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Chronotherapy: Clinical Science Based On Biological Rhythm.

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ABSTRACT

If the organization in time of living system including man is borne in mind, it is easy to conceive that not only must the right amount of the right substance be at right place but also this must occur at the right time therefore in pharmaceuticals Controlled drug delivery systems have acquired a centre stage in the area of pharmaceutical R &D sector. In such cases a chronopharmacotherapy may be more advantageous. In order to increase the effectiveness of drug here one of the techniques is described which is chronotherapeutic drug delivery system. Ideally, these systems should embody spatial and temporal control drug delivery systems.These dosage forms offer many advantages, such as nearly constant drug level at the site of action, prevention of peak-valley fluctuation, reduction in dose of drug, reduced dosage frequency, avoidance of side effects and improved patient compliance.The dependence of our body functions in the certain diseased states depends on the circadian rhythms which occur in the certain diseased conditions like depression, rheumatoid arthritis, myocardial infarction, peptic ulcer etc. Theoretically; such ideal drug delivery system would potentially improve the safety, efficacy and patient compliance of old and new drugs. Our aim in this review is to outline the rational and prominent design strategies behind site-specific oralpulsatile drug delivery system on the principle of Chronodynamics refers to dosing-time, i.e., rhythm-dependent.

Keywords: chronotherapeutics, circadianrhythm, spatial-temporal,Supra chiasmatic nuclei

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INTRODUCTION

Controlled release dosage forms cover a wide range of prolonged action formulations which provide continuous release of their active ingredients at a predetermined rate and for a predetermined time. Ideally, the optimization of therapeutic efficacy and safety may be attained as a result of providing a nearly constant pharmacologic response, thereby avoiding the normal peak and valley pattern associated with multiple dosing of conventional dosing [1].

The shift from conventional dosage form to controlled drug delivery system is for the following reasons:

- Reduction in dosing frequency
- Reduced fluctuations in circulatory drug levels
- Avoidance of night time dosing
- Increased patient compliance
- More uniform effect
- Decreased side effects like reduced GI irritation[2]

In order to increase the effectiveness of drug there are many approaches have been applied, hereone of the technique is described which is chronotherapeutic drug delivery system [3].

Chronotherapy

Chronotherapy refers to the treatment of disease which are dependent on biological rhythm of body.By determining these biological rhythms of a person one can increase or decrease the dose of the drug hence unwanted side effects of particular drug can be avoided [4].

Circadian time structure

The results of numerous biological rhythm studies help define 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 like that shown in Fig. 1. This figure shows the peak time of a select number of human circadian rhythms in relation to the typical synchronizer routine of mosthuman beings-sleep in darkness from 10.30 P.M to 6.30 A.M and activity during the light of the day between 6.30 A.M and 10.30 P.M [5].

The circadian rhythms are controlled by an inherited master clock network composed of the paired supra chiasmatic nuclei (SCN) which are situated in the ventro-rostral part of the hypothalamus function as the master pacemaker of an endogenous circadian timekeeping system.In mammals, the paired(Asst. Prof.) (SCN) located.

The internal clock is influenced to a large extent by light. Although our genetic makeup determines our circadian rhythm, this rhythm has to be resynchronized by daylight each and every day.

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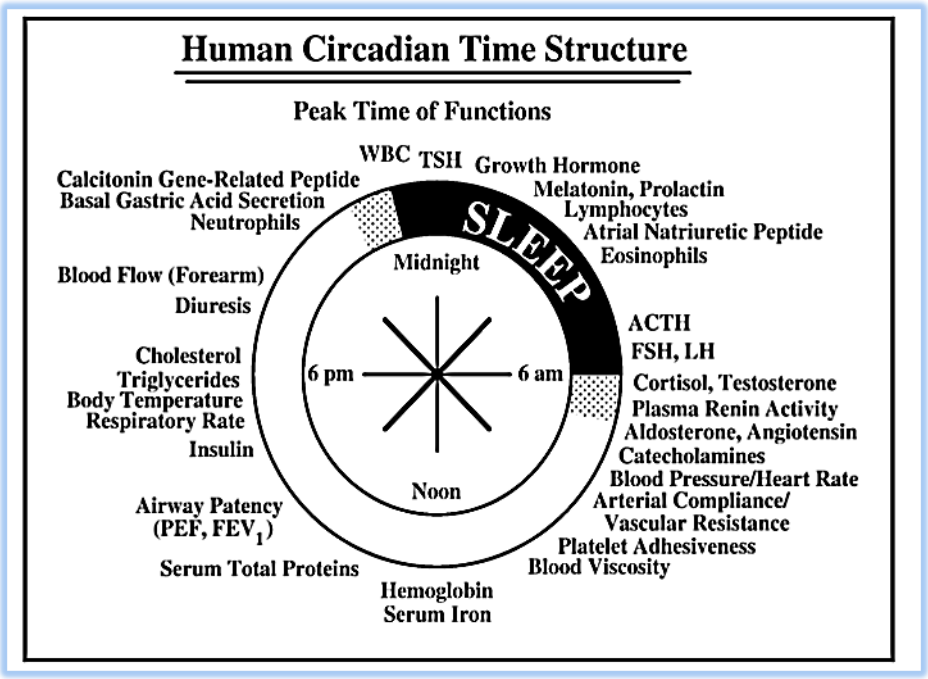

Figure 1: Human circadian time structure.

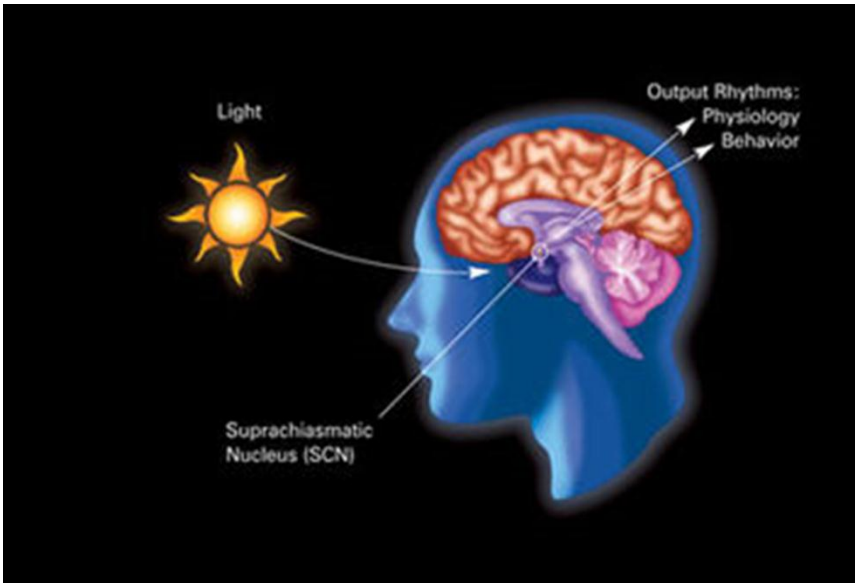

Figure 2: Supra chiasmatic nuclei (SCN) controlling circadian rhythm.

Circadian rhythm hormone secretion

The hormones responsible for the circadian rhythm in humans are melatonin, which is released in response to increasing levels of darkness and which promotes sleep and cortisol which is the biological opposite of melatonin and an indicator of the level of human activeness [6].

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Chronotherapeutics

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 [7].

There are number of conditions which show a circadian pattern and adjusting the administration of drugs according to their circadian rhythm of the disease state as [8,9]

Table no. 1

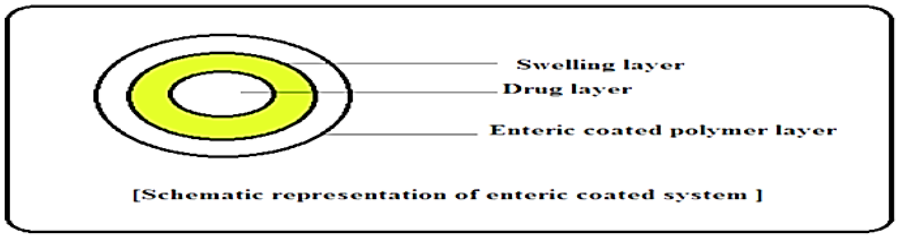
Sr.no.	Disease	Sr.no.	Disease
1	Hypertension	7	Peptic ulcer
2	Myocardial infraction	8	Bronchial asthma
3	Cerebrovascular accidents	9	Arthritis
4	Peptic ulcer	10	Sleep disorders
5	Hypercholesterolemia	11	Cardiovascular diseases
6	Allergic rhinitis	12	Blood coagulation and thrombosis

Technology used inchronotherapeutic drugdelivery

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. Various technologies to develop time controlled per oral drug delivery systemshave been extensively studied in recent decades. Some of these systems are discussed in the following subsections.

Enteric-coated systems

Enteric coatings are pHsensitive and drug is released when pH is raised above 5 in the intestinal fluid.These formulations can be utilized 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 [10].

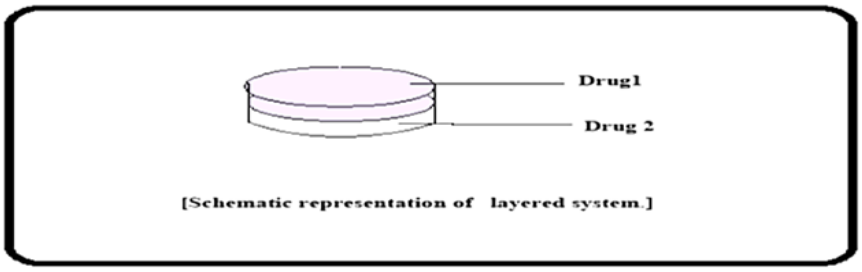


[Schematic representation of enteric coated system]

Layered systems

To allow biphasic drug release, a three-layertablet system was developed.The two layers both contain a drug dose. The outer drug layercontains the immediately available

dose of drug. An intermediate layer, made of swell ablepolymers, separates the drug layers [11].



[Schematic representation of layered system.]

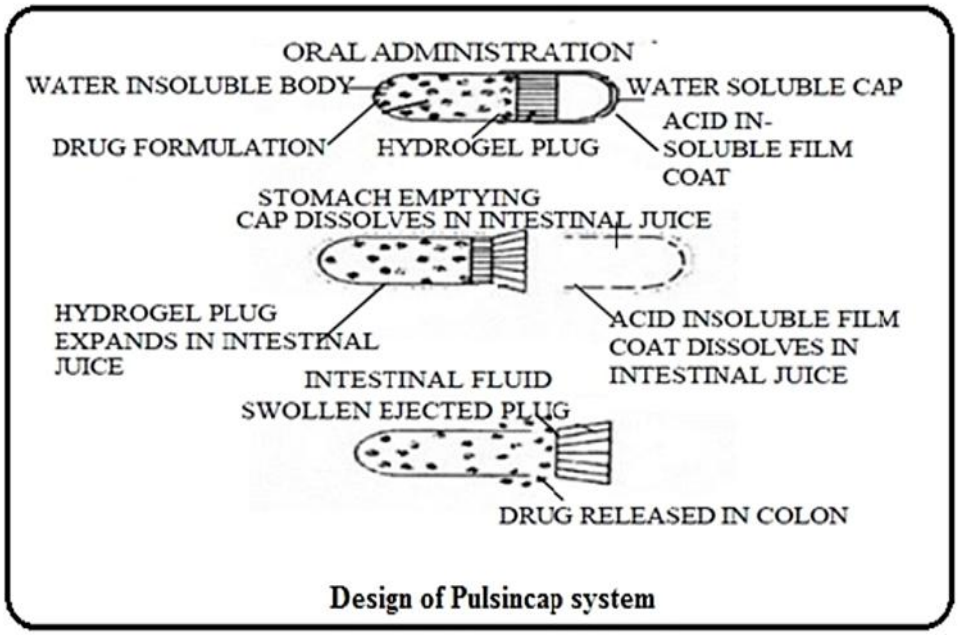
Sigmoidal release systems (SRS)

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 [12].

Pulsincap system

Pulsincap system which consists of an insoluble capsule body, swellable and degradable plugs made of approved substances such as hydrophilic polymers and lipids and bioactive molecule. The lag time is controlled by plug, which is pushed away by swelling or erosion and drug is released as a pulse from the insoluble capsule i.e. Pulsincap**.**

A swellable hydrogel seals the drug contents into the capsule body. When this capsule body comes in contact of dissolution medium, the hydrogel plug swells and after a lag time, the plug pushes itself outside the capsule and rapidly releases the drug [13].



Design of Pulsincap system

Advantages of Chronotherapy [14]

- Less inter- and intra-subject variability.
- Improves bioavailability.
- More effective when a person sleeps for several hours.
- It 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.
- Ease of combining pellets with different compositions or release patterns.
- Improves patient comfort and compliance.
- Achieves a unique release pattern.
- Extends patent protection, globalizes the product, and overcomes competition.

Disadvantages of Chronotherapy [15]

- Person may also be deprived of sleep sometimes.
- Person become less productive during Chronotherapy and staying awake till the other schedule might be bit uncomfortable.
- Person 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 specialists is recommend.
- Person undergoing therapy may feel unusually hot or cold sometimes.
- Patient needs to consult the doctor regularly to avoid side effects.

Recently availablechronopharmaceutical technologies

Chronotropic systems are now emerging as novel trend in drug delivery for chronotherapy among these, multiparticulate systems (beads, pellets, microspheres etc) possess various advantages over single unit various pulsatile technologies.

OROS technology

OROS technology uses an osmotic mechanism to provide pre-programmed, controlled drug delivery to the gastrointestinal tract.The active drug is housed in a reservoir, surrounded by a semi-permeable membrane/wall (e.g. cellulose esters, cellulose ethers and cellulose ester–ethers) and formulated into a tablet [16].

CEFORM® technology

It produces uniformly sized and shaped microspheres of pharmaceutical compounds. This approach is based on 'melt-spinning,' which means subjecting solid feedstock (i.e., biodegradable polymer / bioactive agent combinations) to a combination of temperature, thermal gradients, mechanical forces, and flow and flow rates, during processing.

CONTINR technology

In this technology, molecular coordination complexes are formed between a cellulose polymer and non-polar 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.The CONTINR technology provides benefits to patients in terms of reducing the number of doses they need to take every day [17].

DIFFUCAPS® technology

In the DIFFUCAPS® technology,30 a unit dosage form,such as a capsule for delivering drugs into the body ina circadian release fashion, is comprising of one ormore populations of drug-containing particles (beads,pellets, granules, etc.). Each bead population exhibitsa pre designed rapid or sustained release profile without a predetermined lag time of 3–5 h.

TIMERx® technology

The TIMERx® technology (hydrophilic system) combines primarily xanthan and locust bean gumsmixed with dextrose. The physical interactionbetween these components works to form a strong,binding gel in the presence of water. Drug release is controlled by the rate of water penetration from thegastrointestinal tract into the TIMERx® gum matrix,which expands to form a gel and subsequentlyreleases the active drug substance [18].

REFERENCES

[1] NK Jain. Controlled and Novel Drug Delivery, CBS Publishers and Distributers Pvt.Ltd.First Edition, page no. 1
[2] Suresh P Vyas, Roop K Khar Controlled Drug Delivery Concepts and Advances, VallabhPrakashan, Second Edition, page no. 6
[3] Devdhawala Mehul G and Seth Avinash K. J Chem Pharm Res 2010;2(3):312-328.
[4] P Srinivas, G Sandeep, A Rohan Pridhvi and Y Soujanya. Int J Pharma Bio Sci 2011;2(3):19-23
[5] Chandan Kumar Brahma, G Vidya Sagar Gali. J Global Trends in Pharm Sci 2012;3(3);778-791.
[6] Shweta B Surve, Akshay D Sapakal, Snehal S Naingade. Int J Pharm Bio Sci 2013;3(1): 378-386.
[7] Rupali Singh, Pramod Kumar Sharma and Rishabha Malviya. European J Biol Sci 2010;2(3):67-76.
[8] Seshni Sewlall et al. Current Drug Delivery 2010;7:370-388.
[9] Rajendra Awasthi, Pravin Kumar, Vivek Kumar Pawar. J Chronotherapy and Drug Delivery 2010;1(1):09-18
[10] Chandan Kumar Brahma, G Vidya Sagar Gali. International Journal Of Pharma World Research 2012;3(1):1-17.
[11] J Sajan, TA Cinu, AJ Chacko, J Litty and T Jaseeda. Trop J Pharm Res 2009;8(5):467-475.

[12] Papola Vibhooti, Rajan G, Bisht Seema, Kothiyal Preeti. Indian J Res Pharm Biotechnol 2013;1(3):288-298
[13] Dubal Ashwini, Karigar Asif, Ramana MV, Patel Mitul, Desai Omkar. International Journal Of Research In Ayurveda And Pharmacy 2011;2(6):1692-1700.
[14] Singh Haribansh Narayan, Saxena Shivangi, YadavAjit Kumar, Singh Sunil. International Journal of Medicine and Pharmaceutical Research 2013;1(2):226-234.
[15] Manpreet Kaur and Rajni Bala. Int J Pharm Sci Res 2013;4(1):90-102
[16] Mayank Nagar, Sanjay Singhai, VS Chopra, Namrata Gautam, Piyush Trivedi. International Journal of Pharmaceutical and Clinical Research 2010;2(1):10-19.
[17] Harshida G Patel, Karishma Patel, UM Upadhyay, Viral H Shah. International Journal Of Pharmacy Review & Research 2013;3(1):26-32
[18] Nl Prasanthi, G Swathi, SS Manikiran. International Journal of Pharmaceutical Sciences Review and Research 2011;6(2):68-75