narrow therapeutic range.
- When symptoms of a disease are clearly circadian phase-dependent (e.g. Angina pectoris, myocardial infarction).
- When drug plasma concentrations are well correlated to the therapeutic effect in case the latter is circadian phase-dependent.

- When the drug has some serious adverse effects that can be avoided or minimized because they are related to time of administration.

Hurdles of ChrDDS:⁷

1. Rhythmic biomaterials and system design.
2. Rhythm engineering and modeling.
3. Regulatory guidance related to these types of modified dosage forms.

Chronomodulated drug delivery systems⁸⁻¹¹:

A very little consideration or a very important factor which represent determinant of therapeutic success is "Time". Various drug delivery systems which fulfill this requirement are given discussed as follow:

1. *Pulsatile drug delivery system:*

It is a system where the drug is released suddenly after a well-defined lag time or time gap according to the circadian rhythm of disease states. No drug is released from the device within this lag time. This method is good for drugs with extensive first pass metabolism and those targeted to specific sites in the intestinal tract. Therefore by developing the pulsatile device for specific colonic drug delivery, the plasma peak is obtained at an optimal time, the number of doses per day can be reduced, it is with saturable first pass metabolism, and tolerance development can be reduced.

2. *Enteric-coated system:*

The system contains a core which is film coated with two polymers, first with HPMC and then with a gastro-resistant polymer. In this system the duration of the lag phase in absorption can be controlled by the thickness of the HPMC layer. The disadvantage of this system is the unpredictability of gastric residence.

3. *Osmotic system:*

In this system osmotic pressure acts as a driving force for the pulsatile drug release. It consists of application of a semi-permeable membrane around the core of an osmotically active drug or a drug combined with an osmotic agent. The delivery orifice is drilled into the system by laser technique. A lag time of 1-10 hr can be achieved depending on the thickness, orifice diameter and concentration of an osmotic agent. e.g. port system.

4. *Swelling and erodible system:*

In this system the drug reservoir is surrounded by polymeric barrier layers that swells and get dissolved when it is in contact of dissolution media and drug is released after the lag time. The lag time of the system can be controlled by thickness of the polymeric coat and the viscosity grade of the polymer used.

5. *Press coated system:*

It involves direct compression of both the core and the coat, obviating the need for a separate coating process and the use of coating solution. The limitation of the system is that central position of the core layer cannot be assured. The lag time of the system can be controlled by coating the tablet

with semi-permeable polymer which controls the drug release.

6. *Pulsincap:*

It is a single unit system comprised of a water insoluble capsule body enclosing the drug reservoir. The capsule body is closed at one end with a swellable hydrogel plug. When the capsule comes in contact with water it absorbs water and swells. After a lag time the plug gets pushed out and the drug gets release rapidly in the form of a pulse. Rapid release of the drug can be ensured by the inclusion of effervescent agents, super disintegrants and osmotic agent.

7. *Ultrasound drug delivery system:*

The ultrasound effect enhances degradation of the polymer in which the drug molecules are incorporated. The drug can be released by repeated ultrasound exposure pulse delivery is achieved by on off application of ultrasound.

8. *Multiparticulate system:*

The drug is coated on non-peril sugar beads followed by coating with swellable polymeric layer. The swelling agents include super disintegrant, osmotic agent etc. upon ingress of water, the swellable layer expands resulting in rupture of the film and rapid drug release.

Recently available different chronopharmaceutical technologies:

1. *CONTIN technology¹²⁻¹³:*

Complex formed between cellulose polymer and non polar solid aliphatic alcohol which act as amatrix. This technology is used for aminophylline, morphine etc. more effective control of disease and reduces unwanted side effects.

2. *CODAS technology¹⁴⁻¹⁵:*

The chronotherapeutic oral drug absorption system (CODAS) is a multi-particulate system designed for bedtime drug dosing, incorporating a 4-5 h delay in drug delivery introduced by the non-enteric release-controlling polymer applied to drug loaded beads. E.g. CODAS-verapamil extended release capsules.

3. *CEFORM technology¹⁶⁻¹⁷:*

It produces uniformly sized and shaped microspheres of pharmaceutical compounds. This approach is based on melt-spinning. This technology has been actually used to develop cardizemR LA, a one day diltiazem formulation like ChrDDS.

4. *OROS technology¹⁸⁻¹⁹:*

It is a delivery system that reproducibly delivers a bolus drug dose, in a time or site specific manner to the gastrointestinal tract. It is osmosis-based system and generally used in the designing of an extended release tablet.

5. *DIFFUCAPS technology²⁰⁻²¹:*

In this technology, a unit dosage form, such as capsule is used for delivering drugs into the body in a circadian release fashion. It is a multiparticulate technology by reliant pharmaceuticals LLC, for a chronotherapeutic delivery of a combination of two drugs. This technology has been used to

formulate the first and recently FDA approved propranolol-containing ChrDDS for the management of hypertension.

6. EGALET¹⁷:

It is a delayed release form consisting of an impermeable shell with two lag plugs, enclosing a plug of active drug in the middle of the unit.

7. GEOCLOCK²²:

The concept is designed on the basis of geomatrix technology. The active core is coated partially on one or both bases. Upon erosion more of the planar surface of the active core is exposed with increasing time to the outer environment, which helps drug release.

8. TIMERx²³:

It is a hydrogel-based controlled release device. Drug release is controlled by the rate of water penetration from the gastrointestinal tract into the TIMERx gum matrix, which expands to form a gel and release the drug.

Conclusion

The future of ChrDDS is promising if more creative work can be done based on these pioneering and seminal works. In the era of nanoscience and nanotechnology, it is reasonable to predict that a hybrid approach integrating basic knowledge of biomedical engineering, chronobiology and related fields will be needed in order to optimize the chronopharmaceutics or chronomedicine or nanomedicine of the future. Key point of development of this delivery system is to find out the circadian rhythm, that is, a suitable indicator that will trigger the release of the drug from the device.

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