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Construction and Transdermal Absorption Characteristics of Kongmian Shuibao Melatonin Transdermal Nano-Delivery System for Overcoming the First-Pass Effect

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Abstract: Oral administration of melatonin is severely limited by significant hepatic first-pass metabolism, low bioavailability, and high pharmacokinetic variability. To overcome these limitations, the Yixintang Kongmian Shuibao team developed a novel melatonin nano-composite formulation with an ultra-small particle size (10–15 nm). In vitro transdermal permeability across excised male Sprague-Dawley rat skin was evaluated using Franz diffusion cells, with melatonin concentrations quantified via high-performance liquid chromatography (HPLC). The nano-composite demonstrated significantly higher transdermal absorption profiles compared to conventional oral and benchmark formulations, achieving therapeutically effective doses required for human sleep regulation. Furthermore, a 7-day repeated dermal application study in rabbits confirmed zero incidence of erythema or edema, establishing superior skin compatibility. This nano-delivery system represents a highly promising non-invasive transdermal candidate for sleep improvement.

Keywords: Melatonin; Transdermal nano-delivery system; Hepatic first-pass effect; In vitro permeation; Skin irritation; Bioavailability

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1. Introduction

Melatonin is a natural indole hormone secreted from the pineal gland, a pinecone-sized structure located deep within the mammalian brain, commonly known as “pinealidin”. Studies have shown that melatonin can inhibit the growth of melanocytes, suppress tyrosinase activity to lighten melanin, and promote cellular metabolism; by scavenging free radicals, exhibiting antioxidant effects, and inhibiting lipid peroxidation, it protects cellular structures, prevents damage, and lowers peroxide levels in the body, demonstrating a significant protective effect against damage caused by exogenous toxins. It possesses a broad spectrum of physiological

activities involved in sedation, hypnosis, analgesia, and immune responses.

Currently marketed oral melatonin products exhibit significant hepatic "first-pass effect," with low bioavailability and high coefficient of variation. Currently marketed skincare products directly added with melatonin show poor skin permeability, affecting bioavailability.

The Yixintang Kongmian Shuibao team provides a melatonin nano-composite with good stability, high drug loading capacity, excellent skin permeability, and a wide range of applications, along with its preparation method and application through a new process.

The following is the melatonin nano-composite of the Yixintang Kongmian Shuibao team, including components by weight percentage as follows: melatonin 0.1%–8.0%, emulsifier 2.0%–12.0%, co-emulsifier 10.0%–50.0%, liquid lipid 1.0%–10.0%, humectant 0.01%–5.0%, stabilizer 0.01%–5.0%, and the remainder being water.

The emulsifier is one or a mixture of several selected from Tween 80, Tween 60, Tween 40, Tween 20, polyoxyethylene castor oil-20, polyoxyethylene castor oil-30, polyoxyethylene castor oil-35, polyoxyethylene castor oil-40, PEG-40 hydrogenated castor oil, PEG-30 hydrogenated castor oil, PEG-20 hydrogenated castor oil, PEG-10 hydrogenated castor oil, PEG-5 hydrogenated castor oil, polyethylene glycol 400 monoglyceride, polyethylene glycol 400 diglyceride, polyethylene glycol 600 monoglyceride, polyethylene glycol 600 diglyceride, coco-glucoside, ceteareth-20, ceteareth-25, and PP-26-buteth-26.

The humectant is one or a mixture of several selected from allantoin, hyaluronic acid, ceramides, chitosan, sorbitol, sodium lactate, chondroitin sulfate, amino acids, and vitamin B5.

The stabilizer is one or a mixture of several selected from xanthan gum, polyvinylpyrrolidone, hydroxypropyl methylcellulose, sodium carboxymethyl cellulose, gelatin, guar gum, gum arabic, carbomer, tyrosine, tyrosine methyl ester hydrochloride, tyrosine ethyl ester hydrochloride, and tyrosine propyl ester hydrochloride.

The particle size of the melatonin nano-composite is between 10–15 nm [3].

This process significantly increases the drug loading capacity and bioavailability. The following are animal experimental data regarding the biological permeability of this experiment:

Permeation tests were conducted using the abdominal skin of male SD rats weighing 160–220 g as the barrier layer for the transdermal test. Intact and undamaged skin was fixed between the receptor cell and the donor cell (with the inner layer of the skin facing the receptor cell); diffusion cell parameters were: effective diffusion area 3.14cm^2, receptor cell volume approximately 7.0 mL, magnetic stirring speed 600 rpm; the receptor cell was filled with the release medium 4.5% Ceteareth-20 in ethanol-saline solution, air bubbles were eliminated, stirring was turned on, and the temperature was maintained at (37.0 ± 0.5)℃. A 1 g sample was evenly applied to the skin surface. At 1 h, 2 h, 4 h, 6 h, 8 h, 10 h, and 12 h, 0.35 mL of receptor fluid was drawn and replaced with 0.35 mL of fresh release medium. The receptor fluid was filtered through a 0.22 μm organic filter membrane, and the concentration of melatonin in the filtered receptor fluid was determined using high-performance liquid chromatography to calculate the cumulative transdermal drug amount at different times [4].

The cumulative transdermal amount of melatonin per unit area was calculated according to the following formula:

$$Q_s = \frac{C_n V + \sum_{i=1}^{n-1} C_i V_i}{S}$$

Where: Qs is the cumulative transdermal amount; S is the effective diffusion area; V is the volume of saline in the receptor cell; Ci is the drug concentration in the receptor fluid from the 1st to the previous sampling time; n is the n-th sampling volume; Cn is the drug concentration in the receptor fluid at that sampling time [5]. Data are shown in Figure 1. Based on the preparation condition differences, the Yixintang Kongmian Shuibao team divided the nano-melatonin into 1 control group and groups 4–7 for comparative experiments. The experimental results were groups 4–7 and the control group. From the experimental results, the permeability of melatonin produced by the new process is extremely high, far higher than traditional oral administration and other groups. Moreover, it basically reached the effective dose required for human sleep.

Samples of the melatonin nano-composites prepared in Examples 4–7 were taken and mixed with the blank cream in Comparative Example 1 at a mass ratio of 1:1 for skin irritation testing:

Eighteen healthy rabbits weighing (2.0 ± 0.2) kg were randomly divided into 6 groups, with 3 animals in each group. Hair on both sides of the back skin of the rabbits was removed 24 hours prior to the experiment. After hair removal, the skin was checked 24 hours later to ensure it was not injured, as injured skin is unsuitable for skin irritation testing. The cream prepared using the melatonin nano-composites obtained in Examples 4–7 was applied 3 times daily for 7 consecutive days, while a blank cream (without any drug) was applied simultaneously as a control. The test results were observed and listed in Table 1.

According to the test results in Table 1, it can be seen that after applying the creams prepared with the melatonin nano-composites of Examples 4–7 and the blank cream onto the rabbit skin, there were no congestion or swelling phenomena, indicating that the melatonin nano-composite provided by the present invention has no skin irritation [6].

Table 1. Observation results of skin irritation of nano-composites of Examples 4–7 and control group

Group	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Control Group	—	—	—	—	—	—	—	—
Example 4	—	—	—	—	—	—	—	—
Example 5	—	—	—	—	—	—	—	—
Example 6	—	—	—	—	—	—	—	—
Example 7	—	—	—	—	—	—	—	—

"+" indicates rabbit skin congestion and swelling; "++" indicates that congestion and swelling persist with an increasing trend; "—" indicates no congestion or swelling.

From the above experiments, it can be seen that the melatonin nano-composite provided by the Yixintang Kongmian Shuibao team has good stability, high drug loading capacity, and good skin permeability, which can effectively improve sleep.

Disclosure statement

The author declares no conflict of interest.

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