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Melatonin Modified Release Formulations Designed for Sleep Disorders

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Abstract

Melatonin (*N*-acetyl-5-methoxytryptamine, MLT), a hormone synthesized by the pineal gland and released at night, has a regulatory role on sleep in vertebrates, including humans. It has been shown to have a hypnotic action in animals and humans and it has been used as an agent for restoring circadian rhythms, disturbed by jet-lag, shift-work or aging. The physiological actions of melatonin in regulating seasonal and circadian rhythms are mediated through a family of specific, high affinity G protein-coupled membrane receptors. The beneficial effect of fast-release formulations on sleep initiation may come from the high amount of melatonin released immediately after administration, while the benefit of the sustained release systems comes from the release of melatonin in small dosages during the entire night period. This chapter covers the recent scientific work on melatonin modified release formulations.

Keywords: melatonin, sleep onset, sleep maintenance, modified release, formulations

1. Introduction

Melatonin (MLT), which was originally discovered in the bovine pineal gland in 1958, is a pleiotropic molecule with numerous cellular and physiological functions in vertebrates, including humans. MLT's production is regulated by a multisynaptic pathway from the biological clock in the suprachiasmatic nucleus (SCN), in the hypothalamus, to the pineal gland. The SCN is the primary site for both generation and integration of signals, which regulate melatonin's production by the pineal. Control at this central point ensures the high nocturnal concentration and extremely low diurnal melatonin synthesis.

Melatonin has been shown to have a hypnotic action in animals and humans, and there has been considerable recent interest in the therapeutic potential of melatonin and its analogues as hypnotics and as agents for restoring circadian rhythms, disturbed by jet-lag, shiftwork, and aging. The physiological actions of melatonin in regulating seasonal and circadian rhythms are thought to be mediated through a family of specific, high affinity, and G-protein-coupled cell membrane receptors. One of its main uses is insomnia treatment, particularly among the elderly, with up to 50% of people over the age of 65 reporting trouble sleeping. Night time insomnia is associated with increased daytime sleepiness, reduced motor and cognitive performance, and reduced productivity in the workplace and is an important cause of industrial and road traffic accidents. Current hypnotic drugs are recommended only for short-term treatment of insomnia, but concerns about “hangover” effects and problems upon withdrawal persist. Many people with occasional sleep problems resort to self-medication and over-the-counter sales of medicines for sleep problems are increasing rapidly [1].

The administration of exogenous melatonin is effected via different formulations, but at present, the most studied is the oral route. Also, there are different dosages of melatonin. Because of its pharmacokinetic characteristics, it is necessary to maintain melatonin’s concentration for a long time to imitate its physiological release, especially for insomnia treatment. To this end, prolonged-release formulations of melatonin have been developed covering the entire night cycle and improving sleep disorders. As the toxicology of melatonin’s formulations is concerned, very little is known. However, the acute toxicity of melatonin, as seen in both animal and human studies, is extremely low. Nevertheless, further research needs to be undertaken, including regulatory studies.

2. Formulations of melatonin

Melatonin is traditionally administered orally in immediate and modified release formulations, but has a poor and variable bioavailability. Apart from *per os* administration, melatonin is currently under research with respect to other routes of administration, such as sublingual, transbuccal/transmucosal, and intranasal for topical and systemic exposure, injectables (intravenous, i.v. bolus infusion, intramuscular, subcutaneous, and implant), topical preparations, and transdermal patches. This chapter aims at presenting an overview of all administration routes and different kinds of formulations of melatonin that are currently explored *in vitro* and *in vivo*, including experimental and clinical studies.

2.1. Melatonin *per os* immediate release formulations

Per os immediate release formulations imply that the full dose of the drug is absorbed into the bloodstream all at once. This pattern of fast released melatonin is most effective when against delayed sleep onset [2]. The immediate release dosage forms (fast released, orodispersible, sublingual tablets oral sprays, etc.) are usually administered to patients prior to sleep time in order to facilitate sleep onset. A research group has manufactured fast dissolving disintegrating tablets containing different dosages of melatonin for administration

to pediatric patients that may have potential difficulties taking other oral dosage forms [3]. Dosages of 3 and 5 mg were intended for epileptic children, migraine prevention, neurodevelopmental disability, sleep disorders, and blindness, whereas dosages of 10 and 60 mg were used for Duchenne muscular dystrophy. Tablets have been produced with excipients for direct compression, having disintegration times of less than 25 s and with friability and hardness values that require no special storage or packaging conditions. The results indicated that these orodispersible tablets have been easily produced via direct compression, having low costs and optimal galenic assay results. To explore the therapeutic potential of melatonin, as an antioxidant agent, researchers have analyzed the red blood cell antioxidants and lipid peroxidation after 5 mg/daily immediate-release melatonin treatment of elderly with type 2 diabetes patients and healthy elderly subjects in comparison with 2 mg/daily sustained-release. The results suggest that both immediate and sustained release preparations may exert similar therapeutic effects related to melatonin's action as antioxidant [4].

2.2. Melatonin *per os* modified release formulations

Immediate release oral drug dosage forms are formulated in order to release the active substance immediately after oral administration. On the other hand, modified-release oral drug dosage forms are deliberately modified from those of an immediate release, to achieve a desired therapeutic objective or better patient compliance. The term modified release drug dosage forms is used to describe formulations that alter the time and/or the rate of release. With this in view, scientists have focused on modifying the release of melatonin especially to treat conditions that deal with circadian rhythmic disorders, like sleep syndrome, insomnia, jet lag, seasonal affective disease, shift work syndrome, etc. [5–7]. Modified-release melatonin treatment could be more useful to initiate and maintain sleep, compared with immediate-release therapy.

Many scientists have focused on different ways to manufacture modified release tablets. One of the most common ways is the use of various excipients that facilitate the prolong release when tablet manufacturing [8–13]. These excipients usually involve hydroxypropylmethylcellulose, polyvinylpyrrolidone, and sodium alginate in various molecular weights or forms. Another way to achieve modified release is the production of different tablet formulations, like multilayer or bilayer, coated or uncoated tablets [14–16]. Other researchers have studied the use of liposomal formulations [17] or nanoparticles [18]. Recently, electrospun nanofibrous systems, incorporating melatonin, have been used for its modified release [19]. Another way is to employ a variety of techniques, like for example, the experimental design [20] in order to facilitate the modified release tablet production and therefore, to improve quality of sleep in patients, with minimal side effects. Both in the development of these systems and the immediate release formulations, the fact that melatonin displays both a circadian and circannual rhythm and is secreted only during the night has been taken into account. This physiological rhythm needs to be conserved or modulated (advanced, reversed, diminished, or amplified) according to the appropriate therapeutic indications.

2.3. Melatonin sublingual/transbuccal formulations

The oral cavity is a perfect route of administration for both topical and systemic treatment. Considering melatonin, research has suggested that it is effective in treating pathologies like periodontitis, mucositis, cancers, and cytotoxicity from various drugs or biomaterials. Furthermore, melatonin has been observed to enhance osseointegration “functional ankylosis (bone adherence)” and bone regeneration, to promote the healing of tooth extraction sockets and may also impede the progression of oral cancer [21, 22]. On the other hand, sublingual and transbuccal/transmucosal administration of melatonin in the forms of sublingual tablets or oral sprays has shown comparable systemic results to other routes of administration.

Many scientists have considered the oral cavity as a route of administering melatonin and compared it to other routes. The effect of transdermal, in comparison to oral controlled release and oral transmucosal drug delivery systems, on plasma concentrations of melatonin and its principal metabolite, 6-sulfatoxymelatonin, was evaluated in 12 human volunteers, using a crossover, single dose design. Oral transmucosal delivery provided prompt systemic drug levels with less variability than oral or transdermal delivery and no indication of mucosal deposition. The results indicated that oral transmucosal delivery was able to mimic the physiological plasma profiles of both melatonin and its principal metabolite [23]. Another study involved 60 patients, who were randomly assigned to receive either sublingual melatonin (3 mg) or placebo, 60 min before cataract surgery. The dose of 3 mg of melatonin sublingually, 60 min before surgery, was chosen, because the onset of melatonin-induced sedation is reported to begin approximately 20–30 min after sublingual administration. The results concluded that sublingual melatonin premedication for patients undergoing cataract surgery, under topical anesthesia, reduced the anxiety scores and provided excellent operating conditions [24]. A prospective, randomized, double-blinded, placebo-controlled study was designed to compare the perioperative effects of different doses of melatonin and midazolam [25]. Doses of 0.05, 0.1, or 0.2 mg/kg sublingual midazolam or melatonin or placebo were given to 84 women, approximately 100 min before a typical anesthetic. Sedation, anxiety, and orientation were quantified before, 10, 30, 60, and 90 min after premedication and 15, 30, 60, and 90 min after admission to the recovery room. Patients who received premedication with either midazolam or melatonin had a significant decrease in anxiety levels and increase in preoperative levels of sedation, compared with control subjects. Premedication with 0.05 mg/kg melatonin was associated with preoperative anxiolysis and sedation without the impairment of cognitive and psychomotor skills or affecting the quality of recovery. To evaluate the analgesic dose response of the effects of melatonin on pressure and heat pain threshold, tolerance, and its possible sedative effects, the research group of Stefani et al. [26] recruited 61 healthy subjects aged 19–47 years old and placed them randomly into one of four groups: placebo, 0.05 mg/kg sublingual melatonin, 0.15 mg/kg sublingual melatonin, or 0.25 mg/kg sublingual melatonin. Serum plasma melatonin levels were found to be directly proportional to the melatonin doses given to each subject indicating that the sublingual melatonin has a well-defined dose-dependent antinociceptive activity. These results provided a correlation between the plasma melatonin drug concentration and acute changes in the pain threshold. To compare the perioperative effects of melatonin and midazolam, given in premedication,

on sedation, orientation, anxiety scores, and psychomotor performance, melatonin 5 mg, midazolam 15 mg or placebo was administered 90 min prior to anesthesia, sublingually to 66 patients undergoing laparoscopic cholecystectomy [27]. Sedation, orientation, and anxiety were quantified before 10, 30, 60, and 90 min after premedication and 15, 30, 60 and 90 min after admission to the recovery room. The results indicated that melatonin premedication was associated with preoperative anxiolysis and sedation without postoperative impairment of psychomotor performance.

2.4. Melatonin intranasal formulations

Intranasal administration is a route of administration for drugs used primarily for the treatment of conditions affecting the nasal cavity, but can also be used for cases requiring systemic exposure, since drugs can be absorbed into the circulation through the nasal mucosa. This kind of systemic administration offers lots of advantages, such as rapid onset of action and avoidance of first-pass metabolism [28]. Many researchers have investigated melatonin's intranasal administration and tested their formulations *in vitro* and *in vivo* in rats, rabbits, and humans.

In another study, the role of inclusion complexes of melatonin with modified cyclodextrins (CDs) in order to improve melatonin's solubility and nasal absorption was investigated [29]. The formation of inclusion complex of melatonin with hydroxypropyl β -cyclodextrin (HP β CD) and randomly methylated β -cyclodextrin (RM β CD) was demonstrated in solution and solid state and both CD's at 1% w/v concentration were found to improve the nasal permeability (the *in vitro* permeability studies were carried out with EpiAirwayTM-100 cell cultures from MatTek Corporation) of melatonin from HPMC gel formulations.

Intranasal melatonin encapsulated in nanosized niosomes has been preclinically evaluated in male Wistar rats [30]. It was found that intranasal melatonin niosomes that were bioequivalent to intravenous injection of melatonin could provide therapeutic level doses, deliver melatonin to the brain to induce sleep, and delay systemic circulation. The cross-over study, including eight rats, examined the intranasal administration of melatonin from a nasal formulation consisted of melatonin (2.0 mg/ml), β -cyclodextrin (7.5 mg/ml) dissolved in saline that also contained benzalkonium chloride (0.01% w/v) and EDTA (0.1% w/v) as preservatives, in comparison to the administration from an intravenous bolus injection. T_{max} was recorded at 2.5 min in both routes of administration and an almost zero plasma concentration after 120 min [31].

In another study, the research group [32] prepared melatonin gelatin microspheres (MLT-GMS) for intranasal administration and tested them in comparison to gelatin solution and i.v. injection. The *in vitro* release profile showed sustained effect, while the residence time of MLT-GMS in the rabbits' nasal cavity was longer than that of gelatin solution. After intranasal administration in rabbits, the bioavailability of MLT-GMS was 87.47%, while the bioavailability of melatonin solution was 69.72%, when compared to i.v. administration. The results showed that this formulation could meet the needs of intranasal administration, while increasing melatonin's bioavailability. Other scientists have studied the bioavailability of

melatonin in rabbits after nasal administration of two formulations (1.5 mg melatonin in 40% PEG 300 in the presence and absence of 1% sodium glycocholate) in comparison to the i.v. route [33]. The results documented that the bioavailabilities in rabbits correspond to much higher values, which indicates a potential advantage of using nasal delivery for melatonin and the possibility of producing a clinically relevant nasal formulation. In another study, starch microspheres of melatonin for intranasal administration were prepared by an emulsification crosslinking technique using a uniform design to optimize preparation conditions [34]. The *in vitro* release experiments showed that melatonin was released from the microspheres in a sustained manner. Nasal clearance studies in six healthy, male rabbits showed that >80% of the radioactivity from the starch microspheres was present in the nasal mucosa 2 h after administration, compared to only 30% radioactivity from the solution. The absorption rate after intranasal administration of the microspheres was rapid, and the absolute bioavailability was high, compared to the intranasal solution and a significant correlation between *in vivo* and *in vitro* data was recorded.

In humans, a cross-over study in three volunteers, receiving either intranasally 0.4 mg melatonin or intravenously 0.2 mg on two separate study days, was undertaken. The study reported a T_{max} value of 5 min for intranasal administration and 10 min for intravenous administration [35]. Other researchers [36] have formulated melatonin, as a thermoreversible Pluronic gel for nasal administration for treating sleep disorders. The comparative electroencephalogram (EEG) pattern, derived from five healthy volunteers who participated in this crossover study after administration of melatonin tablet and nasal gel, revealed that nasal absorption of melatonin was faster and the sleep produced resembled to one during nocturnal chronobiological melatonin secretion. The optimized formulation has provided bimodal drug release extending over 5 h at significantly low dose (1 mg intranasal dose) as compared to 3 mg oral dose. The use of the novel thermoreversible Pluronic gel showed the desired bioadhesion to the nasal mucosa, with no sensitizing effect in subjects and reproducible sleep characteristics thus making this formulation an agent with an excellent commercial potential.

2.5. Melatonin injectable formulations

Injectable formulations also play an important role as melatonin modified release systems. Many researchers have focused on intravenous (i.v. bolus infusion), intramuscular, subcutaneous, and implant administration of melatonin formulations in human volunteers, small laboratory animals, as well as in larger animals like ewes, goats, and deer.

A research work showed that during melatonin infusion (n = 4 bolus intravenous injection of 5 or 10 $\mu\text{g}/\text{person}$ and after a 5-h infusion of 20 μg per person in six healthy subjects), the plasma hormone level reached a steady-state after 60 and 120 min, which was equal to the nocturnal level. This particular infusion regime could be valuable in replacing blunted hormonal secretion in disease states [37]. A human positron emission tomography (PET) study, performed in a healthy volunteer with ^{11}C -labeled melatonin, showed maximum activity in the brain 8.5 min following the injection, quite different from the curve observed for the plasma radioactivity (maximum at 3.5 min), confirming that melatonin crosses the blood-brain barrier and that 6-sulfatoxymelatonin is its main plasma metabolite [38]. The

absolute bioavailability of melatonin was studied in 12 young healthy subjects (six males and six females) after administration at midday, on two separate occasions: 23 µg by intravenous infusion and 250 µg by oral solution of D7 melatonin (seven deuterium atoms replace seven hydrogen atoms in the melatonin molecule). Exogenous (D7) and endogenous (D0) melatonin were quantified simultaneously, but separately, by a highly specific assay, gas chromatography/negative ion chemical ionization mass spectrometry. After i.v. administration, the maximum plasma concentration (C_{max}) and the area under the plasma concentration-time curve (AUC) values were found to be significantly different in male and female subjects, but there was no significant gender difference in total body clearance when normalized to body weight. After oral administration, pharmacokinetic parameters used to quantify bioavailability were near 3 times greater in female subjects than in males, with large inter-individual variations [39]. In the review article of Gómez-Moreno et al. [40], the use of melatonin in implant dentistry has been proved to increase the new bone formation and bone-to-implant values, around dental implants, leading to a more stable bone area around the implants. In view of these findings, researchers are currently exploring further possibilities as to how melatonin might benefit implant dentistry.

Two i.v. formulations of melatonin (5 mg/ml) have been tested in Wistar rats: one formulation with hydroxypropyl-β-cyclodextrin and propylene glycol to increase solubility and stability and the other with an antioxidant and chelating agent to minimize oxidation and hydrolysis. The pharmacokinetic profiles and the plasma antioxidant activity results suggested a potential for use in the clinical study for these two i.v. melatonin formulations [41]. Another research group [42] studied the possibility of using high-dose intravenous melatonin as an anesthetic adjuvant and compared its effects with thiopental and propofol using Sprague Dawley rats. By administering to the rats bolus or cumulative i.v. doses of melatonin, thiopental, or propofol, they assessed the righting reflex, hind paw withdrawal to a noxious stimulus, response to tail clamping and hemodynamic effects. The results showed that melatonin caused a dose-dependent increase in paw withdrawal. Melatonin was comparable to thiopental and propofol in terms of its rapid onset of hypnosis and it was concluded that intravenous melatonin can exert hypnotic effects similar to those observed with thiopental and propofol. Other researchers have injected mice daily with 50 µg of melatonin, 12 h after lights on, for 18 weeks. The results indicated that mice underwent gonadal regression after 4–7 weeks and reproductive recrudescence after 15 weeks [43].

The effect of differing doses and routes of administration of melatonin on plasma melatonin levels in sheep and goats has been examined by the researchers Kennaway and Seamark [44]. Melatonin injected subcutaneously in a saline or oil vehicle caused high transitory peaks in plasma melatonin, whereas oral administration, in either saline solution or adsorbed onto pelleted foodstuff, resulted in sustained elevated blood levels for periods exceeding 7 h. Oral dosages of about 2 mg proved adequate to raise the normal daytime plasma levels in both sheep and goats to levels within the normal night-time range. It was concluded that with ruminants the oral route of administration provides a facile and practical way of administering melatonin for physiological study. The review paper of Williams et al. [45] presents data from five research trials and 108 clinical trials conducted in three countries to validate the optimum use of melatonin to advance seasonal breeding patterns of a variety of breeds of

sheep. In order to define the optimum time for treatment in breeding flocks, ewes of three different breeds were treated with controlled-release 18-mg melatonin implants (Regulin®), with treatments commencing at various times ranging from 9 to 3 weeks, prior to joining with fertile rams. Overall, the studies presented in this paper showed that melatonin pretreatment of spring and early summer joined ewe flocks resulted in both a modest decrease in the number of barren ewes and an increase in the number of multiple births concluding that this treatment strategy maximizes the potential advantages expected from the melatonin treatment.

2.6. Melatonin topical preparations

As mentioned previously, melatonin has shown antioxidant and immunological properties and therefore, it may be beneficial as a topical drug for the use against oxidative damage in the skin or even as a potential sun protection element, against UV-induced oxidative damage. Melatonin skin penetration properties have been studied in alcoholic solutions, creams, in various vesicular approaches (liposomes and ethosomes), in undecanoic, lauric, and oleic acids.

The skin penetration properties of melatonin from three galenic preparations (0.01% in a cream and 0.01 and 0.03% in a solution) were investigated by the evaluation of the serum melatonin levels over a 24-h time period in a clinical study (15 healthy volunteers) conducted by a research group [46]. The cumulative melatonin serum values for each preparation were 7.1, 8.6, and 15.7 pg/ml, respectively, showing that the alcoholic solution was superior to the cream formulation for melatonin delivery. The strongly lipophilic substance melatonin is able to penetrate through the skin, leading to dose- and galenic-dependent melatonin levels in the blood.

Novel ethanolic liposomes (ethosomes) bearing melatonin were evaluated for transdermal administration potential [47]. Melatonin loaded ethosomes were prepared and characterized for vesicular shape and surface morphology, vesicular size, entrapment efficiency, stability, *in vitro* skin permeation, and *in vivo* skin tolerability. The results suggested that ethosomes may offer a suitable approach for transdermal delivery of melatonin.

The effects of vehicles and enhancers on skin permeation and lag time were evaluated for a more effective transdermal delivery of melatonin [48]. Skin permeation study was conducted in Franz diffusion cells using excised hairless mouse skins and samples were analyzed by HPLC. As vehicles, ethanol (EtOH), polyethylene glycol 400 (PEG), or propylene glycol (PG) were used alone or mixed with a phosphate buffer. The results indicated that the use of binary vehicles could effectively modulate the skin permeability of melatonin (to the limited extent) and the lag time observed. As enhancers, fatty acids were used and when compared with the binary vehicles, the use of oleic acid drastically enhanced the skin permeation of melatonin as well as shortened its lag time.

Apart from being an established radioprotectant and anticancer agent [49], melatonin has also been found to counteract UV-induced solar damage, which includes the generation of reactive oxygen species, skin aging, mitochondrial, and DNA damage [50]. The presence of melatonin along with the UV filters could provide a synergistic effect for optimum sun protection

as topical application of melatonin along with vitamin E and C in human volunteers has been found to counteract ultraviolet induced erythema and the generation and adverse effects of free radical species [51]. Another research work [52] has dealt with the preclinical safety evaluation of the sunscreen formulation comprising of four US FDA approved UV filters; namely avobenzone, octinoxate, oxybenzone, titanium dioxide along with melatonin and pumpkin seed oil. The results obtained from this study indicated that the sunscreen formulation is nontoxic and safe in animal models and alongside with additional preclinical evaluations may serve as a basis for considering the formulation, as a potential candidate for further trials to establish its efficacy, tolerability, and applicability.

2.7. Transdermal patches

The transdermal delivery of melatonin could be a good route for its administration, given the variability of absorption, short biological half-life, and extensive first-pass metabolism of melatonin when administered orally. The main obstacle is the barrier nature of the stratum corneum of the skin that requires the right choice of a suitable vehicle, where the drug can be dissolved, then released, and finally penetrate the skin.

A research group [53] prepared and evaluated monolithic drug-in-adhesive type transdermal patches of melatonin using Eudragit E 100 as the adhesive polymer, containing penetration enhancers such as fatty alcohols, fatty acids, and terpenes. The results indicated that the addition of enhancers in the patch increased the permeation of melatonin through hairless rat skin. Decanol and undecanoic acid showed the maximum permeation of melatonin among the fatty alcohols and fatty acids, respectively, while menthol showed the maximum permeation of melatonin among all the enhancers studied. The release profile of melatonin from the patches followed first order kinetics. A lag time of 4–6 h was observed before a steady-state flux of melatonin was reached.

The effect of transdermal in comparison to oral controlled-release and oral transmucosal drug delivery systems on plasma concentrations of melatonin and its principal metabolite (6-sulfatoxymelatonin (MT6s)) was evaluated in 12 human subjects using a crossover, single dose design [23]. The plasma concentrations of the parent drug and MT6s were measured by radioimmunoassay. Transdermal drug delivery resulted in a significant delay in systemic drug levels and a gradual decline in drug delivery after patch removal (patch dosage forms were removed after 10 h of application), possibly due to the deposition of melatonin in the skin.

Other researchers suggested that transdermal melatonin may have advantages over fast-release oral melatonin in improving sleep maintenance at adverse circadian cycles [54]. An experimental skin patch designed to deliver melatonin, such that plasma levels steadily increase for 6–8 h, and thus counteract the increasing circadian wake drive and improve daytime sleep was administered to 8 healthy subjects (2.1 mg melatonin or placebo, randomized, double-blind, crossover study) 1 h before an 8 h daytime sleep opportunity (09:00–17:00 h). The results indicated that transdermal melatonin delivery was effective in elevating plasma melatonin levels for an extended duration during the daytime.

Another group of researchers examined the pharmacokinetics of melatonin incorporated in solid lipid nanoparticles, administered by oral or transdermal route [18]. Solid lipid nanoparticles were used as a reservoir system, permitting a constant and prolonged release of melatonin. In comparison to the standard formulation of orally administered melatonin, the absorption and elimination after administration of the solid lipid nanoparticle-melatonin complexes through the transdermal route demonstrated to be slow and melatonin plasma levels above 50 pg/ml were maintained for at least 24 h. Therefore, these systems disclose a potential for the sustained delivery of melatonin.

3. Conclusions

In this chapter, a concise account of the different melatonin delivery routes is given. The choice of the most effective melatonin delivery system is circumstantial and depends on the dysfunction that needs to be treated. However, it seems that modified release formulations mimic closer the endogenous melatonin release pattern and thus a plethora of such systems are currently under thorough investigation.

Conflict of interest

The authors declare no conflict of interest.

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