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...
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.

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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. 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. 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. 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. 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 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. 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 biochemcials 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 ($f_2$) 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. 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,

![Bio-mimetic drug delivery systems](image)
Figure 1 The flow chart for the design of a bio-mimetic DDS for melatonin.

capsules, etc., have many shortcomings, e.g., unstable oral absorption, fast distribution, rapid clearance (t_{1/2} is about 30–50 min) and short residence time (1–3 h)\(^{10}\). Also, some sustained or controlled drug release preparations are available. The efficacy and safety of these modified DDSs can be questioned, if they are designed without plasma profile similarity to that of the endogenous rhythm of MT\(^{11}\). An osmotic pump DDS has a number of unique advantages. The DDS is not affected by medium environment such as pH, enzymes, gastrointestinal peristalsis, and food factors for the release of drug. Therefore, osmotic pump preparations have been shown to be one of the best formulations to achieve good correlation of in vivo and in vitro release behaviors. The characteristics of zero order release can reduce trough-peak effect and adverse reactions. Osmotic pump preparations can minimize administration frequency and improve the medication compliance and effectiveness for patients\(^{12,13}\). A biphasic release osmotic pump DDS has been designed in this research to achieve a bio-mimetic release profile based on analysis of the secreting characteristics of MT naturally occurring in human beings.

2. Materials and methods

2.1. Reagents

MT (RS 12061050) was kindly gifted by Hainan Weikang Pharmaceutical (Qianshan) Co., Ltd. (China). Polyoxymethylene (WSR-N80) was supplied by Shanghai Colorcon Coating Technology Co., Ltd. (China). Lactose (Ludipress\(^{16}\) LC) was produced by Shanghai Yunhong Pharmaceutical Excipients Co., Ltd. (China). Magnesium stearate (MS) was purchased from Anhui Hanhua Pharmaceutical Excipients Co., Ltd. (China). Acetone was of synthetic grade and purchased from Sinopharm Chemical Reagent Co., Ltd. (China). Methanol and glacial acetic acid were of HPLC grade produced by Merck Chemicals (Shanghai) Co., Ltd. (China). Ultra-pure water was prepared with a MilliQ-plus system (Millipore, America).

2.2. Theoretical basis

No reports have been published to report on the various pharmacokinetic parameters of human endogenous MT directly. Thus, the in vivo pharmacokinetic parameters of exogenous MT were calculated from the plasma pharmacokinetic curve of MT ordinary immediate release formulations in human subjects\(^{14}\). These pharmacokinetic parameters include 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).

Based upon the pharmacokinetic parameters of MT, the controlled release system can be designed to simulate the excretive level of MT. According to in vitro release characteristics of controlled release formulations, the cumulative release of each time (R_i), and the release rate constant of each time period (k_0) can be obtained by dose-division method. The results show that the cumulative release curves of physiological levels conform to two stages of zero-order release.

2.2.1. Calculation of pharmacokinetic parameters for exogenous MT

The residual method\(^{15}\) is a routine approach in pharmacokinetics to obtain the first order rate constants of absorption (k_a) and elimination rate constant (k_e) as well as the ratio of absorption rate to the apparent distribution volume (F/V). From the in vivo plasma level profile, k_a, k_e and F/V of exogenous MT were obtained by the residual method based on the plasma concentration curve of 0.5 mg MT immediate release formulations by oral administration for all volunteers at 10:30 am\(^{14}\) (Fig. 2), namely, k_a was 1.36 h\(^{-1}\), k_e was 1.21 h\(^{-1}\), and F/V was 3.07 x 10\(^{-6}\) mL\(^{-1}\).

2.2.2. Calculation of MT in vivo release characteristics

The dose-division method\(^{15}\) uses zero-order release sub-doses to approximate atypical release. Since the plasma levels of MT in human populations are available, the theoretical in vivo release profiles can be obtained through the dose-division method. Thus, corresponding to the time \(0, t_1, t_2, \ldots, t_n\), in vivo plasma concentrations are marked by \(0, C_1, C_2, \ldots, C_n\). The calculation process of in vivo drug release kinetics in sustained or controlled release formulations by the dose-division method is a process to calculate the sub-doses with zero-order release rate k_t at each time period.

The drug release of the first time period can be divided into two parts, one part is the amount absorbed by the body, and the other part is that present at the absorption site ready to be absorbed This portion is absorbed gradually when \(t > t_1\). During the release process, the contribution of the absorbed part at \(t = t_1\) \((C_{k1,1})\) is obtained as follows:

\[ C_{k1,1} = \frac{F k_1}{k_e V} \left(1 - \frac{k_e e^{-k_1 t} - k_e e^{-k_t t}}{k_a - k_e} \right) \]  

(1)
Release rate \((k_i)\) is obtained as follows:
\[
k_i = \frac{C_i k_i V}{F(1-(k_i e^{-k_i t_i} - k_0 e^{-k_0 t_0} / k_0 - k_0))}
\]

(2)

The plasma concentrations contributed by the elimination phase of the absorbed part on the subsequent time points \((C_{E,i})\) are
\[
C_{E,i} = C_{E,i} e^{-k_i t_i}
\]

(3)

The concentrations contributed by the residues at the site to be absorbed on the subsequent time points \((C_{S,i})\) are
\[
C_{S,i} = \frac{F k_i (1-e^{-k_i t_i})}{V (k_i - k_0)} \left(e^{-k_i t_i} - e^{-k_0 t_i}ight)
\]

(4)

According to Eqs. (3) and (4), plasma concentrations \([C_2, ..., C_n]\) deduced \(C_{E,i}\) \(C_{S,i}\) respectively. The plasma concentrations \([C_{R,2}, ..., C_{R,n}]\) are obviously contributed by the other release rates except \(k_i\). According to Eq. (1), \(k_2\) is calculated by \(C_{R,2}\). Similar processes may help to get the drug release rate constants \([k_2, ..., k_n]\) on subsequent periods of time. Thereafter, the cumulative in vivo release profile \((R_i)\) is obtained as follows:
\[
R_i = \frac{\sum_{j=1}^{i} k_j (t_j - t_{j-1})}{\sum_{j=1}^{n} k_j (t_j - t_{j-1})} \times 100\%
\]

(5)

It is obvious that plasma concentrations can be derived by inverse direction, if the cumulative release \((R_i)\) and release rate constant \((k_i)\) are known.

2.2.3. Characteristics of MT bio-mimetic DDS

The pineal gland usually begins to secrete MT and other neuropeptides during the night. Ward\(^{16}\) pointed out that under normal circumstances, a healthy younger population began to secrete MT at about 18:00, and a peak concentration appeared at 02:00 in the morning. Relative to this younger population, the MT peak concentration in a senior population group was delayed for an hour, and the maximum plasma concentration was only half of the younger group. The change of plasma concentration in different gender and age of populations also presented some differences. Specifically, the plasma concentration of the younger group was significantly higher than that of the senior group, and the area under the curve (AUC) was approximately two fold larger than that of the senior group (Fig. 3).

From the in vivo levels of endogenous MT in different populations (Fig. 3), the secretion time of 18:00 was selected to be the initial time to administer MT (0 h). Then, the cumulative release percentage at each time point (0–12 h) was calculated by the dose-division method. From this analysis, Fig. 4 shows the calculated in vivo drug release profiles of MT for the four different populations given in Fig. 3.

From Fig. 4, the similarity factor between the calculated in vivo drug release profiles of younger women and younger men was 73.1, and the similarity factor between the calculated in vivo drug release profiles of senior women and senior men was 69.6. The calculated in vivo drug release profiles for people of different gender at the same age were similar.

The in vivo level of MT declines with age increasing, and begins to decline after puberty. Thus the plasma concentration of the senior population is lower than that of younger population which may be due to the calcification of the pineal gland\(^{17}\). However, the profile of the cumulative release graph is almost the same. In all further studies reported, the bio-mimetic DDS of MT was designed by considering the in vivo level of MT for younger women. The bio-mimetic DDS of MT applying to other populations can then be achieved by adjusting the dosage of the DDS.

![Figure 3: Plasma concentration profiles of endogenous MT in different populations\(^{16}\) (* younger women, ■ senior women, ▲ younger men, ◆ senior men).](image)

![Figure 4: Calculated in vivo drug release profiles of MT by dose-division method in different populations (* younger women, ■ senior women, ▲ younger men, ◆ senior men).](image)

2.3. Design of MT bio-mimetic DDS

The calculated in vivo accumulative release curve of MT in younger women (Fig. 4) was fitted according to a number of different drug release models\(^{18}\). As a consequence, the in vivo release of MT in younger women is best fitted by a model based on two phases of zero order release. With the advantages of zero order drug release, high correlation between in vitro–in vivo release and being less affected by factors other than related to the dosage form itself, osmotic pump preparations were selected to be used as the bio-mimetic DDS.

2.4. Preparation of MT osmotic pump tablets

For senior people, a certain amount of MT can still be expected to be secreted. Therefore, the expected in vivo level of MT should be equal to the difference between the plasma concentration of MT for younger people and that for the senior people. From the positive correlation between the AUC and the drug dosage, the dosage of the tablet was calculated to be 115 μg compared with that of the immediate release preparations of MT (the dosage was 0.5 mg) reported with human plasma pharmacokinetics\(^{14}\).

For the preparation of the osmotic pump tablets, MT and other excipients were all sieved through 100 mesh sieve and mixed thoroughly. Then, a mixture containing 49 mg Ludipress\(^{16}\) LC,
115 μg MT and 1 mg MS for each inner core was weighed 50 ± 2 mg and tableted. The tablets were directly prepared with a rotary tablet press (ZP-5, Tianjiu Machinery factory, Shanghai, China) equipped with 5 mm D-tooling slightly concave-faced punch tips. For the outer layer, a mixture of 10 mg WSR-N80, 39 mg Ludipress\textsuperscript{10} LC and 1 mg MS, half was put into the bottom of the die fitted with similar D-tooling but 6 mm diameter, the other half of the outer materials was filled after the inner core being placed into the center of the die. The outer layer materials were weighed 50 ± 2 mg, and the total weigh of each tablet was weighed 100 ± 5 mg, with content of MT as 115 ± 0.5 μg. In order to ensure equal pressure, the thickness of inner core was kept at 1 ± 0.07 mm, and that of the whole each tablet was kept at 2 ± 0.05 mm.

Tablet coating was carried out with a coating pan (BY-300A, Shanghai Huanghui Medicine Checking Instrument Co., Ltd., Shanghai, China). CA in acetone containing PEG-4000 was used as the coating solution (CA:PEG 4000 = 5:1, w/w). The temperature of the coating pan was kept at 37 ± 0.5 °C. Each osmotic pump tablet was entrapped into a small cup and 100 mL of water was added. At 0.5, 1, 2, 4, 6, 8, 10 and 12 h, one milliliter of the dissolution solution was withdrawn and 12 h (Fig. 5). The solution was filtered through a 0.22 μm membrane. Because of the small dose of MT, the concentrations of MT in dissolution samples were determined by LC/MS/MS analysis.

2.5. In vitro release test

In vitro drug release test was conducted in a dissolution apparatus (ZRS-8G, Tianjin Haiyida Tech Co., Ltd., Tianjin, China) with the small cup paddle method according to Chinese Pharmacopeia (2010, Department II, Appendix XC). The temperature was maintained at 37 ± 0.5 °C. Each osmotic pump tablet was centrifuged at 4000 rpm for 15 min. Weight increase after coating was controlled to 5%. The coated tablets were then dried to remove any residual solvent at 40 °C for 1 h. A laser perforation in the coating tablets was made by a drilling laser (SD-20W, Ceres Wuhan Photoelectric Technology Co., Ltd., Wuhan, China), and the diameter of the pore was 0.6 mm.

2.6. Evaluation of MT bio-mimetic DDS

The similarity factor (f\textsubscript{2})\textsuperscript{11} was employed to evaluate the uniformity of the experimental average release profiles for six osmotic pump tablets compared with the ideal release profile.

\[
 f_2 = 50 \times \lg \left\{ \frac{\left( 1 + (1/n) \sum (R_i - T_i)^2 \right)^{0.5}}{100} \right\}
\]

where \( f_2 \) is a logarithmic transformation of the sum-squared error of differences between the experimental drug release \( R_i \) and the ideal release \( T_i \) over all time points \( n \). If the \( f_2 \) value is larger than 50, the mean deviation of two profiles over all time points is less than 10% and the profiles are believed to be similar. Then, it is close to the goal of obtaining a bio-mimetic DDS.

3. Results and discussion

3.1. Design of MT bio-mimetic DDS

The calculated in vivo cumulative release curve of MT in younger women was fitted to a two stage zero order release model. The release was slower in 0–4 h, and faster in 4–12 h (Fig. 5). The equations defining these periods of release were \( y = 4.919x + 0.136 \) \( (r = 0.9992) \) for 0–4 h and \( y = 11.09x - 28.14 \) \( (r = 0.9886) \) for 4–12 h, respectively.

The in vitro drug release can be seen as a “slow–fast” biphasic profile\textsuperscript{12}, which exhibited two different release rates or two different phases of release. The current sustained or controlled release preparations, osmotic pump preparations generally provide a high correlation between in vivo and in vitro drug release\textsuperscript{20}, and the in vitro release characteristics of osmotic pump preparations can better reflect the in vivo release behavior. Thus, osmotic pump DDS is a good choice to achieve the goal of biomimetic DDS.

The simulation of “slow–fast” biphasic delivery system in Fig. 5 was carried out by the preparation of osmotic pump preparations with “tablet-in-tablet” characteristics\textsuperscript{31}. Osmotic pump tablets were composed of three sections, the inner core of tablets containing the drug and immediate-release excipients, the middle section made up of hydrophilic polymer materials, and the outer coating layer. This structure was designed to achieve the “slow–fast” release characteristics required.

3.2. LC/MS/MS analysis

The chromatographic separation was performed on an Agilent 1260 series HPLC system (Agilent Technologies Inc., China). The separation was carried out on a Diamonsil C18 column (150 mm × 4.6 mm, 5 μm) with the column temperature of 40 °C. The mobile phase consisted of methanol-0.1% formic acid aqueous solution (60:40, v/v), at a flow rate of 0.6 mL/min. A sample solution of 1 μL was injected. The total run time for each sample analysis was 5.5 min.

Mass spectrometric detection was performed using a G6460 tandem mass spectrometer (Agilent Technologies Inc., China) equipped with an ESI. Nitrogen was used as nebulizer gas at 45 psi and the drying gas under flow of 5 L/min at 300 °C. The instrument was operated with the capillary voltage at 3.5 kV. Multiple reactions monitoring (MRM) was employed for data acquisition. The optimized MRM fragmentation transition for MT was \( m/z 233 \rightarrow m/z 174 \) with a fragment voltage of 95 V and collision energy (CE) of 9 V.

The stock standard solution of MT (10 μg/mL) was prepared by dissolving the drug in methanol and stored at 4 °C. Standard solutions (5, 10, 20, 50, 100 and 200 ng/mL) were prepared by dilution of the stock standard solution with pure water.
The peak area ratios of standard solutions were proportional to the concentration of MT in each assay over the concentration range of 5.0–200.0 ng/mL. The calibration curves were linear with a correlation coefficient $\geq 0.9973$ by least-squares linear regression with the weighing factor of $1/x^2$. This validated linearity range justified the concentration observed during real sample analysis. The LLOQ (lower limit of quantification) of the analysis was 0.1 ng/mL with the signal-to-noise ratio (S/N) $\geq 10$. The accuracy and precision for MT determination were 102.3%–107.2% and 6.5%, respectively. Recovery of the analysis for the LQC (80 ng/mL) and HQC (160 ng/mL) samples was calculated, which were found to be 106.2 ± 3.9%, 95.9 ± 2.5% and 101.9 ± 0.7%, respectively. For the experiment, these data for the samples met the acceptance criteria at all concentration tested.

### 3.3 Evaluation of bio-mimetic DDS in comparison with the theoretical physiological MT release

Three batches of osmotic pump tablets were prepared in this study. The drug release curves are shown in Fig. 6. Depending on Eq. (6), values of $f_2$ between the experimental and the theoretical in vitro MT release profile were all larger than 50 for periods of 0–4 h and 4–12 h. Namely, the $f_2$ values were 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. In addition, the similarity factors were also larger than 50 over the total drug release period of 0–12 h, namely, 61.5, 53.4 and 55.6, respectively. These results showed that the characteristics of the experimental in vitro release of MT were similar to that of the theoretical calculation and that the bio-mimetic simulation of the MT in vitro release has been achieved by the prepared osmotic pump tablets.

#### 3.4 Evaluation of bio-mimetic DDS by the expected in vivo MT levels

Due to differences of absorption and elimination process between animals and human, it was unable to evaluate that whether in vivo pharmacokinetic behavior of MT osmotic pump tablets accorded with bionic requirements from experiments in animals. In this research, the expected in vivo plasma concentrations of MT were inversely derived by the experimental release results. Then the similarity of data can be obtained by comparing the experimental in vivo level of MT with that of the physiological characteristics. According to the similarity results, the in vivo bio-mimetic result of the DDS can be evaluated.

On the basis of the dose-division method, in vivo plasma concentrations of exogenous MT were calculated based on the release rate of three batches of MT osmotic pump tablets. The plasma concentration of conventional MT, and the maximum plasma concentration was half that of a younger population. Thus, the final plasma concentration of MT in the body should be the sum of the concentration of endogenous and exogenous MT. The plasma concentration of conventional MT sustained release tablets with a dose of 2 mg had been predicted by the way. If all the MT dosage forms were administered at 18:00 p.m., the predicted plasma profiles of MT for the osmotic pump tablets and the conventional sustained release tablets at different times (Fig. 7). The correlation analysis between the predicted plasma concentration curves for MT osmotic pump tablets in the senior population and physiological MT plasma concentration was carried out. Results indicated that osmotic pump tablets were similar to the physiological MT plasma profile, namely, the correlation coefficients ($r$) were 0.9366 (Batch No. 20131031), 0.9163 (Batch No. 20131101), 0.9264 (Batch No. 20131126) respectively (Fig. 7, left), while the predicted plasma concentration curve for MT conventional sustained release tablets was not similar to that of MT physiological profile ($r$=0.1218) (Fig. 7, right). The results suggested that the conventional controlled/sustained release systems were not bio-mimetic and the design in this research was achieved at the goal of a bio-mimetic DDS.
4. Conclusions
The secretion of endogenous MT has a time rhythm. However, the dose levels of the conventional oral pharmaceutical preparations are much higher than the physiological ones. In addition, the time rhythm of endogenous MT was not considered in the design of ordinary preparations, which may cause side effects following treatment, and be unable to achieve the best therapeutic effect. In this study, the novel design methodology of bio-mimetic DDS was investigated. Due to the differences of absorption and elimination process between animals and human beings, it is not possible to test whether the goal of bio-mimetic DDS is achieved using animal experimentation. Therefore, prediction of the plasma level based upon the release of a bio-mimetic DDS is of interest to enable the delivery of appropriate amounts at the correct rates of the endogenous material for replacement therapy.

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