Chronopharmaceutical Drug Delivery Systems: Present Scenario

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ABSTRACT

Chronopharmaceutics is an emerging discipline which combines the knowledge of chronobiology and pharmaceutics to maximize the therapeutic output in the diseases which follows circadian rhythms. Recent advances in the field of chronobiology and chronopharmacology have generated a plethora of data related to the biological rhythms that may be used for the development of time dependent drug delivery systems to optimize their safety and efficacy. Optimum therapeutic response is achieved when a bioactive agent is released at rhythm that ideally matches in real time the biological requirement of a disease. Chronopharmaceutical drug delivery systems embody time controlled and site-specific drug delivery systems. Some of the disease conditions which follow circadian rhythms include cardiovascular diseases, asthma, diabetes, neurological disorders, hypertension, ulcer etc. The current key technologies employed in Chronopharmaceutics are Diffucaps, OROS, Codas, Egalet, 3D printing, Port, etc. As a new and evolving discipline, Chronopharmaceutics has attracted the attention of academician and industry. The present article focuses on the newer approaches in the Chronopharmaceutics and Chronotherapeutics, their applications and the real challenges ahead in the designing and manufacturing of chronopharmaceutical drug delivery systems.

INTRODUCTION

Traditionally, drug delivery systems have focused constant/sustained drug release with the objective of minimizing peaks and valleys of drug concentrations in the body to optimize drug efficacy and to reduce adverse effects. A reduced dosing frequency and improved patient compliance can also be expected for the controlled/sustained release drug delivery systems compared to immediate release preparations but in the field of controlled drug delivery, the challenge is to develop sustained zero-order systems because living organisms are not “zero-order” in the requirement or response to drugs. They are predictable resonating dynamic, which require different amounts of drugs at predictably different times within the circadian cycle in order to maximize desired and minimize undesired drug effects. Here the concept of chronotherapeutics and chronopharmaceutics arises. Coordination of biological rhythms with medical treatment is called chronotherapy. Chronotherapy considers a person’s biological rhythms in determining timing and medication to optimize drugs desired effects [1, 2].

Chronopharmaceutics is a branch of pharmaceutics (science and technology of drug dosage forms) devoted to the design and evaluation of drug delivery systems that release a bioactive agent at a rhythm that ideally matches in real time the biological requirement for a given disease therapy or prevention. Ideally, chronopharmaceutical drug delivery systems should embody time-controlled and site specific drug delivery systems regardless of the route of administration. The safety and efficacy of the drug is achieved by coordinating the peak plasma concentration of the drug with circadian rhythm of the body [3].

The chrDDS are relevant when the risk or intensity of the symptoms of disease vary with time as in the case of asthma, allergic rhinitis, cardiovascular diseases, cancer, diabetes, rheumatoid arthritis, peptic ulcers, attention deficit syndrome, osteoarthritis etc [4]. Now days many number of new technologies of chrDDS are developing to treat those diseases. The various technologies and marketed products are summarized in this review article.

ADVANTAGES & LIMITATIONS OF ChrDDS [5, 6]

Advantages

- Predictable, reproducible and short gastric residence time
- Less inter- and intra-subject variability
- Improve bioavailability
- Reduced adverse effects and improved tolerability
- Limited risk of local irritation
- No risk of dose dumping
- Flexibility in design
- Improve stability
- Improve patient comfort and compliance
- Achieve a unique release pattern
- Extend patent protection, globalize product, and overcome competition

Limitations

- Lack of manufacturing reproducibility and efficacy
- Large number of process variables
- Multiple formulation steps
- Higher cost of production
- Need of advanced technology
- Trained/skilled personal needed for manufacturing

DISEASES REQUIRED CHRONOTHERAPY

The biological rhythm studies help in defining the temporal organization of human beings. One means of illustrating the human circadian time structure is to depict the peak time of 24-h rhythms on a clock—like diagram. The 24 h clock pattern of diseases showing prominent day-night patterns when symptoms of disease are most frequent. Variation in the severity of many diseases over a 24-hour period is well known diseases such as bronchial asthma, myocardial infarction, angina pectoris, rheumatic disease, arthritis, cancer, ulcers, diabetes, and attention deficit syndrome, hypercholesterolemia and hypertension show symptomatic changes due to...
circadian rhythm city. Aggravation of asthmatic attacks occur after midnight or in the early morning due to limited lung function promoted by circadian changes at that time. Many common diseases also display a marked circadian variation during onset or exacerbation of symptoms [7]. The circadian pattern of diseases are given in Table no.1 and Fig.1 [8]

Table 1: Diseases that require chronotherapy

<table>
<thead>
<tr>
<th>Disease/syndrome</th>
<th>Circadian Rhythmacity</th>
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<tbody>
<tr>
<td>Asthma</td>
<td>Precipitation of attacks during night or at early morning.</td>
</tr>
<tr>
<td>Allergic rhinitis</td>
<td>Symptoms exacerbate in early morning.</td>
</tr>
<tr>
<td>Arthritis</td>
<td>Level of pain increases at night.</td>
</tr>
<tr>
<td>Attention deficit syndrome</td>
<td>Increase in DOPA level in afternoon.</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Increase in the blood sugar level after meal.</td>
</tr>
<tr>
<td>Peptic ulcer</td>
<td>Acid secretion is high in the afternoon and at night.</td>
</tr>
<tr>
<td>Cancer</td>
<td>The blood flow to tumors is threefold greater during each daily activity phase of the circadian cycle than during the daily rest phase.</td>
</tr>
<tr>
<td>Cardiovascular diseases</td>
<td>BP is at its lowest during the sleep cycle and rises steeply during the early morning.</td>
</tr>
<tr>
<td>Hyper cholesterolemia</td>
<td>Cholesterol synthesis is generally higher during night than day time.</td>
</tr>
</tbody>
</table>

Fig 1: The circadian pattern of diseases

CLASSIFICATION OF CHRONOPHARMACEUTICAL DRUG DELIVERY SYSTEMS

From the existing published data, it is clear that the chrdds approaches to disease management have a clinical advantage across all medical disciplines. Clearly, a pattern of real-time drug input at different release rates would be preferred to that of a constant rate. This drug delivery objective may be achieved by stimuli-sensitive and pulsatile drug delivery systems. Based on their physicochemical properties, different classifications have been provided for such drug delivery systems. However, for practical reasons, it may be reasonable to classify ChrDDSs based on the main routes of drug administration (parenteral, oral, and transdermal) [7, 9, 10, 11]. The classification system is given in Fig.2.

Chronopharmaceutical drug delivery systems for parenteral route

Chromomadulating infusion pump

Melodie®, programmable Synchromed®, Panomat® V5 infusion and the Rhythmic® pumps which are used in the chronotherapy of several diseases such as cancer and diabetes [13].

Micro fabrication Technology/Controlled release microchip

It consist a solid state silicon microchip that can provide controlled release of medication by electrochemical dissolution of thin anode membranes covering micro reservoirs filled with chemicals in solid, liquid or gel form. This technique is used in diabetes, Parkinson’s disease, congestive heart failure [13].

Chromopharmaceutical drug delivery systems for transdermal route

Crystal reservoir system

A thermo responsive membrane was developed to achieve an on-off switching drug delivery for transdermal application via the externally repeated cycle of temperature change was first reported by Kato et.al for the treatment of asthma.

Chronodose™ system

It is a programmable device which can be worn like a wrist watch to administer drug doses automatically in to the body at different times of the day & with varying dose sizes.

Chemical oscillator

Chemical oscillator system is based on the observation that a drug may be rendered charged or uncharged relative to its pKa value. Since only the uncharged form of a drug can permeate across lipophilic membranes, including the skin, a periodic delivery profile may be obtained by oscillating the pH of the drug solution.

Chromopharmaceutical drug delivery systems for oral route

Contin® Technology

In the Contin® technology, molecular coordination complexes are formed between a cellulose polymer and a nonpolar solid aliphatic alcohol optionally substituted with an aliphatic group by solvating the polymer with a volatile polar solvent and reacting the solvated cellulose polymer directly with the aliphatic alcohol, preferably as a melt. This constitutes the complex having utility as a matrix in controlled release formulations since it has a uniform porosity (semi permeable matrixes) that may be varied [16].

Oros® technology

It is an osmotic-controlled release oral delivery system developed by Alza corporation. Chronset® is a proprietary OROSs delivery system that re-
The pulsys™ technology
This technique was developed by PENWEST Pharmaceuticals, USA. This system contains drug reservoir covered with hydrophilic TIMERx gum matrix, drug release is controlled by penetration of water into gum matrix which expands to form a gel and subsequently release the active drug substance \( [21] \).

Pulsincap™ technology
This technology was developed by FUISZ Technology Ltd, USA. This Chrrds approach is based on “melt spinning” to produce uniformly sized microspheres. The microspheres may be coated for controlled release either with an enteric coating or combined into a fast/slow release combination \( [19] \).

Diffucaps™ technology
This technology was developed by EURAND Pharmaceuticals Ltd, Italy. In this technology a unit dosage form, such as a capsule for delivering drugs into the body in a circadian release fashion is comprised of one or more populations of drug-containing particles (beads, pellets, granules, etc.). Each bead population exhibits predesigned rapid or sustained release profile with or without a predetermined lag time of 3–5 hours \( [20] \).

Chronotropic™ technology
It contains a drug reservoir (solid dosage form) coated with hydrophilic polymer HPMC which release drug after lag time depending on the thickness and viscosity grade of polymer.

Egalet® technology
It was developed by EGALET Ltd, Denmark. This technique was developed to release the drug in delayed pattern. In this it contain an impermeable sell with two plugs and the drug is placed between those two plugs. The plugs are made up of biodegradable polymers and is released after the erosion of inert plugs.

Port® technology
The Port® (Programmable Oral Release Technologies) uses a uniquely coated, encapsulated system that can provide multiple programmed release of drug. The basic design of the Port technology tablet consists of a polymer core matrix coated with a semi permeable, rate-controlling polymer. Poorly soluble drugs can be coated with proprietary solubilisation agents to ensure uniform controlled release from the dosage form.

Three dimensional printing
Three dimensional printing® (3DP) is a novel technique used in the fabrication of complex oral dosage delivery pharmaceuticals based on solid freeform fabrication methods. It is possible to engineer devices with complicated internal geometries, varying densities, diffusivities, and chemicals. Different types of complex oral drug delivery devices have been fabricated using the 3DP process: immediate-extended release tablets, pulse release, breakaway tablets, and dual pulsatory tablets \( [22] \).

Physico-chemical modification of the API
In this method the physico-chemical properties of the medicaments like solubility, partition coefficient, and membrane permeability can be modified to achieve the chronopharmaceutical drug delivery.

Pulsincap® technology
These are the well-designed pulsatile release drug delivery systems capable
of releasing drug at a predetermined time. Drug formulation is contained within the insoluble capsule body this is sealed by means of a hydrogel plug. On oral administration the water soluble capsule cap dissolves in the gastric juices and hydrogel plug swells. At a controlled and predetermined time point after the ingestion, the swollen plug is ejected from the pulsincapdosage form after which the encapsulated dosage formulation is then released [23].

MARKETED PRODUCTS
Chronopharmaceutical drug delivery is a novel approach to treat many diseases and disorders so many pharmaceutical industries have shown interest in formulating chrDDs [7, 24, 25, 26, 27]. Those products are given in table no 2.

RECENT RESEARCH IN CHRONOPHARMACEUTICAL DRUG DELIVERY SYSTEMS:
Chronopharmaceutical drug delivery is an evolving field of research. For the last two decades many researchers and pharmaceutical industries are working on developing new approaches and designs for chrDDS so that many number of patents are filed and granted in USPTO. The list of patents in the field of chrDDS are given in table no.3 [28, 29, 30]

CONCLUSION
Therapeutic outcome of the dosage form depends not only on the dose and dose intervals but also on the dosing time, as most diseases follow circadian rhythms. Chronopharmaceutical drug delivery system encompasses the knowledge of chronobiology and drug delivery systems to synchronize the drug release to the biological rhythms of the disease states. With the advances in the field of Chronobiology, a plethora of information has been generated which enables to design a drug delivery system to deliver the drug when it is most needed. Chronopharmaceutics offers a powerful alternative to conventional dosage forms in the management of disease states like hypertension, asthma, peptic ulcer, cancer, etc which follows biological clock. This article elucidates the importance of the biological rhythms in the management of the disease states by the designing suitable drug delivery systems to best suit ones need to maximize the therapeutic outcome and reduce the adverse effects.

Current research

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