A Continuous-Release Ion Powered Pump Melatonin Delivery System that Overcomes Challenges of Release and Absorption in the Intestines

Syed M. Shah, PhD[1], David C. Brodner, MD[2]

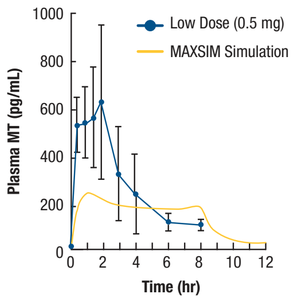
1. Physician's Seal LLC, Boca Raton, FL 2. The Center for Sleep, Allergy, and Sinus Wellness, Boynton Beach, FL

Introduction

Several modified release formulations of melatonin have been developed with the goal of providing exogenous melatonin profiles that mimic normal endogenous levels, i.e., Mesa Wave-shaped plasma pharmacokinetic profile for sleep maintenance. There have been difficulties in overcoming the challenges of release and absorption of melatonin in the higher pH environments in the small and large intestines. The initial attempts at employing hydroxypropylmethylcellulose (HPMC) to provide sustained-release and absorption showed that there was a problem in maintaining high plasma melatonin levels after the first 4 hours after administration.[1] Various approaches, including adding a controlled-release coating to melatonin beads,[2] administering immediate-release and controlled-release melatonin tablets simultaneously,[3] using melatonin soft gels instead of powder,[4] and slow-release pills of melatonin suspended in an 80:20 mixture of peanut oil:beeswax,[5] have been tried. Further improvements in these delivery systems are needed to get closer to the body's own Mesa Wave-shaped profile (Figure 1A-D).[2-5] The patented Ion Powered Pump (IPP) delivery system utilized in continuous-release and absorption melatonin (CRA-melatonin) was developed to overcome the challenges of release and absorption in the intestines.[6]

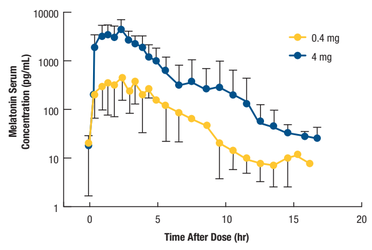
Figure 1. Melatonin Plasma Concentration Time Profiles for Modified-Release Formulations of Melatonin

A Coated Beads[2]



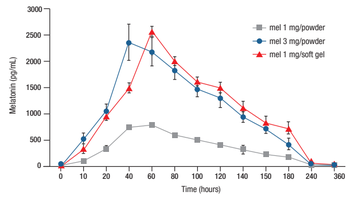
Observed plasma melatonin concentrations (pg/mL) following 0.5 mg melatonin compared with computer simulation (Mesa Wave-like) predicted plasma melatonin concentrations.[2]

B Bilayer Tablet[3]



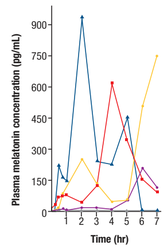
Serum melatonin concentrations measured 0-24 h after 0.4 mg or 4 mg of melatonin. For both doses, immediate-release (25% of the total dose) and controlled-release (75% of the total dose) melatonin tablets were simultaneously administered to create a surge-sustained release effect.[3]

C Softgel/Powder[4]



Melatonin plasma concentrations (pg/ml) from 0-360 min after 1 mg powder, 1 mg soft gel, or 3 mg powder of melatonin.[4]

D Wax Matrix[5]



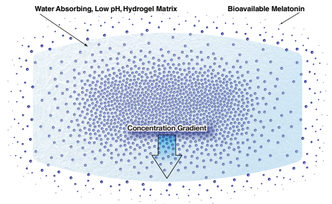
Plasma concentrations of melatonin in individual subjects after 2 mg of a slow-release preparation of melatonin.[5]

Methods

- The melatonin was formulated in a polymer matrix that maintains a solubility-enhancing and concentration gradient driven low pH environment (Ion Powered Pump). This facilitates the continuous release and absorption of melatonin in the GI tract, independent of local pH conditions
- The active ingredient in CRA-melatonin (Ultramel) is an ultra pure (99%) proprietary synthetic melatonin
- Randomized, crossover clinical PK evaluation comparing 5 mg CRA-melatonin (REMfresh) with the market-leading 5 mg immediate-release melatonin (IR-melatonin) in 10 healthy non-smoking adults
- Blood was taken pre-dose and at 0.25, 0.5, 0.75, 1, 2, 3, 4, 5, 6, 8 and 12 hours following administration and was assayed for melatonin by a validated LC-MS/MS method
- Pharmacokinetic (PK) parameters, including the time course, C_{max}, T_{max}, and plateau time for melatonin were determined by inspection

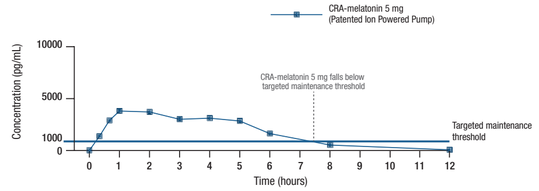
Results

Figure 2. Ion Powered Pump Melatonin Delivery System



CRA-melatonin was designed as a hydrogel matrix tablet. There is rapid release of the melatonin from the surface of the tablet, as the hydrogel release controlling matrix is setting up in the acidic environment (pH of 1 to 3.5) in the stomach. As the tablet moves into the higher pH (5.5 to 6.5) environment of the small intestine, which is above the pKa of melatonin (~4.0), the acidic moiety in the tablet maintains the pH within the tablet below 4.0 for 7+ hours. The hydrogel matrix, after proper hydration, allows continuous release of the active melatonin and acidic moiety into the lumen of the intestines. This proprietary approach facilitates delivery of the active melatonin to the brush border of the epithelial layers of the small and large intestines for uptake into the bloodstream.

Figure 3. Median Concentrations of Plasma Melatonin after 5 mg CRA-melatonin



Median concentrations of plasma melatonin 0-12 h after 5 mg of CRA-melatonin. The CRA-melatonin delivery technology allowed burst release and absorption of approximately 50% of the melatonin within the first 3 hours, helping facilitate sleep onset, coupled with sustained-release and absorption of approximately 50% of the remaining melatonin within the next 4 hours, to optimize sleep maintenance.

Conclusions

- The patented CRA-melatonin provides a burst release for rapid absorption above threshold levels and maintains successful melatonin release and absorption to address the historical challenges with exogenous melatonin delivery
- CRA-melatonin provides the desired PK profile, anticipated to result in faster onset of sleep and then helping with sleep maintenance for up to 7 hours

References

1. Zisapel N, inventor; Neurim Pharmaceuticals Ltd., assignee. Method and pharmaceutical formulation for treating benign prostatic hyperplasia. US patent 5,750,557. May 12, 1998. Column 10, lines 21-25. **2.** Lee B-J, Parrott KA, Ayres JW, Sack RL. Design and evaluation of an oral controlled release delivery system for melatonin in human subjects. *Int J Pharm.* 1995;124(1):119-127. **3.** Gooneratne NS, Edwards AY, Zhou C, Cuellar N, Grandner MA, Barrett JS. Melatonin pharmacokinetics following two different oral surge-sustained release doses in older adults. *J Pineal Res.* 2012;52(4):437-445. **4.** Proietti S, Carlomagno G, Dinicola S, Bizzarri M. Soft gel capsules improve melatonin's bioavailability in humans. *Expert Opin Drug Metab Toxicol.* 2014;10(9):1193-1198. **5.** Aldhous M, Franey C, Wright J, Arendt J. Plasma concentrations of melatonin in man following oral absorption of different preparations. *Br J Clin Pharmacol.* 1985;19(4):517-521. **6.** Zisapel N, inventor; Neurim Pharmaceuticals Ltd., assignee. United States Patent Application Publication: Methods for treating patients suffering from drug dependencies which lead to plasma melatonin deficiencies. Pub. No. US 2003/0040539. February 27, 2003.

DISCLOSURES

Syed M. Shah, PhD, Scientific Advisor, Physician's Seal, LLC

David C. Brodner, MD, Senior Medical Advisor, Physician's Seal, LLC