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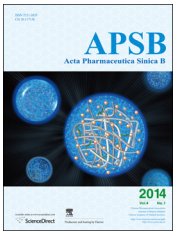

ORIGINAL ARTICLE

Bio-mimetic drug delivery systems designed to help the senior population reconstruct melatonin plasma profiles similar to those of the healthy younger population

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Abstract The secretion of melatonin (MT) is obviously different in the younger and the senior sectors of the population, and the maximum plasma concentration of seniors is only half of that in the younger population group. If exogenous MT can be supplied to senior citizens based on the secretion rate and amount of endogenous MT in the younger population by a bio-mimetic drug delivery system (DDS), an improved therapeutic effect and reduced side effects can be expected. Based upon this hypothesis, the pharmacokinetic parameters of MT, namely, the absorption rate constant (k_a), the elimination rate constant (k_e), and the ratio of absorption rate (F) to the apparent volume of distribution (V) were obtained by a residual method depending on the plasma concentration curve of immediate release preparations in the healthy younger population. The dose-division method was applied to calculate the cumulative release profiles of MT achieved by oral administration of a controlled release drug delivery system (DDS) to

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generate plasma MT profiles similar to the physiological level-time profiles. The *in vivo* release of MT deduced from the healthy younger population physiological MT profiles as the pharmacokinetic output of the bio-mimetic DDS showed a two-phase profile with two different zero order release rates, namely, 4.919 μg/h during 0–4 h ($r=0.9992$), and 11.097 μg/h during 4–12 h ($r=0.9886$), respectively. Since the osmotic pump type of DDS generally exhibits a good correlation between *in vivo* and *in vitro* release behaviors, an osmotic pump controlled delivery system was designed in combination with dry coating technology targeting on the cumulative release characteristics to mimic the physiological MT profiles in the healthy younger population. The high similarity between the experimental drug release profiles and the theoretical profiles (similarity factor $f_2>50$) and the high correlation between the predicted plasma concentration profiles and the theoretical plasma concentration profiles ($r=0.9366$, 0.9163, 0.9264) indicated that a prototype bio-mimetic drug delivery system of MT was established. The similarity factors between the experimental drug release profiles and the theoretical release profile were all larger than 50 both in periods of 0–4 h and 4–12 h, namely, 68.8 and 57.3 for the first batch (Batch No. 20131031), 76.7 and 50.2 for the second batch (Batch No. 20131101), and 73.7 and 51.1 for the third batch (Batch No. 20131126), respectively. The correlation coefficients between the predicted plasma concentration profiles based on the release profiles of the bio-mimetic DDS and physiological profiles were 0.9366 (Batch No. 20131031), 0.9163 (Batch No. 20131101), 0.9264 (Batch No. 20131126), respectively. Since the pharmacokinetic profile of MT in any kind of animal differs markedly from that of human beings, it is impossible to test the bio-mimetic DDS in animals directly. Therefore, the predicted pharmacokinetic profile based upon the *in vitro* release kinetics is an acceptable surrogate for the conventional animal test. In this research, a bio-mimetic DDS for replacement of MT was designed with *in silico* evaluation.

1. Introduction

Biological systems and physiological processes with amazing properties and functions have been recognized and understood over many years. Today, numerous engineers and scientists have an appreciation for the sophistication of biological systems, and they look into these for inspiration in their own research efforts[1]. For example, by studying and imitating complex biological system, researchers have used hormone replacement therapy (HRT) to treat menopausal symptoms of senior women. A number of senior women suffer from hot flashes, anxiety, insomnia, depression, genital tract inflammation by the decrease of estrogen causing in menopause stage. HRT can improve and treat these symptoms in menopause[2]. Another example is an intelligent drug delivery system of insulin where insulin release has been regulated by the different blood glucose levels, with the design aimed to simulate the feedback mechanism of pancreas secreting insulin[3]. However, these designs have not been developed according to the secreting trend of endogenous substances, and bionic function has only been achieved in part in these studies.

Currently, researchers have designed dosage forms according to the circadian rhythm of endogenous substances or physiological phenomena[4]. However, these designs represent a rough conventional replacement, and fail to mimic the endogenous substance fate in human bodies. These designs might cause plasma concentrations larger than desired maxima of endogenous substances with the consequent side effects such as the case for corticosteroids, and an idealized treatment regime is not obtained.

In this study, the concept of bio-mimetic drug delivery system (DDS) was termed as a well tailored system to administrate the active physiological component at a predetermined rate profile based on optimized absorption and elimination of endogenous substances. Firstly, the pharmacokinetic parameters of the endogenous substance administered were calculated by the residual method[5] depending on the plasma concentration curve of immediate release preparations, and then the *in vitro* release profile to produce similar plasma level-time profile as that by natural secretion of endogenous substances were processed by the dose-division method[6]. For the maintenance of physiological plasma level-time profiles of different endogenous biochemicals, appropriate drug delivery systems should be designed.

Since the pharmacokinetic profile of human natural biochemicals in any kind of test animal is dramatically different from that of human beings, it is impossible to test the bio-mimetic DDS in animals directly. Therefore, the predicted pharmacokinetic profile based upon the *in vitro* release kinetics is considered a suitable surrogate for the conventional animal test. The plasma concentration of the active product of the bio-mimetic DDS can be predicted in a reverse way to that of the dose-division method. A similarity factor (f_2)[7] can be used to calculate the similarity between drug release curves of experimental results and that of theoretical calculations, and the similarity between plasma concentration of experimental results and that of predicted plasma levels. Thus it is possible to estimate if the DDS is bio-mimetic, if the above two similarities are determined.

The flow chart (Fig. 1) details an appropriate and meaningful method for designing a suitable formulation for the bio-mimetic DDS by theoretical calculation and evaluation.

Melatonin (MT, *N*-acetyl-5-methoxyl primary amine) is an indole amide neurohormone secreted by the pineal gland, which exhibits distinct circadian rhythm of characteristics with extensive physiological function and immunity[8,9]. MT can promote the proliferation of B lymphocyte, inhibit the growth of tumor cells, and activate endogenous antioxidant defense system and radical scavenging system. MT can effectively prevent the occurrence of cancer caused by oxidative DNA damage, and improve sleep regulation to play a role of biological clock in human bodies. However, ordinary dosage forms like immediate release tablets,