Multiparticulate and matrix-based strategies for modified Melatonin release

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INTRODUCTION: What is melatonin?

A natural hormone produced by the pineal gland in the brain. It regulates the sleep-wake cycle (circadian rhythm) and signals the body when it's time to sleep. (1)

- Secreted mainly at night
- Production increases in darkness
- Peak levels: 2 - 4 AM

Suppressed by light exposure, especially blue light

FACTORS AFFECTING MELATONIN LEVELS

- Artificial light at night (mobile, TV, LED)
- Stress & Anxiety
- Irregular sleep schedules
- Aging
- Caffeine
- Alcohol

STUDY RATIONALE

- Immediate release is effective for delayed sleep onset, while modified release systems are designed to provide better control of plasma profiles.
- Various formulation approaches, including multilayer tablets and multiple-dose systems, often use different modify release polymers. (2)
- Pulsatile or delayed-release formulations that deliver an initial dose for sleep induction followed by delayed release may better mimic endogenous melatonin secretion. (3)

Pharmacokinetics

Absorption	Complete and well absorbed in GIT. Extensive first pass metabolism.
Oral Bioavailability	15%
Metabolism	Metabolized to its inactive metabolite, 6-sulphatoxy-melatonin.
Half Life	Short, 20 to 50 minutes
pKa	1176 pg/mL (fasted), 1020 pg/mL (fed state)
Tmax	**0.75 hours (fasted state)** **3 hours (fed state)**

METHODOLOGY

MUPS production

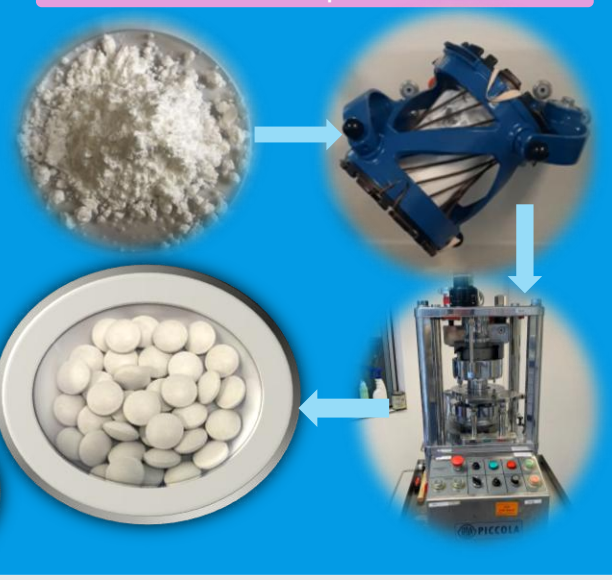
PHASE 1 Melatonin-loaded sugar pellets (Drug Layering)

PHASE 2 Enteric coating

PHASE 3 Drug layering for 1 mg initial release

PHASE 4 Capsule filling

Tablet DC process



FORMULATION STUDIES

Proposed formula- MUPS

Ingredient	%/ capsule	Function
Cellets 18/20 # (850 - 1000µ)	**88.91**	**Neutral pellets**
Drug solution		
Melatonin	**5.84**	**Active substance**
Hydroxypropyl methylcellulose (5 mPa.s)	**2.33**	**Binder**
Talc	**2.92**	**Antistatic agent**
Solvent System	**-**	
Ethanol: water (8:2)	**q.s.**	**Solvent**
Enteric Coating		
Methacrylic acid- ethyl acrylate copolymer (1:1)	**8, 10, 15% w/w**	**Enteric coat**
Ethanol: water (8:2)	**q.s.**	**Solvent**

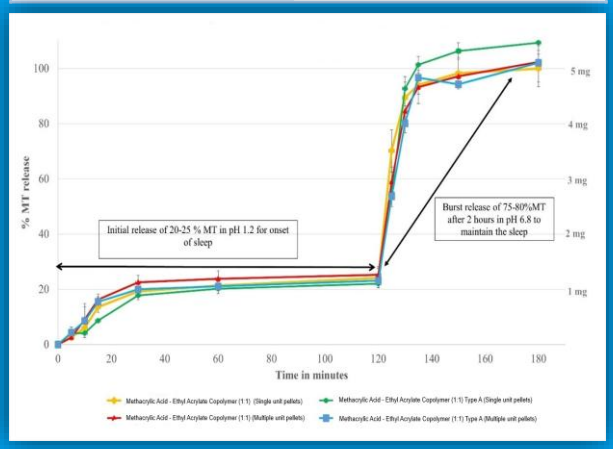
Proposed formulas – sustained release tablets

Ingredient	%/ tablet	Function
Melatonin	2	Active substance
Hydroxypropyl methylcellulose (100,000 mPa.s)	20/ 30/ 40	Controlled release polymer
Cellulose, microcrystalline 102	77/ 67/ 57	Filler
Magnesium stearate	1	Lubricant

RESULTS

***In vitro* release study - MUPS**

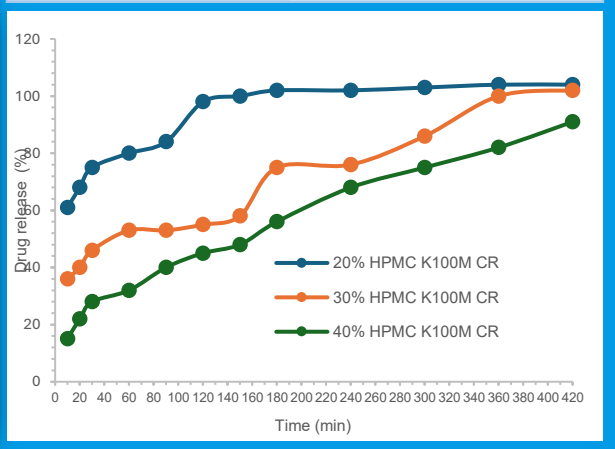
Apparatus	USP Dissolution Apparatus Type II (Paddle)
Media	0.1N HCL Buffer pH 1.2 (for 2 hours) phosphate buffer pH 6.8
Volume	900 mL
Temperature	37°C ± 0.5°C
Time intervals	5 min, 10 min, 15 min, 30 min, 60 min, 120 min, 130 min, 150 min, 180 min
Sample volume withdrawn	8 mL
RPM	50
Wavelength	278 nm



Dissolution profile of Melatonin MUPS

***In vitro* release study – sustained release tablet**

Apparatus	USP Dissolution Apparatus Type II (Paddle)
Media	Phosphate buffer pH 6.8
Volume	900 mL
Temperature	37°C ± 0.5°C
Time intervals	10 min, 20 min, 30 min, 60 min, 90 min, 120 min, 150 min, 180 min, 240 min, 300 min, 360 min, 420 min
Sample volume withdrawn	8 mL
RPM	50
Wavelength	278 nm



Dissolution profile of Melatonin 4 mg SR tablets

CONCLUSION

Pulsatile and sustained-release formulations of melatonin have been developed using single and multiple pellet capsules and hydrophilic HPMC matrix tablets. Pulsatile release can better mimic endogenous melatonin secretion in circadian rhythm disorders, while matrix-based systems offer scalable, industry-accepted platforms. Ongoing studies are expected to further explore the influence of specific range of HPMC concentration, molecular weight, and substitution on release optimization.

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REFERENCES

1) Hardeland R. Cell Mol Life Sci. 2001-2018,65.
2) Jan JE, Hamilton D, Seward N, Fast DK, Freeman RD, Laudon M.J Pineal Res. 2000; 29:34-39.
3) Vlachou M, Siamidi A, Pareli I, Zampakola A, Konstantinidou S. J Pharm Sci. 2016.105(1):10-14.