FINAL REPORT TO THE SLEEP RESEACH SOCIETY FOUNDATION

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CONTROLLED RELEASE MELATONIN IN A PHYSIOLOGICAL WASHOUT PROFILE

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When we administer melatonin as a nighttime sleep promoter, we want it to wash out the next morning like endogenous melatonin.

When we administer melatonin in late afternoon or early evening to phase-advance the circadian clock, we want it to wash out during the night, before the melatonin PRC crosses over to phase delays.

When we administer immediate release melatonin, doses ≥0.5 mg (possibly >0.1 mg) deliver a rapid supraphysiological spike >>300 pg/mL, followed by washout ($t_{1/2} \approx$ 45-60 min across most studies).

Controlled release formulations dampen the spike and spread absorption. However, with most past formulations absorption extends well into the next day.

OBJECTIVE

To formulate a controlled release melatonin tablet that:

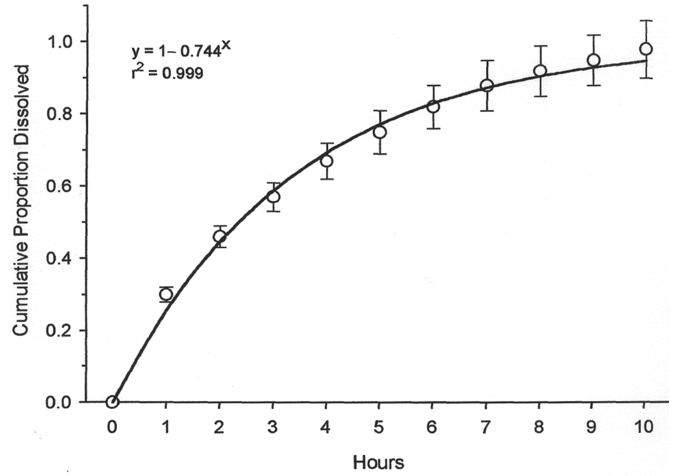
☽ restricts absorption to the physiological range (up to ~300 pg/mL in plasma).

☽ delivers the hormone gradually, with final washout no later than that of the endogenous pattern.

Our study had two phases: (a) *in vitro* evaluation of dissolution rate, and (b) *in vivo* administration with monitoring of plasma concentration.

Tablets were formulated with micronized melatonin compressed with safflower oil, carnauba wax, Micoselle, ProSolv and Methocel. Methocel concentration was varied to achieve the desired duration of melatonin release.

DISSOLUTION RATE



Tablets were dissolved for 10 hours in a series of media designed to mimic the pH progression of the digestive tract: 0-1 h, pH=1.2; 1-2 h, pH=4.5; 3-10 h, pH=6.8.

Melatonin release rate was ~30% in hour 1 (6% within the first 15 min, a short lag time), 10% each in hours 2-4, with further decreases over the next 6 hours.

The curve is a simple exponential approach to maximum.

QUALITY CONTROL

API certificate of analysis: HPLC vs. reference standard, 100.99%; HPLC area, 99.7%; impurities <1%. Meets specification.

UVA assay for dissolution testing: concentration vs. absorbance was linear from 0.003-0.02 mg/mL, r^2=0.996.

Tablet weight variation: % relative standard deviation, 0.71. Well within the 6% limit.

Dose uniformity (HPLC): melatonin weight CV <6%. Well within the 10% limit.

Accelerated shelf life: formulation estimated stable >3 years.

USP microbial limits tests: no organisms detected.

IN VIVO PHARMACOKINETICS

Participants: 10 healthy adults (6F, 4M), 50.3 ± 3.9 years old, no sleep disturbance. Baseline actigraphic sleep onset, 2334 h ± 31 min; offset, 0705 h ± 44 min; duration, 7.5 h ± 42 min.

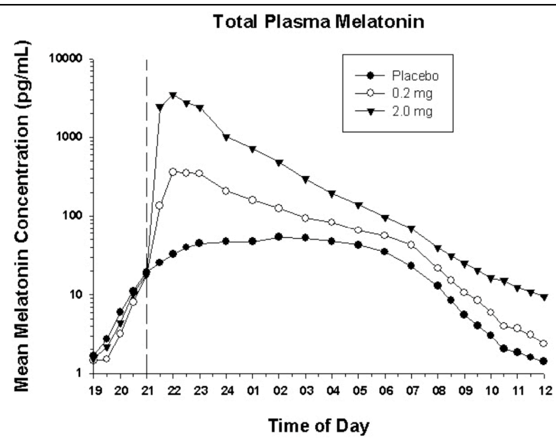
Single tablet tests: Three overnight sessions at 1-week intervals. Randomized 0.2 mg, 2.0 mg, placebo, administered at 2100 h.

Posture and lighting level:

1400-1830 h: on recliner, ≤50 lux
1830-2300 h: on recliner, ≤5 lux
2300-0700 h: in bed, ≤0.03 lux
0700-1200 h: on recliner, ≤5 lux

Plasma sampling schedule:

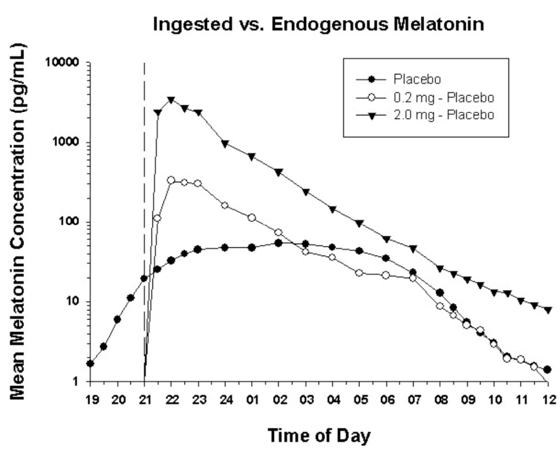
1900-2300 h: q30min
2300-0800 h: q60min
0800-1200 h: q30min



Full profile: Endogenous melatonin rose from ~1 to 20 pg/mL between 1900-2100 h.

There were significant dose dependent increases in plasma concentration in a surge-sustain pattern with gradual decreases into the morning.

Endogenous washout showed a simple exponential decline, with final washout beginning ~0700 h ($t_{1/2}$ = 63 min).



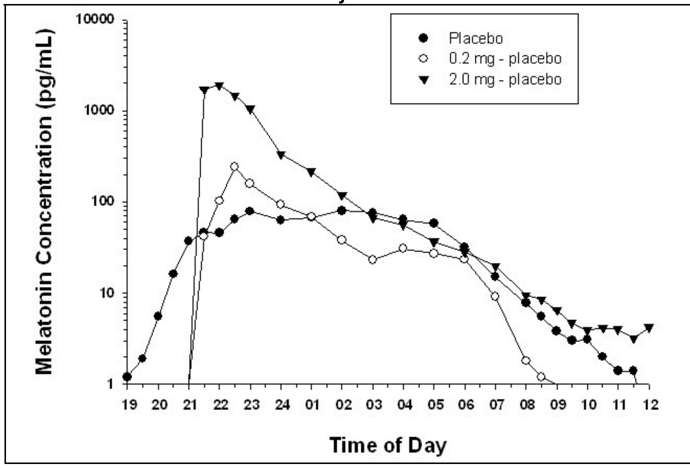
Adjusted profile: Peak exogenous melatonin concentration occur-red 0.5 to 2 h after tablet ingestion. The two curves were separated by ~1 log unit, linearly proportional to dose.

The placebo and 0.2 mg curves converge on a common exponential washout at ~0700 h, both with $t_{1/2}$ = 63 min.

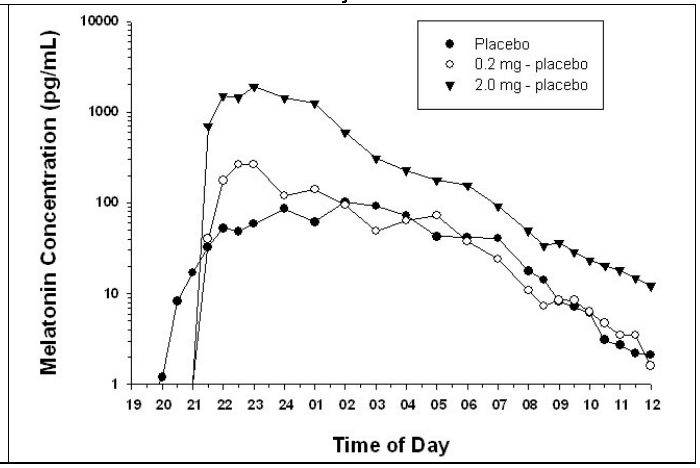
The 2.0 mg curve declines to only ~10 pg/mL at 1200 h, without commencement of final washout.

CONTRASTING CASES

Early 0.2 mg washout
Subject 9



Late 0.2 mg washout
Subject 8



ANCILLARY MEASURES

UBC Adverse Events Scale (Day 1, 1600 h; Day 2, 1200 h): No treatment emergent effects were detected other than a few specifically related to venous catheterization, e.g., swelling at insertion site.

Vital signs (2100-2300 h, q60min; 0800 h; 1200 h): All remained stable in the normal range. There were no dose-dependent differences in blood pressure, oral temperature, heart rate or respiration rate.

Mental alertness, physical energy, sleepiness (100 mm VAS; 2030-2300 h and 0800-1200 h, q30min): There were no significant dose-dependent differences. Sleepiness increased monotonically from 2100-2300 h, and decreased monotonically from 0800-1200 h. Alertness and energy followed the opposite pattern but with smaller changes.

CONCLUSIONS

The 0.2 mg formulation provides maximal levels of melatonin of ~300 pg/mL for ~2 hours, followed by a gradual decline. Taken at 2100 h, final washout coincides with that of endogenous melatonin.

Duration of endogenous melatonin production prior to final washout: ~12 hours, compared with ~10 hours for the melatonin tablet (well within the duration of subjective night).

The pharmacokinetics of our 0.2 mg formulation appears well suited for administration as a physiological-dose nighttime supplement taken 2 hours before bedtime[1] or as a circadian rhythm phase advancing agent taken 5-6 hours before bedtime,[2,3] as suggested by:

1. Zhdanova IV, Wurtman RJ, Regan MM, Taylor JA, Shi JP, Leclair OU. Melatonin treatment for age-related insomnia. J Clin Endocrinol Metab. 2001;86:4727-30.

2. Deacon S, Arendt J. Melatonin-induced temperature suppression and its acute phase-shifting effects correlate in a dose-dependent manner in humans. Brain Res. 1995;688:77-85.

3. Lewy AJ, Lefler BJ, Emens JS, Bauer VK. The circadian basis of winter depression. Proc Natl Acad Sci USA. 2006;103:7414-9.

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