Formulation of modified release melatonin tablets comprised of new polylactic acid (PLA) derivatives

Chrystalla Protopapa, George Bolbasis, Anna Trikali, Nikolaos Bikiaris, Paraskevi Saranti, Rafail Ioannidis, Angeliki Siamidi, Marilena Vlachou

School of Health Sciences, Department of Pharmacy, Section of Pharmaceutical Technology, National and Kapodistrian University of Athens, Athens, Greece

Laboratory of Polymer Chemistry and Technology, Department of Chemistry, Aristotle University of Thessaloniki, GR-54124 Thessaloniki, Greece

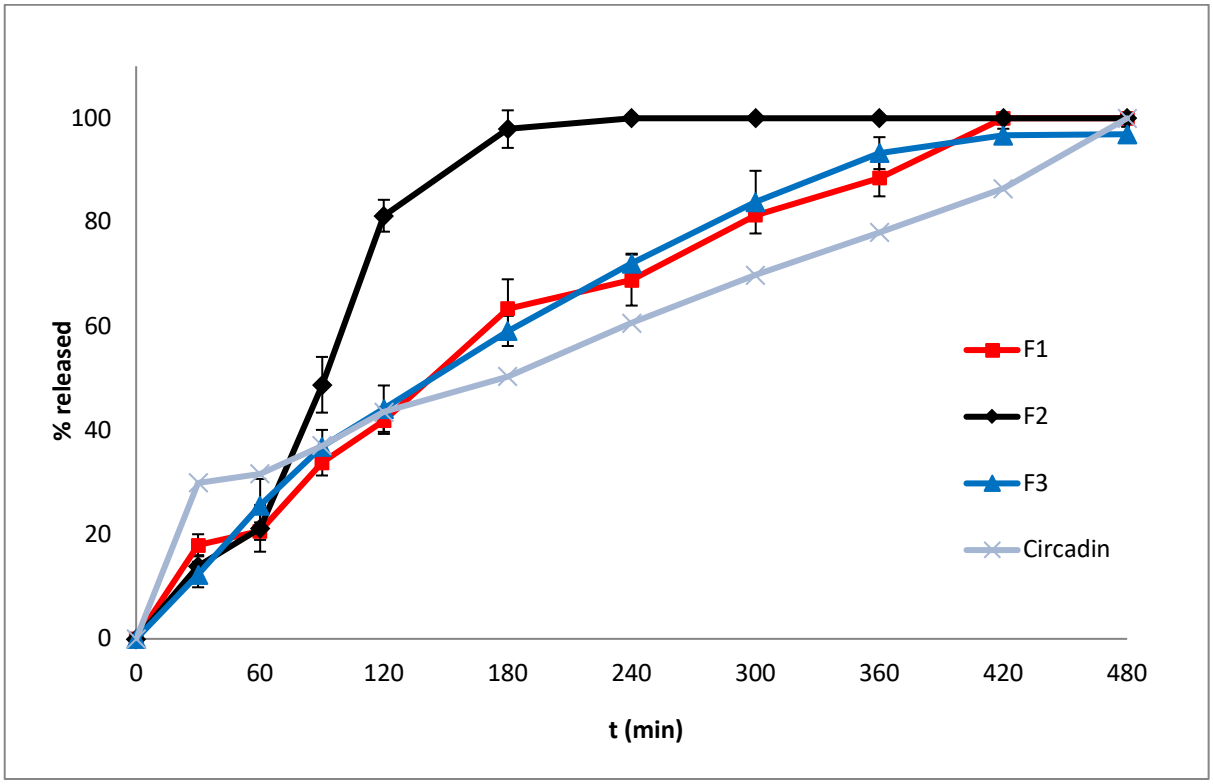
Background: Melatonin (*N*-acetyl 5-methoxytryptamine, **MLT**), a hormone synthesized by the pineal gland and released at night, has a regulatory role in the onset of sleep in mammals, including humans. It has been shown to have a hypnotic action in animals and humans, and has been used as an agent for restoring circadian rhythms disturbed by jet-lag, shift-work or ageing. 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. However, MLT's action is hampered by its poor bioavailability and short half-life, and that is why the exogenously administered hormone's preparations are of the modified release type, using the appropriate excipients.

Due to its biocompatibility, biodegradability, and excellent physicochemical and mechanical qualities, poly(*L*-lactic acid) (PLA), a commercially accessible synthetic polymer, finds ample use in a variety of applications, including biomedical applications, tissue engineering and drug delivery. PLA can be produced *via* a variety of polymerization techniques. In the present work, neat PLA and the PLA derivatives, PLA-sorbitol and PLA-glycerol, were utilized for the preparation of MLT modified-release tablet formulations, to further investigate their potential in the hormone's release.

Methods: The matrix tablets were comprised of MLT (2 mg) and combinations of the following excipients: neat PLA, the two new PLA derivatives (PLA-sorbitol and PLA-glycerol), HPMC K15M, lactose monohydrate, sodium alginate, Avicel, and magnesium stearate, as a lubricant. All the components (except of the lubricant) were blended in a mixing apparatus (Wab Turbula Type T2F) for 10 min (32 rpm). Magnesium stearate was then added to the mixture, which was blended for another 5 min. The total weight of each tablet was 200 mg, regardless of the composition, and tablets were produced using a 10 mm diameter die and a hydraulic press (Massen type, MP 150). The *in vitro* dissolution tests of the tablets were performed, using a USP dissolution apparatus II (Pharmatest Hainerp, Germany). The dissolution medium was 900 mL of a buffer solution (pH 4.5), in order to simulate the stomach pH at fed state. The system was maintained at a constant temperature of 37.0±0.5 °C and the paddles were rotated at a rate of 50 rpm. Samples (5 mL) were withdrawn at predetermined time intervals and passed through a 0.45 μm cellulose filter. At each time point, the volume was replenished with an equal volume of fresh medium. The concentration of MLT released into the medium was measured using a Perkin-Elmer UV spectrophotometer (Norwalk, CT), at a wavelength of 278 nm.

Results: In order to compare the dissolution profiles of the formulations produced, graphs of the percent drug release *vs.* time were constructed. All formulations indicated modified MLT release. The formulations containing neat PLA and PLA-glycerol had comparable release profiles to the commercially available drug Circadin®. From the formulation containing PLA-sorbitol, melatonin was released in more than 90%, after 180min.

Conclusions: In general, the formulations used in this study promoted the modified release of MLT. The formulation containing PLA-sorbitol showed higher MLT release, at t=180 min, compared with the neat PLA and PLA-glycerol.



Ingredients	1	2	3
Melatonin	2	2	2
PLA neat	67		
PLA sorbitol		67	
PLA glycerol			67
HPMC K15M	16	16	16
Sod. Alginate	77	77	77
Lactose	16	16	16
Avicel PH102	20	20	20
Mg Stearate	2	2	2
Total	200	200	200