Formulation of an Extended-Release Melatonin Dietary Supplement

Application Data Sheet

Formulation of Dietary Supplements

Direct compression of dietary supplements presents several challenges, primarily due to low or high concentration and poor physicochemical properties of active ingredients. Common issues include:

- Poor flow and compressibility
- Difficulty achieving content uniformity
- Sensitivity to environmental factors such as heat, humidity, and light
- Strong odor and/or bitter taste

To address these challenges, formulators must understand and carefully evaluate the properties of each active ingredient and select appropriate excipients to ensure successful manufacture and long-term stability of the final dosage form.

The Challenge

Melatonin acts by inducing sleep and restoring the inherent sleep rhythm that is related to the rise and fall of blood melatonin concentrations. Melatonin treatment helps to restore these human circadian rhythms, resulting in better cognition and less daytime fatigue.[1] As a dietary supplement, synthetic melatonin is available over the counter (OTC) in many forms, including tablets, liquids, patches, gummies, and sprays.[2] As a tablet, melatonin is available in immediate release (IR), extended release (ER), and combination forms. Exogenous administered melatonin has a short half-life (< 1-hour)[3] so ER forms of melatonin are marketed as improving sleep duration and may help patients who wake up frequently or too early.

This study shows the use of AnyCoat®-C Hypromellose Polymer (LOTTE Fine Chemical) to formulate a melatonin tablet that provides fast onset of drowsiness and ER to improve sleep duration and avoid morning drowsiness.

Materials and Methods

In this study, both IR and ER melatonin tablets (5 mg dose) were formulated to assess the impact of hypromellose polymers on dissolution performance. Microcrystalline cellulose (Avicel 102, Dupont) and Starch 1500® Partially Pregelatinized Maize Starch (Colorcon, Inc.) were used as diluents to help improve blend compressibility and flow (Table 1).

Table 1: Tablet Composition of IR and ER Melatonin Tablets

Core Tablet Ingredients	Category	IR		MR	
		%w/w	Mg Tablet $^{-1}$	%w/w	Mg Tablet $^{-1}$
Melatonin	Active	1.67	5.00	1.67	5.00
MCC (90-micron)	Diluent	61.50	184.50	56.50	169.50
Starch 1500®	Diluent	35.83	107.49	30.83	92.49
AnyCoat-C CN10M (HPMC 2208, 100 cP)	ER Polymer	-	-	5.00	15.00
AnyCoat-C AN50 (HPMC 2910, 50 cP)	ER Polymer	-	-	5.00	15.00
Colloidal Silicon Dioxide	Glidant	0.50	1.50	0.50	1.50
Magnesium Stearate	Lubricant	0.50	1.50	0.50	1.50
TOTAL		100.00	300.00	100.00	300.00

A portion of the Starch 1500 was combined with the colloidal silicon dioxide (10:1) and passed through a 40 US mesh (425 micron) screen to break up agglomerates. A 50gram batch was prepared by mixing the active and other ingredients for 10 minutes, adding lubricant (pre-screened with a 60-mesh screen) and mixing for a further 3 minutes.

Tablets were compressed using 13/32" (10.3 mm) standard round concave B-tooling using 2000 psi compression force.

Tablet physical testing includes weight, thickness, and breaking force (n=10 tablets). The weight of each tablet was measured to the nearest 0.1 mg using an analytical balance. Thickness of each tablet was measured using a digital caliper and reported to the nearest 0.1 mm. Tablet breaking force (hardness) was measured using a hardness tester. For the friability test, 10 tablets were tested for 100 drops. Initial weight of 10 tablets and weight of the 10 tablets after 100 drops were recorded to calculate the friability result.

ER dissolution testing (n=6) was performed in 900 mL of water at 37.0°C ±0.5°C using USP Apparatus II (paddles) at 50 rpm for 12 hours, with samples taken at 0.5, 1.0, 1.5, 2.0, 3.0, 4.0, 6.0, 8.0, and 12.0-hour intervals. Ultraviolet absorbance spectroscopy (UV) at 222 nm wavelength and cell size of 5.0 mm was used for all readings.

Uniformity of dosage testing (n=10) was performed in 50 mL of 25:75; Acetonitrile: Buffer (pH 3.5) diluent at a wavelength of 222 nm and blank correction at 400 nm and cell size of 5.0 mm.[4] One tablet was placed in 50 mL of diluent and homogenized for 5 minutes at 5,000 rpms. The solution was transferred to a 50 mL centrifuge tube and centrifuge for approximately ten minutes at 3,000 rpms.

The supernatant liquid was used for analysis with the diluent as the blank.

Tablets were coated with blue pigmented Nutrafinish® Titanium Dioxide-Free Film Coating (Colorcon, Inc.), to 3% weight gain (w/w), in a perforated Labcoat™ Benchtop Tablet Coating System coating pan (O'Hara Technologies (Table 2)).

Table 2: Film Coating Process Parameters

Coating System	Nutrafinish® TiO2 Free Coating
Dispersion Solids Content (%)	20
Pan Speed (rpm)	25
Air Volume (cfm)	80
Atomizing Air Pressure (psi)	10
Pattern Air Pressure (psi)	10
Spray Rate (g/min)	6
Inlet Temperature (°C)	60
Exhaust Temperature (°C)	43-44

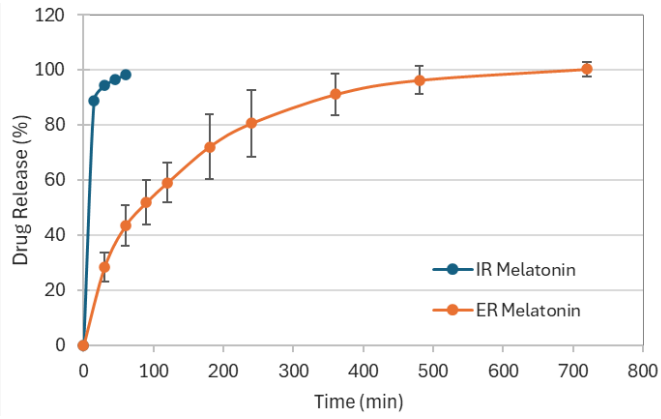
Results

Both IR and ER formulations were compressed without any issues and yielded defect-free tablets with good physical properties (Table 3). Content uniformity showed an Acceptance Value of 2.84 demonstrating suitability of the formulation for direct compression. Tablets were successfully coated with Nutrafinish Titanium Dioxide-Free coating, providing the added benefit of protection for the light sensitive melatonin active. As expected, the IR formulation released greater than 90% of the active release in less than 30 minutes. The ER formulation showed 30% active release in the first 30 minutes followed by extended release (Figure 1). This release pattern demonstrates the ability of the tablet formulation to provide fast onset and ER to improve sleep duration and avoid morning drowsiness.

Table 3: Tablet Properties of IR and ER Melatonin Tablets

Property	IR Tablets	ER Tablets
Weight (mg)	300.1 ±0.00	308.4 ±0.00
Thickness (mm)	4.127 ±0.03	3.910 ±0.02
Hardness (kP)	16.9 ±0.8	16.7 ±0.5
Friability (%)	0.02	0.01
Acceptance Value (CU)	2.84 (PASS)	

Figure 1: Dissolution profile for IR and ER Melatonin Tablets



Summary

A low dose extended-release melatonin tablet was produced with hypromellose (AnyCoat-C) as the rate controlling polymer in combination with Starch 1500 and MCC as diluents. The formulation produced a robust tablet with good content uniformity demonstrating the applicability of direct compression for the formulation. The resulting release pattern of the melatonin active exhibited fast onset and ER to help improve sleep duration and avoid morning drowsiness.

References:

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