UNIVERSITI TEKNOLOGI MARA

DESIGN OF MULTI-PARTICULATE COMPACT AND "DOME MATRIX" WITH SUSTAINED-RELEASE MELATONIN AND DELAYED-RELEASE CAFFEINE FOR JET LAG TREATMENT

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ABSTRACT

Multi-particulate Dome matrix with sustained-release melatonin and delayed-release caffeine was designed to restore jet lag sleep-wake cycle. The polymeric pellets were produced using extrusion-spheronization technique and fluid-bed coated when applicable. The compact and Dome module were produced by compressing pellets with cushioning agent unless otherwise stated. Dome matrix was assembly of modules with pre-determined compact formulation and drug release characteristics. Melatonin loaded alginate/chitosan-less matrix exhibited almost 100% melatonin release within 8 h gastrointestinal transit with low viscosity hydroxypropyl methylcellulose as cushioning agent. Delayed-release alginate-chitosan caffeine matrix was not attainable through polymer coating due to the premature coat detachment. Admixing of cushioning agent high viscosity hydroxypropyl methylcellulose and high viscosity ethyl cellulose (9:1 weight ratio) with coat-free caffeine loaded particulates introduced delayed-release response via hydroxypropyl methylcellulose swelled in early dissolution phase and ethyl cellulose sustained matrix hydrophobicity at prolonged phase. The caffeine was release substantially in colonic fluid in response to matrix polymers being degraded by rat colonic content. Dome matrix with gastric-specific sustained-release melatonin and intestinal-specific delayed-release caffeine was introduced as an alternative design to introduce melatonin-induced sleep phase then caffeine-stimulated wake phase in restoration of jet lag sleep-wake cycle. To enable efficient gastric and intestinal targeting, intermediate dispersible modules were introduced to detach the melatonin module from the caffeine module along the gastrointestinal transit. The Dome matrix was an assembly of caffeine module with melatonin modules capped at both ends via intermediate dispersible modules (75:25 weight ratio of crospovidone and low viscosity hydroxypropyl methylcellulose). Dome matrix was designed with melatonin module in void configuration and caffeine module in pile configuration to enable the melatonin module to float in the gastric cavity and caffeine module to transit downwards into the intestinal tract. Through using intermediate dispersible module, the melatonin module was detachable from the Dome matrix without incurring surface damages to the caffeine module. The detachment of melatonin module with minimal caffeine module damage further prolonged the caffeine release, with majority of caffeine being delivered in the colonic region (> 85 %). Dome matrix with dual drug release kinetics and targeting sites was produced to introduce melatonin-induced sleep phase then caffeine-stimulated wake phase.

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CHAPTER ONE
INTRODUCTION

1.1 Background to the research

1.1.1 Circadian rhythms of sleep-wake cycle

Circadian rhythms of a sleep-wake cycle in healthy human is a 24-h cycle of approximately one-third sleep and two-thirds wake (Roehrs and Roth, 2019). Daily biological cycles are generated from endogenous circadian oscillator exclusively coordinate approximately 24 h of daily behavioral and physiological rhythms under the influences of genetic, hormonal and environment factors (Schwartz and Klerman, 2019). The summative effects include modulation of sleep-wake cycle, motor activity, cardiovascular activity, secretion and metabolism to adapt to the internal and external alterations and desires. Clock genes are organized by two distinct components namely central clock and peripheral clock. The central clock is located in suprachiasmatic nuclei found within hypothalamus. It serves to form and preserve circadian rhythmicity in human. The peripheral clock is located in almost all tissues and organ in a body. It serves to regulate circadian rhythm corresponding to specific sites of the body (Çakmur, 2018; Cooper et al., 2018; Riganello et al., 2019).

1.1.2 Circadian rhythm sleep disorder

Circadian rhythm sleep disorder arises from chronic or recurrent pattern of sleep and wake disturbance that is due to dysfunction of the circadian clock system or misalignment between the timing of endogenous circadian rhythm and externally imposed social and work cycles resulting in clinically significant functional impairments (Amaike et al., 2020). The misalignment occurs when the entraining agent of circadian clock such as light is out of phase with the internal timing of a human body. Inappropriate timing, intensity, pattern and duration of light exposure may acutely disrupt the activity of the pineal enzyme serotonin-N acetyltransferase in