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TRANSDERMAL MELATONIN DELIVERY SYSTEM FOR INSOMNIA TREATMENT

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Abstract: Melatonin, a pineal gland hormone can play an important role on circadian rhythms and worked as an internal sleep facilitator in human. Recently, melatonin was used as a drug for treatment of insomnia. The transdermal drug delivery is a good alternative for melatonin delivery because of its variable oral absorption, short half-life, highly first pass metabolism, and a favorable partition coefficient. Recently, transdermal delivery of melatonin is prepared as solutions, patches, nanovesicles and nanoparticles, and hydrogels. Many studies are successful in development and evaluation of transdermal melatonin delivery system with high drug released, high drug permeated, and high permeation rate with short lag time. Furthermore, vehicles and penetration enhancers have a major effect on melatonin permeation via the skin. Some clinical trials that studied the effectiveness of transdermal melatonin patch showed that the patch can increase plasma melatonin level for an extended duration. However, these clinical trials were performed in few numbers of subjects, thus the study in a larger number of subject is still necessary. In conclusion, transdermal melatonin delivery may be a more effective way in the treatment of insomnia.

Keywords: melatonin, transdermal drug delivery system, insomnia

บทคัดย่อ: เมลาโทนิน เป็นฮอร์โมนจากต่อมไพเนียล มีบทบาทสำคัญในการควบคุม circadian rhythms และควบคุมการนอนหลับของมนุษย์ ปัจจุบันเมลาโทนินใช้เป็นยารักษาอาการนอนไม่หลับ การนำส่งยาทางผิวหนังเป็นทางเลือกที่ดีอย่างหนึ่งในการนำส่งเมลาโทนิน เนื่องจากเมลาโทนินมีการดูดซึมในทางเดินอาหารที่แปรปรวน ค่าครึ่งชีวิตสั้น การทำลายยาที่ตับสูง และมีค่าสัมประสิทธิ์การแบ่งภาคที่เหมาะสมสำหรับการนำส่งทางผิวหนัง ในปัจจุบันระบบนำส่งเมลาโทนินทางผิวหนังมีหลายรูปแบบ เช่น สารละลาย แผ่นแปะ นาโนเวสิเคิลและนาโนพาร์ทิเคิล และไฮโดรเจล มีการศึกษาหลายการศึกษาที่ประสบความสำเร็จในการพัฒนาและประเมินระบบนำส่งเมลาโทนินทางผิวหนังที่มีการปลดปล่อยยาสูง การซึมผ่านผิวหนังสูง อัตราการซึมผ่านผิวหนังสูง และระยะเวลาเริ่มปลดปล่อยยาสั้น นอกจากนี้กระสายยาและสารเพิ่มการแทรกซึมมีบทบาทสำคัญในการซึมผ่านผิวของเมลาโทนิน การศึกษาทางคลินิกที่ศึกษาประสิทธิภาพของแผ่นแปะเมลาโทนิน พบว่า แผ่นแปะเมลาโทนินช่วยเพิ่มระดับเมลาโทนินในพลาสมาและคงระดับยาได้นาน แต่อย่างไรก็ตามการศึกษาทางคลินิกเหล่านี้ใช้จำนวนอาสาสมัครขนาดเล็ก ดังนั้นการศึกษาในอาสาสมัครขนาดใหญ่ขึ้นยังคงมีความจำเป็น กล่าวโดยสรุปคือ การนำส่งเมลาโทนินทางผิวหนังอาจจะเป็นทางเลือกหนึ่งที่มีประสิทธิภาพในการรักษาอาการนอนไม่หลับต่อไป

คำสำคัญ: เมลาโทนิน, ระบบนำส่งยาทางผิวหนัง, นอนไม่หลับ

INTRODUCTION

Insomnia is the most common symptom of sleeping disorder which affected people around the world. It can characterize into three types; difficulty falling asleep, difficulty staying asleep, and poor quality sleep (Walsh, 2004). The high prevalence of insomnia is reported in some countries such as the United Kingdom (37%) (Morphy *et al.*, 2007), Indonesia (33.8%) (Zailinawati *et al.*, 2008), and Japan (23.5%) (Kaneita *et al.*, 2006). In Thailand, elderly people have a high prevalence of insomnia, approximately 46.3% is reported (Sukying *et al.*, 2003). This problem affects daytime functioning (Komada *et al.*, 2012) and has an impact on health and quality of life. Anxiety, depression, pain, increase the risk of cardiovascular events especially myocardial infarction are associated with insomnia (Morphy *et al.*, 2007; Westerlund *et al.*, 2013). Furthermore, accidents at home, workplace, or car are also related to insomnia (Leger *et al.*, 2014). The associated factors of insomnia are gender, poor mental health, smoking, alcohol consumption, college-bound, late bedtime, and lifestyle (Doi, 2009; Kaneita *et al.*, 2006).

Both behavioral and pharmacological treatment is included in insomnia treatment. Melatonin is one of many drugs use for the treatment of insomnia. Prolonged-release oral melatonin (2 mg) tablet is available in Thailand. However, other dosage forms of melatonin are under development and clinical trials. Transdermal melatonin delivery system in various dosage forms will be reviewed in following topics.

MELATONIN

Melatonin is hormone of mammals and human. The source of melatonin synthesis is tryptophan. It is converted into 5-hydroxytryptophan and serotonin by tryptophan-5-hydroxylase and aromatic L-amino acid decarboxylase, respectively. Then, serotonin is metabolized into melatonin in two steps by serotonin N-acetyltransferase and hydroxyindole-O-methyltransferase, respectively (Schomerus and Korf, 2005). Melatonin synthesis pathway is shown in Figure 1.

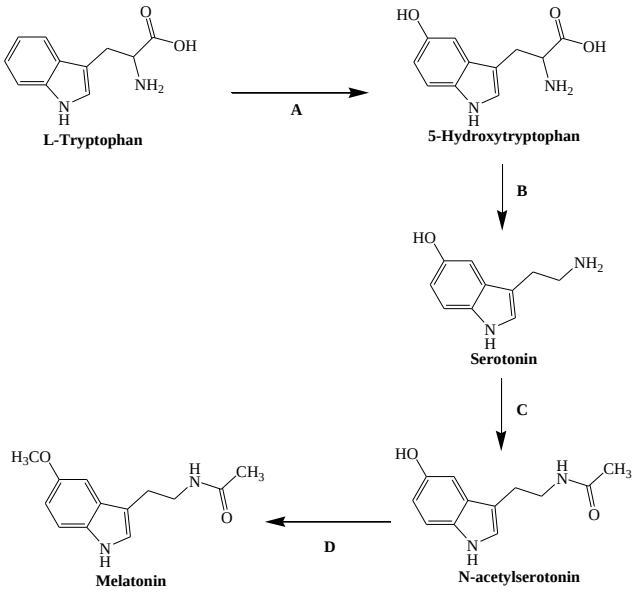

Figure 1. Melatonin synthesis pathway. Where, A-D are tryptophan-5-hydroxylase, aromatic L-amino acid decarboxylase, serotonin N-acetyltransferase, and hydroxyindole-O-methyltransferase, respectively

The pineal gland is a major endocrine effector of the photoendocrine system. Each night, pineal gland creates a message encoding darkness via melatonin. Melatonin has lipophilic property, thus it is not stored in pinealocytes, but immediately release upon it is produced from the pineal gland into blood circulation (Schomerus and Korf, 2005). Normally, melatonin production of healthy volunteers is 28.8 µg/day (Lane and Moss, 1985). During midnight to 3 a.m., serum melatonin reaches peak values (80-150 pg/mL). Conversely, during the day, serum melatonin concentration is low (10-20 pg/mL) (Dziegiel *et al.*, 2008).

Melatonin has a major effect on sleep and circadian rhythm. Other physiological effects are also reported, it is involved in the regulation of seasonal reproduction, body weight, and energy balance (Barrenetxe *et al.*, 2004).

TRANSDERMAL DRUG DELIVERY SYSTEM

Transdermal drug delivery system (TDDS) is the dosage form designed to deliver active pharmaceutical ingredient across the skin (Wokovich *et al.*, 2006). The first approved TDDS for systemic drug delivery in 1979 is scopolamine patch for treatment of motion sickness. Recently, many transdermal delivery systems are approved by the United States Food and Drug Administration and launched in the market (Prausnitz and Langer, 2008). TDDS has many advantages over oral route. It is useful for patients that cannot be swallowed especially for vomiting and unconscious patients. It can avoid first pass drug metabolism by the liver, thus it is suitable for high first pass metabolized drugs. TDDS has a potential for sustained release manner, therefore it is useful for short biological half-life drug. Comparing to injections. TDDS is non-invasive manner, it can avoid the risk of infection due to the unsuitable injection procedure. Furthermore, it is a self-administered system, in the case of toxicity occurrence, patients can remove it by themselves. Unfortunately, the only partial number of drugs are probably transported across the skin (Prausnitz and Langer, 2008; Ruby *et al.*, 2014).

Stratum corneum is the outer layer of the skin played important roles as a rate-controlling barrier for almost all of the compounds. It is composed of dead, flattened, keratin-rich cell, the corneocytes. These dense cells are surrounded by intercellular lipids; ceramides, free fatty acids, cholesterol, and cholesterol sulphate (Hadgraft and Guy, 2003). There are three pathways for transport the compound through stratum corneum; transcellular, intercellular (paracellular), and transappendageal pathway. Transcellular pathway, compound directly pass both phospholipid membrane and cytoplasm of the dead keratinocytes that constitute the stratum corneum. It involved the repeated partitioning of the compound between hydrophobic and hydrophilic compartment of the skin. Polar and nonpolar solute permeated the stratum corneum by a different mechanism. The polar solute is diffuse through the immobilized water near the outer surface of keratin filament. Conversely, nonpolar solute diffused through interstitial lipid pathway (Roberts *et al.*, 2007). However, recently evidence suggested that most compound transport through the stratum corneum by intercellular route (Roberts *et al.*, 2007; Rougier *et al.*, 2001). Drug cross the skin by intercellular route must pass through the intercellular space between the cells of the skin, thus this route is more tortuous compared to the transcellular route. In addition, the transappendageal pathway is a delivery of compound through skin appendage such as hair follicles, sweat ducts, pilosebaceous glands, which particle size is the most important effect for delivery of this route. However, this route is occupied a small area, thus very little compound actually crosses the skin via this route (Roberts *et al.*, 2007).

Typically, low molecular weight drug (less than 400 Da), log P between 2-3 (Ranade and Cannon, 2011; Wiedersberg and Guy, 2014), and daily dose less than 10 mg is proper for

transdermal delivery (Ranade and Cannon, 2011). However, some approved drugs with log P 1-4 (Dragicevic-Curic and Maibach, 2013) or 1-5 (Wiedersberg and Guy, 2014) can deliver via the skin. Melatonin has many properties that can be delivered via the skin. Their partition coefficient is appropriate for transdermal delivery (log P = 1.20) (Kandimalla *et al.*, 2010) and low molecular weight (232.3 Da), thus, melatonin has highly potential to delivery through the skin. In addition, melatonin has a fluctuation on their absorption, short half-life (≈ 40 min) (Andersen *et al.*, 2016), high first pass effect (Lane and Moss, 1985). Consequently, delivery of melatonin using TDDS can resolve these problems.

TRANSDERMAL MELATONIN DELIVERY SYSTEM

Sustained release formulation can decrease dosing frequency and increase bioavailability by penetration enhancement of melatonin. Thus, sustained release and penetration enhancement of melatonin are major aims of formulation design of transdermal melatonin delivery. Many studies prepared various dosage forms of melatonin delivery through the skin such as solutions, patches, nanovesicles and nanoparticles, and hydrogels. Each dosage form is showed on the following topic.

Solutions

Initially, transdermal melatonin delivery prepared in solutions. The effect of vehicles and penetration enhancers is studied. Type of vehicle is varied; ethanol, polyethylene glycol (PEG) 400, and propylene glycol (PG). Solubility result showed that melatonin can soluble in ethanol and PEG 400 higher than PG. The increment of vehicle concentration, the solubility of melatonin increased. Melatonin dissolved in 40% ethanol in the buffer can permeate skin better than melatonin dissolved in 40% PEG 400 in the buffer and 40% PG in the buffer. Melatonin dissolved in 40% PG in the buffer can permeate skin as well as in buffer. Unfortunately, melatonin dissolved in 40% PEG 400 promoted lower skin permeation compare to melatonin dissolved in buffer alone. Flux and permeability coefficient (K_p) of melatonin in ethanol have the highest value. When the concentration of ethanol increasing, these two parameters also increased. Thus, ethanol is the most appropriate solvent for melatonin delivery (Oh *et al.*, 2001). Other types of vehicle are also studied. Top three of vehicles promoted the highest flux of melatonin via porcine skin are isopropyl myristate, Lauroglycol^{TM} FCC, and ethanol; 3.45±0.53, 3.18±0.51, and 2.86±0.54 μg/cm^2/h, respectively (Kikwai *et al.*, 2002). Type of penetration enhancer also investigated. Six fatty acids with different carbon chain length are used as a penetration enhancer; capric acid, lauric acid, myristic acid, palmitic acid, stearic acid, and oleic acid. Increasing of carbon chain length, K_p decreased. Which, oleic acid has the highest K_p value. In addition, oleic acid promoted the lowest lag time of melatonin permeation. This result indicated that oleic acid is the most suitable penetration enhancer for melatonin in solution dosage form (Oh *et al.*, 2001). Other research reported the parabolic relationship between carbon chain length of saturated fatty alcohols (octanol, nonanol, decanol, undecanol, lauryl alcohol, tridecanol, myristyl alcohol) and permeation enhancement of melatonin. Maximum permeation is found when carbon chain length is 10. In the case of unsaturated fatty alcohols (oleyl alcohol, linoleyl alcohol, linolenyl alcohol), when unsaturation level increased from one to two double bonds, melatonin permeation is increased. However, three double bonds unsaturated fatty alcohol decreased melatonin permeation (Andega *et al.*, 2001).

Patches

Melatonin-loaded adhesive patch is prepared. Eudragit® E100 is used as the adhesive polymer. Three groups of penetration enhancer are compared; fatty alcohols (octanol,

decanol, myristyl alcohol), fatty acids (nonanoic acid, undecanoic acid, myristic acid), and terpenes (menthol, limonene). Melatonin release study showed that with or without penetration enhancers unaffected drug release. However, these penetration enhancers are affected drug permeation. Octanol 2.5% and 5% promoted the highest drug permeation compare to other fatty alcohols. For fatty acids, undecanoic acid 5% promoted the highest drug permeation. According to terpenes group, menthol 2.5% promoted higher drug permeation compare to limonene 2.5%, however, increasing of menthol and limonene to 5%, drug permeation promoted by these two terpenes is similar. Calculated enhancement ratio showed that menthol 5%, limonene 5%, and decanol 5% are the top three penetration enhancer promoted the maximum enhancement ratio of 2.1, 2.0 and 1.7, respectively when compare to control group (Kanikkannan *et al.*, 2004).

Transdermal patches are very popular for delivery of melatonin due to it is easily scale-up compared to another dosage form. A clinical trial in seven healthy subjects showed 3 mg melatonin-loaded solid lipid nanoparticles incorporating patch can enhance half-life of melatonin up to 25 h. In addition, melatonin plasma level is maintained higher than 50 pg/mL for 24 h (Priano *et al.*, 2007). In 2009, there is a randomized, double-blind, crossover study in eight healthy volunteers. Subjects received skin patch containing 2.1 mg melatonin or placebo. After 3 h of patch application, plasma melatonin level significant higher than placebo group as well as 3 h after patch removed. Reported C_{max} and T_{max} of the melatonin patch group are 690.4±138.8 pmol/L and 8.58±0.63 h, respectively. Furthermore, melatonin patch reduces waking after sleep onset about 56 min, increase the duration of REM sleep about 21 min, and increase sleep efficiency about 30% after applied patch for 7 h (Aeschbach *et al.*, 2009). However, Bénès et al. reported that transdermal melatonin delivery had higher variability of systemic drug level compare to transmucosal delivery (Bénès *et al.*, 1997).

Nanovesicles and nanoparticles

Liposome, transfersome, and ethosome are some types of nanovesicles. Dubey et al. compare melatonin delivery using these three nanovesicles. Penetration parameters are shown in Table 1. This result showed that ethosomes had the highest efficiency to delivery melatonin via the skin due to the highest release rate, flux, and K_p, and the lowest lag time compares to transfersomes and conventional liposomes. Furthermore, ethosomes can penetrate into deeper skin compare to transfersomes and conventional liposomes (Dubey *et al.*, 2006; Dubey *et al.*, 2007). This result may be associated with ethanol containing in ethosomes that play an important role as a penetration enhancer (Williams and Barry, 2004). However, the particle size of nanovesicles may be also affected drug permeation.

Table 1. Some penetration parameters of three nanovesicles (Dubey *et al.*, 2006; Dubey *et al.*, 2007).

Parameters	Ethosomes	Transfersomes	Conventional liposomes
Release rate (μg/cm^2/h)	63.2±1.48	59.2±2.21	16.9±1.65
Transdermal flux (μg/cm^2/h)	59.2±1.22	51.2±2.21	10.9±1.65
K_p ($\times 10^3$ cm/h)	15.80	15.06±0.52	3.21±0.51
Lag time (h)	0.9	1.1	2.7

Note: Particle size of ethosomes, transfersomes, and conventional liposomes are 122±3.5, 118±10, and 148±9.0 nm, respectively

Lecithin/chitosan nanoparticles are prepared for delivery of melatonin via the skin. Two grades of lecithin are used; S100 and S45. The cumulative amount of drug permeated from two grades lecithin nanoparticles compare to lecithin aqueous solution is similar.

Lecithin S100/chitosan nanoparticles in the ratio of 20:1 promoted melatonin permeation closed to lecithin aqueous solution. However, lecithin S45/chitosan nanoparticles in the ratio of 20:1 showed the highest drug permeation. Decreasing of lecithin/chitosan ratio to 10:1, drug permeation from lecithin S100/chitosan nanoparticles increased, conversely, drug permeation from lecithin S45/chitosan nanoparticles decreased. This study showed the maximum flux, 9.0±0.21 μg/cm^2/h, is found for lecithin S45/chitosan nanoparticles in the ratio of 20:1 (Hafner *et al.*, 2011).

Hydrogels

Hydrogels containing redispersible spray-dried melatonin-loaded nanocapsules is also prepared for control release of melatonin through the skin. Polymeric nanocapsules are prepared from caprylic/capric triglyceride mixture and Eudragit® S100. Melatonin in a final concentration of 0.5 mg/mL is added during nanocapsule preparation. After that, polymeric nanocapsule suspension is spray dried using lactose and maltodextrin as drying adjuvants. Finally, spray dried melatonin-loaded nanocapsule is incorporated into carbomer hydrogel. The best controlled release of melatonin is obtained from hydrogel prepared with spray-dried nanocapsule as well as skin permeation result compare to redispersible spray-dried nanocapsule, nanocapsule suspension, and melatonin solution, respectively (Hoffmeister *et al.*, 2012).

CONCLUSION

Melatonin is one of drug that suitable for delivery via the skin. Many dosage forms of melatonin are prepared such as solutions, patches, nanovesicles and nanoparticles, and hydrogels. Most of the formulations are successful to delivery melatonin through the skin. The high amount of drug release and drug permeation is achieved. In summary, transdermal drug delivery system is an effective way for delivery of melatonin for treatment of insomnia.

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