Nasal melatonin gels using pluronic PF-127 for chronobiological treatment of sleep disorder

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Melatonin, a neurohormone, is formulated as a thermoreversible pluronic gel for nasal administration as an 'overlap dosage form' for chronobiological treatment of sleep disorders. Aqueous PF gels containing drug (0.5 mg & 1 mg/0.1 ml), PEG 400 and PEG 15,000 were prepared by cold method. Pluronic gels were evaluated for gelation and gel melting. Gelation temperature (T1) decreased with pluronic concentration while gel melting temperature (T2) increased. Melatonin shifted gelation range to higher temperature while PEG narrowed the gel range. Flux of diffusion decreased with PF concentration. Drug flux decreased in higher drug strength gels due to more partitioning in micellar phase. Pluronic gel (20%w/w, 1 mg/0.1 ml) showed bimodal pattern with a desired second peak flux (0.248 μg/min/cm²) at 300 min. Flux pattern changed invariably with PEG. Bioadhesion time and strength to sheep nasal mucosa were more for gels containing melatonin and PEG 400. Nasal gels produced fast onset of action and induced sleep within fifteen minutes. The low intensity and rounded α-EEG wave pattern was observed for sleep duration of 5 hrs. Good correlation was observed in sleep pattern and low intensity α-EEG. The results are encouraging and nasal melatonin gels have potential in the treatment of circadian cycle sleep disorders.

Keywords: pluronic gels, melatonin, nasal, chronobiological release, sleep pattern

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Introduction

Melatonin (MT) is an indolamine neurohormone secreted by pineal gland. The phase shifting effect of circadian rhythm by melatonin is mediated by MT2 receptors.1 Pineal gland functions as biological clock by secreting melatonin according to circadian cycle. Normal plasma level of melatonin during daytime hours is 10 pg/ml; after sunset the level rises continuously eventually peaking around 2 A M (50 pg/ml), then gradually declines, reaching minimum in the morning.2 The disturbed melatonin secretion leads to changes in sleep-wake up cycle. Impairment in melatonin production contributes to well-known incidences of insomnia and delayed sleep syndrome.

Lerner was the first to characterize the sleep enhancing properties of melatonin.3 Sleep, after the administration of melatonin, resembles natural sleep unlike currently available hypnotic agents. Oral melatonin administration undergoes extensive hepatic-first pass (70%) and has a biological half-life of 45 min. Many conventional formulations of melatonin have very slow onset of action and require higher dose for therapeutic effect. These are intended to facilitate the sleep (5 mg), regulate the body clock (propounding or postponing sleep, 5-10 mg), supplement in jet lag and major depression4,6. Researchers have established clinical usefulness of melatonin in the treatment of oxidative stress, breast cancer and Alzheimer's disease7-12. The conventional tablet, solution and tea of melatonin have been marketed as a supplementary nutrient in USA. Transdermal films of melatonin containing propylene glycol showed poor systemic bioavailability (18 %). Transdermal administration does not stimulate the nocturnal release pattern. A sugar spheres loaded melatonin with additional aquacoat, and HPMC matrix tablet showed sustained release for 8 hrs.13 Oral formulations showed large intersubject variability in plasma profiles. Steady state plasma levels were also achieved after oral TMD patch.

Exogenous nasal melatonin formulation could be used as circadian rhythm synchronizer in humans. Crucial for successful treatment of chronological disorders with melatonin is its correct timing according to phase response curve. An 'overlap' dosage regimen in which exogenous and endogenous melatonin peaks

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overlap is desired\textsuperscript{14,15}. Recently, an attempt to formulate nasal melatonin using ethanol caused serious mucosal irritation, painful administration and hence poor patient compliance\textsuperscript{16}. Transnasal drug administration avoids first pass metabolism, gastric degradation of peptide and gives rapid drug absorption e.g. calcitonin, propranolol and gentamycin\textsuperscript{17}. However, short nasal residence of solutions results in non-uniform absorption profiles. Attempts have been made to prolong the nasal residence by designing powder sprays, microspheres, and erythrocyte based bioadhesive systems\textsuperscript{18-21}.

Pluronic PF127 (a poloxamer block copolymer) has been accorded GRAS status and has high solubilizing capacity\textsuperscript{22}. Aqueous pluronic dispersions (20-35\%) are solutions at low temperature and are converted into semisolid gel at higher (or body) temperature. These useful physico-chemical properties of pluronic have been evaluated for controlled release of drugs for topical, rectal and ophthalmic routes\textsuperscript{23-25}. Nasal melatonin gels are aimed to obtain the release resembling the nocturnal pattern. The effect of formulation variables like pluronic concentration, PEG (400, 15,000), drug, solvent (ethanol) on thermal properties of gels and drug release has been studied. The optimal nasal gel and marketed tablets are clinically compared using four-channel EEG recorder and Biopack software.

Materials and Methods

Pluronic PF127 (Lutrol, Batch No. 62/0441) was a gift sample from BASF Corporation, New Jersey. Melatonin (Batch No. 20/2001) was provided by Aristo Pharmaceuticals (MP), India. Polyethylene glycol (PEG 400 and PEG 15,000) were obtained from Merck-Schuchardt, Hohenbrunn, Beimunchen. Methanol (HPLC grade) was purchased from E Merck (India) Ltd., Mumbai. All chemicals of highest purity were used throughout the research.

Preparation of Gels

Aqueous gels containing 20, 25 and 30\% w/w of PF127 were prepared by cool method described by Schmolka et al\textsuperscript{26}. The method involved slow addition of polymer in cold water with continuous agitation. The mixture was stored overnight at $-4^\circ\text{C}$. PF127 gels containing melatonin (0.5\%w/w) and 1\%w/w (with 5\% w/w ethanol) were prepared separately in 20, 25 and 30\% w/w each of PF 127 in deionized water. Similarly, gels containing 20\% (w/w) PF127, 1\% (w/w) melatonin, 5\% (w/w) ethanol with PEG 400 [equivalent to 1, 3 & 5\% (w/w)], and PEG 15,000 [0.5, 1 & 1.5\% (w/w)] each were prepared separately. Gels containing 1\% w/w melatonin were prepared by dissolving drug in ethanol and following the cold method. In case of PEG 400 and PEG 15,000 containing PF 127 gels, the required amount of PEG was dissolved in distilled water, prior to polymer addition.

Evaluation of Gels

Gelation and Gel Melting

A modified Millar et al technique using 2 ml of gel in test tubes sealed with aluminum foil, immersed in water bath at 4\textdegree C was used\textsuperscript{27}. Water bath (Haake C25 P) temperature was increased by 1\textdegree C and left to equilibrate at each new setting. Gelation ($T_1$) occurred when the meniscus would no longer move upon tilting through 90\textdegree. The gel melting temperature ($T_2$) was recorded when the gel started flowing.

Permeation Studies

A water-jacketed nasal diffusion cell having, 60 ml total capacity, flanged top (3 mm) and donor chamber (10 cm long, 1.13 cm i.d.) was fabricated with glass\textsuperscript{28}. Sheep nasal mucosa separated from sublayer bony tissues and blood was mounted onto donor chamber with serosal surface towards receptor chamber and the mucosa just touching water. Receptor chamber with 40 ml distilled water was agitated magnetically. The diffusion cell wrapped in aluminium foil was equilibrated at 37 ± 2\textdegree C. Melatonin gel sample, 0.1 ml, was placed on dorsal surface of nasal mucosa and lowered to touch diffusion medium. The 0.5 ml of diffusion samples collected in amber coloured ampoules each at 15 to 480 min was diluted to 1 ml with methanol. The drug content was estimated by RP-HPLC method\textsuperscript{29}. Release profiles and fluxes were calculated. In vitro dissolution of oral marketed melatonin tablets (3 mg) was performed in triplicate using USP paddle apparatus (900 ml DW, 100 rpm, 37\textdegree C, 1 ml sample, LOD and LOQ were 5 and 10 ng/ml, respectively).

Biodhesion Strength

Biodhesion of gels was determined by Hang-Gon Choi method\textsuperscript{30}. The modified balance technique using two-glass vials and sheep nasal mucosa was used. The 0.5 ml of the gel sample was placed between the two mucosal membranes attached to the bottom of the vials. Weights were added on other side of the balance after 30 min. The minimum weight required to break the mucosal adhesion was measured (g/sq cm).
In vivo Sleep Pattern with Optimized Nasal Gel

Optimized melatonin gel (20% w/w PF-127, 1mg / 0.1ml nasal dose) was subjected for in vivo studies using the Biopack software and α EEG pattern was recorded in an isolated dark room. Five healthy volunteers participated in a crossover study after the study protocol was explained and a written consent was obtained from the drug and ethical committee of the institute. Three electrodes were attached to scalp surface after removing the hairs as per the EEG experimental procedure. For each volunteer, normal EEG was recorded for six hrs. Oral tablet (3 mg) was similarly evaluated after a washout period. The sleep onset time and duration of the sleep was recorded simultaneously. The volunteers were asked to fill sleep logs indicating sleep characteristics.

Results and Discussion

Gelation and Gel Melting of Pluronic PF127 Gels

Aqueous pluronic gels containing melatonin (0.5%,1% w/w), release and gel point modifiers (PEG 400, PEG 15,000) and solvent for drug were prepared in 20-30% w/w PF-127 concentration. This affected gel formation and gel melting temperature of PF127 gels, in a manner depending upon the physico-chemical nature of additive and their interaction with polymer during phase transitions. The sol-gel phase transition temperature of nasal melatonin gels is important for understanding the drug release kinetics and stability. The observed T1 and T2 for gels under investigation are shown in Table.1. Gel formation temperature T1 decreased and gel melting temperature T2 increased with increasing concentration of PF127, therefore, gel range broadened with concentration of polymer. Gelation temperature increased in the presence of melatonin in dose dependent manner. Similar trend was observed at gel melting temperature for 20% w/w PF gels. The T2 for 25 and 30% w/w PF gels increased sufficiently and hence outside the experimental range (above 95°C). The effect of ethanol, used to incorporate the drug, was predominant in low strength of melatonin gels. These gels containing, 0.5 % w/w drug, showed higher values of T1 as compared to respective plain gels, but slightly less than only melatonin containing gels, signifying decrease in T1 due to ethanol. In case of 1 % w/w melatonin gels (all three PF concentration) the ethanol effect of decrease in both T1 and T2 has been masked by melatonin effect of increase in T1 and T2. Gel forming ability decreased (T1 increase) in concentration dependent manner with PEG 400 and PEG 15,000. Here, gel melting was promoted and occurred at lower temperature (T2). This effect on T1 and T2 was more pronounced for higher molecular weight PEG 15,000 (combined data in Fig.1).

The surface-active poloxamer (PF127) consisted of water insoluble polyoxypropylene (30%) portion sandwiched between two polyoxyethylene chains (70%) with an average molecular weight 12,500. Concentrated aqueous solutions of PF127 (above 20% w/w) exhibited reverse thermal gelation. As the temperature increased, micellar entanglement was promoted, leading to gel formation and an overall increase in bulk viscosity. Temperature played an important role in the micelle formation process through hydration of the ethylene oxide units. At low temperature water was a good solvent for polyoxyethylene and a good solvent for polyoxypropylene also. At higher temperature the solubility of polyoxypropylene was reduced and micelle formation occurred.

Ultrasonic velocity, light scattering and small angle neutron scattering studies have reported gelation of PF127 due to body-center-cubic packing of spherical micelles. The 13C NMR studies have concluded that increased temperatures produced conformational changes in the methyl group of the polyoxypropylene

<table>
<thead>
<tr>
<th>PF Conc.</th>
<th>Phase change temp.</th>
<th>Plain PF gel</th>
<th>Melatonin conc. (% w/w)</th>
<th>0.5 + ethanol</th>
<th>1% + ethanol</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 % w/w</td>
<td>T1 → 27.12°C</td>
<td>30.12°C</td>
<td>28.16°C</td>
<td>31.10°C</td>
<td></td>
</tr>
<tr>
<td></td>
<td>T2 → 66.66°C</td>
<td>82.66°C</td>
<td>74.45°C</td>
<td>80.12°C</td>
<td></td>
</tr>
<tr>
<td>25 % w/w</td>
<td>T1 → 21.34°C</td>
<td>24.85°C</td>
<td>22.46°C</td>
<td>26.21°C</td>
<td></td>
</tr>
<tr>
<td></td>
<td>T2 → 88.30°C</td>
<td>Solid at 95°C</td>
<td>Solid at 95°C</td>
<td>Solid at 95°C</td>
<td></td>
</tr>
<tr>
<td>30 % w/w</td>
<td>T1 → 17.21°C</td>
<td>20.85°C</td>
<td>18.26°C</td>
<td>22.15°C</td>
<td></td>
</tr>
<tr>
<td></td>
<td>T2 → Solid at 95°C</td>
<td>Solid at 95°C</td>
<td>Solid at 95°C</td>
<td>Solid at 95°C</td>
<td></td>
</tr>
</tbody>
</table>

T1 and T2 are gel formation and gel melting temperatures, respectively
within the hydrophobic micellar region, and in the motion of the hydrophilic end chains. The subsequent dehydration increased chain friction and caused gelation. According to a thermodynamic model, there existed a local higher order of water molecules around the hydrophobic unit of the polymer in solution. As gelation occurred, the interaction between the hydrophobic units of polymer molecules squeezed out these ordered water molecules into the bulk solution of lower order. This resulted in an overall disorder, which was the driving force for hydrophobic association.

These fundamental physico-chemical approaches reported above can be used to illustrate and explain the results presented. The decrease in the gelation temperature with increase in PF127 concentration may be attributed to the higher number and volume occupied by micelles at lower temperatures. As the concentration of PF127 increases, the gel structure becomes more closely packed with the arrangement in a lattice pattern. Gel melting increases with PF127 concentration because weight fraction of PF127 micelles increase. Micelles in gel phase become more tightly packed leading to increase in T2 with PF127. Thus, the disruption of the lattice melting of gel occurs at higher temperatures. Addition of water-soluble polymer PEG produces increase in the gel-sol transition temperature of PF127 depending on the concentration of PEG. The phenomenon may be mediated through modification of the process of micellar association of the PF127 molecules. In addition, the PEG molecules may form mixed micelles with PF127. Addition of PEG causes an increase in sol-gel transition temperature of PF127 solutions. The hydrophilic end chains of PF127 comprises the same polyoxyethylene chains that are present in PEG. It is suggested that the esters bind to these chains, promoting dehydration and causing an increase in entanglement of adjacent micelles. The results are in agreement with the effect of solutes and polymers on gelation of PF127. The effect of PF concentration and PEG on temperature-viscosity profile of the gels (data not shown) shows a Newtonian behaviour at low temperature and an abrupt increase in viscosity in the vicinity of gelation onset temperatures (non-Newtonian). Thus, the confirmed micellar gelation was dependent on polymer concentration. The gels strengthening and weakening effects (as revealed by phase change temperatures) of viscosity coincides well with the gel range widening and narrowing, respectively.

Melatonin is amphoteric in nature and capable of hydrogen bonding through oxygen atom (C=O, C-O-CH3 groups) with polyoxyethylene chains of PF127. Pluronic PF127 hydrates with water absorption and swells extensively. The –OH and ethereal oxygen of the polymer structure is capable of hydrogen bonding with the like molecules. Such an additive binding of solutes with PF127 has been reported. This increased T1 to a significant extent compared to plain gels. Melatonin increased T2 due to entanglement of large size molecules in the outer polyoxyethylene chains favouring hydration. However, in a similar study performed in our laboratory (unpublished results), water soluble vitamin B12 (0.52% w/w) incorporated in PF127 gels (20-20% w/w) showed decrease in gel formation temperature (T1) and increase in T2. Ethanol used as solvent (5% w/w) to incorporate melatonin in micellar gel of PF127 is expected to cause dehydration and a subsequent decrease in gelation temperature (T1). However, in the presence of drug, melatonin effect of increase in T1 is predominant and hence the gels showed decreased gel-forming ability (i.e. increase in T1).

**Nasal Melatonin Permeation Studies**

Pluronic PF127 gels containing melatonin were analyzed by RP-HPLC method using an equation of standard curve, \( y=94.732+262.28 \) (\( R^2=0.998 \), LOD and LOQ were 5 and 10 ng/ml, respectively). The melatonin content was identical (98-100%) with 2%± S.D. The formulation additives did not interfere with the melatonin estimation. With increasing concentration of the polymer the release of the drug decreased significantly i.e. for 20, 25 and 30% w/w gels amounts...
released were 88, 79, and 58%, respectively in 8 hrs (Fig. 2). A 20 %w/w PF 127 gel, 0.5 mg without solvent, has shown initial high flux (0.67 mcg/min/sq cm, 15 min) because of the resultant weak gel structure. The flux of drug diffusion was lowered with increase in PF127 concentration. Peak flux (0.312 and 0.28 mcg/min/sq cm) and peak flux time (80-90 min) was decreased for 25 and 30 % gels, because of increase in pluronic concentration (Fig. 3). The decrease in release may be due to increase in number and size of micelles, and increase in overall and micro viscosity of aqueous channels.

Peak flux of melatonin from similar gel (0.5 mg/0.1 ml, 20%w/w PF) prepared using ethanol (5%w/w) was (0.88 mcg/min/sq cm), as the presence of ethanol increased the membrane mobility and hence, the diffusion rate. However, the release rate of melatonin with and without solvent in 25 and 30 %w/w PF gels was identical, indicating that the penetration enhancement effect of ethanol had been masked by release retardant effect of higher PF concentration. Also, partitioning of the drug into micellar core of PF 127 was responsible for retard release.

The higher strength melatonin gels (1%w/w) needed ethanol compulsory to incorporate drug in micellar gel system. A trend in drug release, similar to low drug strength gels, was observed for 1 mg/0.1 ml gels (20, 25, 30% w/w PF-127, Fig. 4). These gels with increasing PF127 concentrations showed decreased drug release. Compared to 0.5 mg/0.1 ml gels, 1 mg/0.1 ml gels at all the three PF127 concentrations have shown decreased flux of release with corresponding peak flux of 0.354, 0.283, 0.263 mcg/ml/sq cm, respectively (Fig. 5). However, melatonin gel (20% w/w PF127, 5% w/w ethanol, and 1 mg/0.1 ml drug) showed a desired second peak flux (0.248 mcg/min/sq cm) at 300 min of diffusion. The diffusion results of 1 mg/0.1 ml gels revealed that more drug was partitioned into the micellar core, leading to decrease in flux. The optimized nasal melatonin gel showed a second peak flux at 300 min. This indicated that the pluronic 127 gel (20%w/w PF127, 5%w/w ethanol, and 1 mg/0.1 ml drug) required 300 min to absorb sufficient water from nasal secretions to break the gel structure. This released higher amount of drug and hence, the second peak flux.

The drug release pattern of 20%w/w PF127 gels (1%w/w drug) increased in the presence of PEG 400 and PEG 15,000. Increase might be due to interference of PEG with micellar association thereby in-
creasing gel fluidity and decreasing the release retardant effect of PF. This has been reflected in decreased gel formation ability of PF127 (increase in $T_1$ proportional to PEG concentration) in the presence of PEG. Insignificant difference in the drug release pattern and amount diffused (85-95%) in 8 hrs was observed for all the formulations containing PEG. The flux of melatonin diffusion decreased in the order of 5% > 3% > 1% w/w PEG 400. In the presence of PEG the gel integrity was compromised and PEG also acted as co-solvent for drug, producing faster drug release. Peak flux of 1.5% PEG-15,000 gel was high (0.44 mcg/min/sq cm, 15 min), which diffused out quickly. The 1 and 0.5% PEG 15,000 gel gave an initial peak flux of 0.382 and 0.345 in about 15 min. Thereafter, flux of melatonin in all the PEG 15,000 containing gels changed invariably throughout the diffusion period. The increased polarity and fluidity of the gels, and continuous changes in state and structure of gels on the nasal mucosa might be responsible. The conventional oral tablets release 60% drug in 15 min and the release was complete in 1.5 hrs indicating rapid drug release from tablets.

**Bioadhesion of Gels**

The force with which PF127 gels bound to sheep nasal mucosa, obtained by modified balance method, is shown in Fig. 6. The bioadhesion of PF127 gels containing PEG-400 (1%, 3% and 5%w/w) and PEG-15,000 (0.5, 1 and 1.5% w/w) were found to be 2.81, 2.90, 3.01 and 6.406, 6.169, 3.716 g/sq cm, respectively. Nasal membrane consisted of glycoproteins, capable of interacting with diverse materials$^{43}$. PF127 gels possessed moderate bioadhesive force through hydrogen bonding and chain penetration effect in mucosa. Bioadhesion increased with polymer concentration due to extensive bonding with glycoproteins. Alcohol decreased the adhesion due to dehydration effect. Melatonin increased the gel strength by hydrogen bond formation (effect on $T_1$) with number of functional groups of polymer but reduced the chances of bond formation with mucosal membrane. The increased PEG concentration showed little increase in adhesion. Bioadhesion of PEG 15,000 gels was significantly higher to PEG 400 but declined with higher concentration. This may be attributed for more spreading and increase in hydrophobic interactions. The increased fluidity and hence flexibility of polymer chains above optimum value with PEG 15,000 (1 and 1.5%w/w) caused less mucosal adhesion. The optimized melatonin gel showed desired nasal resi-

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**In vivo Sleep Pattern with Optimized Nasal Melatonin Gels**

Most of the formulation researches of melatonin are mainly based on the *in vitro* release characteristics. Analysis of sleep pattern and EEG will provide direct indication of the drug availability. Melatonin undergoes extensive gastric metabolism and hence it is difficult to rely on *in vitro* drug release performance of the formulation. The spontaneous, rhythmic variations in the voltage originating from human brain can be recorded and analyzed systemically using electroencephalogram (EEG). Bipolar recording of EEGs (most accepted method) involves the measurement of voltage generated between two active electrodes placed upon the skull. EEG reflects alterations in electric potential and provides information of interest to clinicians as an index of function of brain, especially its functioning during the waking and sleeping states$^{44}$. The intensity and pattern of electrical activity
of α rhythms originating from thalamus has a frequency and amplitude of 8-13 cycles/sec and 50 μv, respectively. α Waves are present in the EEG of all normal individuals when they are awake and disappear entirely during sleep. High frequency waves of short duration indicate fast activity (excitation), whereas low frequency waves of long duration reflect slow activity.

The α-EEG waves obtained after administration of melatonin as oral tablet and optimized nasal gel at different time periods post administration has been presented in Fig.7. Intensity and pattern of waves after oral administration of tablet does not show any significant change in first 30 min. The voltage (μv) and frequency decreased after 50 min. The effect on α waves lasted up to 150 min. Normal wave recovery was attained in 180 min. Reduction in the amplitude and frequency of α waves occurred within 15 min after nasal administration of 1 mg/0.1ml melatonin gel. The characteristic low voltage spindle wave pattern indicating sleep onset was observed at 30 min. The effect of transnasal melatonin on α-EEG waves i.e. reduction in intensity to 10-15μv and frequency (4-5 cycles/sec) lasted up to 300 min. The low intensity α wave pattern between 15 to 300 min was invariably observed in all the five volunteers. The recovery of normal α wave pattern started appearing at 300 min post-nasal dosing. The self-rated sleep characteristics in subjects with the treatment of melatonin oral tablet (3 mg) and optimized nasal gel (1 mg) are reported in Table 2. The two formulations produced significantly different effects on sleep quality. The nasal melatonin administration produced the best overall sleep quality. The total sleep time was longest (299.4±11 min) with subjects taking nasal gel and their sleep latency was 15 to 20 min. Furthermore, subjects fell asleep more easily, their sleep was deeper and felt more rested. However, in a crossover study with oral melatonin tablets, subjects showed extended sleep latency of 50-60 min, the acrophase of shorter duration (up to 2 hrs) and experienced difficulty in waking up or becoming fully alert.

![Representative α-EEG wave pattern, a. normal with tablet (3 mg) at b.30 c. 60 d. 120 e. 180 min, and nasal gel (1 mg) at f. 15 g. 30 hrs. 60 i. 120 j. 300 k. 360 min, respectively.](image)

**Table 2—Sleep pattern with oral tablet and optimized nasal melatonin gel**

<table>
<thead>
<tr>
<th>Volunteer</th>
<th>Dosage form/Melatonin dose</th>
<th>Sleep latency (min)</th>
<th>Acrophase of sleep (min)</th>
<th>Self-rated sleep quality</th>
<th>Post sleep effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Oral tablet / 3mg</td>
<td>50</td>
<td>104</td>
<td>Superficial</td>
<td>++</td>
</tr>
<tr>
<td></td>
<td>Nasal gel / 1mg</td>
<td>20</td>
<td>298</td>
<td>Deep</td>
<td>+++</td>
</tr>
<tr>
<td>II</td>
<td>Oral tablet / 3mg</td>
<td>60</td>
<td>118</td>
<td>Superficial</td>
<td>++</td>
</tr>
<tr>
<td></td>
<td>Nasal gel / 1mg</td>
<td>20</td>
<td>287</td>
<td>Deep</td>
<td>+++</td>
</tr>
<tr>
<td>III</td>
<td>Oral tablet / 3mg</td>
<td>55</td>
<td>125</td>
<td>Superficial</td>
<td>++</td>
</tr>
<tr>
<td></td>
<td>Nasal gel / 1mg</td>
<td>20</td>
<td>306</td>
<td>Quiet</td>
<td>+++</td>
</tr>
<tr>
<td>IV</td>
<td>Oral tablet / 3mg</td>
<td>55</td>
<td>100</td>
<td>Superficial</td>
<td>++</td>
</tr>
<tr>
<td></td>
<td>Nasal gel / 1mg</td>
<td>20</td>
<td>295</td>
<td>Deep</td>
<td>+++</td>
</tr>
<tr>
<td>V</td>
<td>Oral tablet / 3mg</td>
<td>50</td>
<td>117</td>
<td>Superficial</td>
<td>++</td>
</tr>
<tr>
<td></td>
<td>Nasal gel / 1mg</td>
<td>15</td>
<td>311</td>
<td>Very good</td>
<td>+++</td>
</tr>
</tbody>
</table>

++ drowsiness, +++ refreshing feeling, sleep quality = deep (5), very good (4), Quiet (3), Superficial (2), bad (1)
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 hrs at significantly low dose i.e. 1 mg as compared to 3 mg oral dose. Good correlation was observed in sleep pattern and low intensity α-EEG indicating suitability of technique. The thermoreversible pluronic gel had desired bioadhesion and showed reproducible sleep characteristics. The formulation does not show any sensitizing effect in subjects and is expected to improve patient acceptance. In conclusion, observed EEG changes and sleep patterns reveal that the optimized thermoreversible nasal melatonin gels are suited in the treatment of circadian cycle sleep disorders and has excellent commercial potential.

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