CHRONOTHERAPEUTIC DRUG DELIVERY SYSTEMS

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ABSTRACT

Chronopharmaceutics has been described as a branch of pharmaceutics that refers to the fabrication and evaluation of drug delivery systems that releases active pharmaceutical ingredient (or) drug in the optimum dose at the circadian rhythm (biological rhythm) that suitably matches the drug need in the treatment of the disease with minimizing the adverse drug reactions.

KEY WORDS: Chronotherapeutic, Circadian rhythm, Lag time.

1.INTRODUCTION

Chronotherapeutic drug delivery systems are also called as time dependent drug delivery systems or chronotropic drug delivery systems.The term "chrono" means metabolic reactions or events that undergoes rhythmic changes with respect to time.

Advantages of Chronotherapeutic drug delivery systems:

1. Chronotherapeutic drug delivery systems considers the patients biological rhythms in determining the timing and amount of medication to optimize drug desired effects (Subal,2005).
2. Chronotherapeutic drug delivery systems are suitable for the drugs with chronobiological behaviour or site specific absorption in the gastrointestinal tract (Subal, 2005).
3. Chronotherapeutic drug delivery systems helps to reduce dosage regimen or dosing frequency, thereby it improves patient compliance .
4. These are promising delivery systems for delivering the drugs in the treatment of several chronic disorders i.e. chronic obstructive pulmonary disorders like asthma and cardiovascular diseases like hypertension , angina pectoris.
5. Minimize the toxic effects of drugs.

LIMITATIONS :

Chronotherapy becomes complicated to the patients who perform shift work (alternate day and night) like Industrial workers (Subal, 2005).

CHRONOTHERAPEUTICS:

The term "Chronothrapeutics" originated from greek words "chrono" metabolic events that undergoes rhythmic changes with respect to time." Therapy"- for the cure and treatment of the disorder.

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It is based on the observation that there is some interdependent relation between pharmacodynamic responses , peak to trough rhythmic actions, manifestations of disease, absorption ,distribution, biotransformation and excretion of drugs (Sajan, 2009).

The frequency of rhythmic changes varies from few seconds to seasons (Sajan, 2009). chronotherapeutic regimens are designed to elicit the desired pharmacological responses that is accomplishes through appropriate dose scheduling (scheduling means facilitating the release of higher doses during greater disease activity and lower doses during low disease activity) or through unique drug delivery systems (Glasser, 1999). eg. Controlled –onset extended – release verapamil formulation (COER) (Subal, 2005).

CIRCADIAN RHYTHM :

The term "circadian" was coined since in 1959. The term "circadian" was derived from latin words." circa"- around, "diem" – a day, "rhythm"- activity.

Hence circadian rhythm means activities occurring around a day (www.medicinenet.com). circadian rhythm is also called as "diurnal rhythm" or " biological rhythm" or "variations".

Circadian rhythm is defined as the cyclical changes in physiological processes , functions and biological processes that occur in 24 hour diurnal cycle.circadian rhythm not confined to human beings, it was also takes place in all living entitities that includes plants, animals, fungi and bacteria like cyanobacteria (Wikipedia.org/circadian_rhythm).Without cues provided by the light, The human circadian cycle lasts for 25.9 hours (www. Joint commission.org).

The diurnal cycle facilitates the cyclical release of hormones (eg. Somatostatin releases during sleep) and restoration of energy levels and helps to perform other

body functions includes heart rate, blood pressure, body temperature , gastric pH and renal function (Sajan,2009).Several diseases that follows body's circadian rhythm. Epidemiological studies documented the elevated risk of disease symptoms during 24 hour cycle(shown in the table).

DISEASES	AFFECTED TIME	REFERENCES
Allergic rhinitis	Morning	Sajan,2009
Hypertension	Morning after awakening	Sajan,2009
Migraine	Morning	Pranaywal,2009
Myocardial infraction	Morning	Pranaywal,2009
Ischemic heart disease	Morning	Sajan,2009
Stroke	Morning	Pranaywal,2009
Angina pectoris	Morning	Pranaywal,2009
Parkinson's disease	Morning	Sajan,2009
Epilepsy	Morning	Sajan,2009
Rheumatoid arthritis	Morning	Sajan,2009
Sickle cell anemia	After noon	Sajan,2009
Haemorrhagic ulcer	After noon	Sajan,2009
Perforated ulcer	After noon	Sajan,2009
Osteoarthritis	Evening time	Sajan,2009
Epistaxis	Evening time	Sajan,2009
Peptic ulcer	Late evening and early morning	Pranaywal,2009
Tumour growth rate	day time	Pranaywal,2009
Bronchial asthma	Night	Pranaywal,2009
Gasro-oesophageal reflux disease (GERD)	Night	Pranaywal,2009
Urinary incontinence	late night	Sajan,2009
Insomnia	late night	Sajan,2009
Sleep disorders	late night	Sajan,2009
Renal colic	late night	Pranaywal,2009

Diurnal rhythm affects the organism – drugs interactions, decreasesd ranitidine (H2- Receptor blocker used in ulcer therapy) activity during overnight hours, probably due to blockade of H2 – receptors (Pranaywal, 2009).

LAG TIME:

Lag time is defined as the difference in the time period between when the dosage form is placed in an aqueous environment and the time at which the drug starts to get releases from the dosage form. The lag time of at least 30 mins(0.5 hour) or longer is considered. Lag time of> 4hr is desirable for the release of the drug into the lower portion of the small intestine. Lag time between 0.5 hr and 4 hr are desirable for the release of drug in the upper regions of gut.

MARKETED PRODUCTS OF CHRONOTHERAPEUTIC DRUG DELIVERY SYSTEMS:

GENERIC NAMES	PRODUCTS	MANUFACTURERS
Diltiazem Hcl	Cardizem LA	Biovail corporation, Mississauga, Canada
Propranolol	Innopran XL	Glaxo Smithkline . USA.
Verapamil	VerElan PM	Schwars Pharma, Monheim, Germany
Verapamil	Covera HS	G.D.Searle, (A division of Pfizer), NY, USA

CONCLUSION

Chronotherapeutic drug delivery systems are gaining much importance in the recent trends of novel drug delivery systems. Pharmaceutical research scientists have developed several Chronotherapeutic drug delivery systems but they are under clinical trials and some of them cannot be in force due to facing difficulties in large scale –up operations, cost ineffectiveness and potential or obivious limitations of the materials used for the preparation of the dosage forms hence there is an extensive research work is needed to design suitable devices for the preparation of Chronotheraputic drug delivery systems. The complex technologies includes the application of microchips in the Chronotheraputic drug delivery systems, stimuli sensitive hydrogels and temperature sensitive hydrogels are to be reviewed as interesting advanced drug delivery technology for Chronotheraputic drug delivery systems .

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