Chapter 1

INTRODUCTION

Over a few decades, scientists have recognized the importance of circadian in physiological functions as well as diseases. Generally in all the living organisms, this circadian pacemaker is situated in suprachiasmatic nuclei of hypothalamus and pineal gland; which control various biological processes like sleep-activity, hormonal level-secretions, immune system, gastric and renal functions and other biological functions of the body. 1-3 In today’s world most of the diseases have been associated with the one’s own genetic make up similarly, this circadian activity is also due to clock gene which is situated in different cells, tissues and organ systems which are capable of controlling the various physiological functions and pathology of diseases. 4,5 In regard to this biological rhythm the concept of chronopharmacology has evolved, which deals with the administration of medicaments based on the day-light cycle. Such a therapy of drug administration in coordination with biological rhythm produces a maximum therapeutic effect and minimum side-effects to the patients.6 Among the various diseases, some of the following medical conditions depend on the 24hr rhythm for which symptoms are life threatening occur at precise timings. Sneezing, running nose, allergic rhinitis, migraine headache etc. are more intense in the early morning hours. Similarly, the most of cardiac associated symptoms (angina pectoris, myocardial infarction etc.), thrombotic and hemorrhagic stroke are most
frequent in the early morning hours where as in case of perforated bleeding in peptic ulcer which is intense in the afternoon and symptoms of osteoarthritis worsen in the later part of the day. \textsuperscript{7-11}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{human_circadian.png}
\caption{Human circadian time structure (Reproduced from reference 33)}
\end{figure}

Asthma or bronchial asthma is a chronic inflammatory disorder of the airways leading to reversible precincts of airway. In susceptible patients, the symptoms are wheezing, breathlessness, chest tightening and severe cough. These symptoms are exacerbated in the early morning hours. Nocturnal asthma is a phenotype of asthma in which, an increased airway inflammation occurs during the sleeping hours. The most commonly occurring symptoms are increased airway hyper-responsiveness, worsened expiratory air flow, in combination lead to cough and dyspnea. The exact mechanism of nocturnal asthma is not
clear and it varies from patient to patient. The postulated mechanisms are airway cooling, allergen exposure, gastro-esophageal reflux, decreased plasma cortisol level, increased circulating eosinophils either alone or in combinations. Many researchers have reported that the symptoms of nocturnal asthma is worst in the early morning hours between 4 am to 6 am, when cortisol levels in the body are low and histamine concentrations are at the highest level. \(^{12,13}\)

In such cases, chronotherapeutics play a pivotal role in which the formulations are administered in the late evening, release the drug where symptoms are experienced in the early morning hours or making the *in vivo* drug availability according to the natural circadian rhythm to produce maximum health benefits. Chronotherapeutic drug delivery systems have been recognized as potentially beneficial to the chronotherapy for nocturnal asthma that display time-dependent symptoms according to the circadian rhythms. Thus they increase the efficacy and safety of drugs by proportioning their peak plasma concentrations during the 24hr in synchrony with natural rhythm. The principal advantage of chronotherapeutic pharmaceuticals is to provide optimum plasma levels of drug, resulting in maximum health benefits and minimize the undesired ones. As a consequence there is reduction of dose requirement and this is likely to improve the patient compliance.\(^{14,15}\)

Different types of chronotherapeutic drug delivery systems\(^{16-29}\) are:

1.1 **Enteric-coated systems**

Enteric coatings are pH sensitive, which protected the drug release in acidic region of stomach but releases the drug in the small or large
intestine. Such formulations can be utilised for time-controlled administration of drug with a required lag time. The lag time and the onset of drug release can be controlled by the thickness, pH and type of the polymers.

1.2 **Pulsincap systems**

It consists of an insoluble capsule body (coated with pH dependent polymer) with soluble cap. This formulation contains drug and excipients at the bottom of the capsule body and the open end consists of different polymeric materials as a plug. The plug material can be insoluble but permeable or swellable or pH dependent erodible polymers. After the expulsion of plug material, the drug releases from the system. The thickness/type of plug material controls the lag time.

1.3 **Membrane diffusion controlled systems**

In this case, the drug and excipients mixture acts as a core material which is coated with polymeric coatings. The polymeric coating comprises of both water soluble polymer and insoluble polymer. Upon contact with gastric fluid, the water soluble polymer dissolves and makes sufficient pores through the water insoluble coating membrane allowing the penetration of dissolution fluid leading to diffusion of drug from the pores of the coating membrane.

1.4 **Osmotic systems**

In this drug delivery system, the drug is placed in the core reservoir along with an osmotic agent. This reservoir is coated with semi permeable polymer, capable of controlling the influx of diffusion fluid into the reservoir leading to time-delayed release of the drug through the orifice.
The osmotic agent present along with the drug generates the osmotic pressure and acts as a driving force for the drug release.

1.5 **Diffucaps/Surecaps® Technology**

In this patented technology, the drug release can be a combination of sustained release, immediate release or time-delayed release. Accordingly, the drug is coated over sugar beads or nonpareil seeds which are further coated with a water insoluble polymer or pH dependent soluble polymer capable of releasing the drug after a lag period.

1.6 **Compression coated system**

They are also called as press-coated technology wherein, it consists of tablet in tablet concept. As per this system, the drug is incorporated in the core layer along with excipients which are capable of undergoing rapid disintegration. This core tablet is compression coated with various swellable or pH sensitive polymers which release the core tablet after an appropriate lag time.

1.7 **Layered system**

This system can be either bilayered or three layered that incorporates two different drugs of immediate release layer followed by sustained release layer. Usually, the drug is matrixed along with pH dependent swellable or erodible polymers and compressed as bilayered for immediate release or sustained release of two different drugs according to the pH of the GI tract.