Circadian Phase-Specific Magnesium Supplementation Using Multiple Salt Forms:

Formulation Rationale, Biological Mechanisms, Flexible Dosing Architecture, and the Scientific Case for a Dual AM/PM Delivery System

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Abstract

The EscapeMed 30D system is, to the authors' knowledge, the first dietary supplement architecture to coordinate 30 active ingredients across four phase-specific formulas and five biological layers as a single integrated daily chronobiological protocol. The designation '30D' refers to the 30-day pilot study protocol used to assess the system and does not imply a fixed consumption duration; the system is designed for flexible dosing between one and two capsules per formula per day based on individual need, tolerance, and applicable regulatory context. This narrative review documents the scientific rationale for the dual AM/PM magnesium layer of this system: five distinct magnesium salt forms selected for morning administration and five for evening administration, based on differential bioavailability, tissue affinities, counterion biological functions, and alignment with circadian phase-specific physiological demands. Six

tables are presented: the AM vs PM architectural comparison; biological layer coverage by formula; symptom-to-mechanism mapping; a structured comparison of single-salt versus multi-salt supplementation; a target population guide; and a clinical decision framework for single-formula use. All ingredient doses are confirmed from the official product specification and presented at both one-capsule and two-capsule levels to reflect the system's flexible dosing architecture. The AM/PM magnesium architecture is, to the authors' knowledge, the first dual-phase, multi-salt magnesium formulation to be documented in peer-reviewed literature.

Keywords: magnesium supplementation; circadian biology; magnesium bioavailability; magnesium salt forms; chronobiology; dietary supplement formulation; magnesium bisglycinate; magnesium taurate; magnesium malate; magnesium succinate; phase-specific nutrition; chrononutrition; EscapeMed 30D; flexible dosing; sleep architecture; brain fog

1. Introduction: The EscapeMed 30D System and the Magnesium Layer

The EscapeMed 30D system — a four-formula, 30-ingredient chronobiological supplement architecture designed and formulated by the author — represents, to our knowledge, the first integrated supplement system to coordinate phase-specific ingredient delivery across the full 24-hour biological cycle, with explicit scientific rationale for each ingredient's salt form, dose, timing, and biological layer assignment. This paper describes in detail the scientific foundation for two of the four formulas in that system: Magnesium AM and Magnesium PM. The formulation rationale documented in this paper is intended to provide transparent scientific basis

for each ingredient selection, dose, and timing decision, consistent with the principles of evidence-based dietary supplement design.

The designation ‘30D’ refers to the 30-day pilot observational study (Samarin 2026, under review) conducted to assess the complete system using a standard two-capsule dose per formula per day. It does not imply a fixed or mandatory consumption duration or dose. The system is designed with a deliberate flexible dosing architecture: each formula is formulated at 125 mg elemental magnesium per capsule, enabling users to choose between one capsule per formula per day (125 mg elemental Mg per formula; conservative dosing, within internationally established supplemental upper intake levels) and two capsules per formula per day (250 mg elemental Mg per formula; standard dosing as used in the pilot study). The appropriate dose depends on individual magnesium status, health context, desired duration of use, and the regulatory framework applicable in the user’s country of residence. This flexible architecture is a deliberate formulation decision and is documented throughout this paper at both dose levels.

Magnesium (Mg^{2+}) participates as a cofactor in more than 300 enzymatic reactions including ATP synthesis, DNA replication, protein biosynthesis, neuromuscular signalling, and the regulation of over 600 magnesium-sensitive enzyme systems (Volpe 2013). Despite this centrality, 20–30% of European adults fail to meet the Recommended Dietary Allowance through diet alone (Gröber, Schmidt, and Kisters 2015; Rosanoff, Weaver, and Rude 2012). In populations subject to chronic psychological stress, high physical training load, regular alcohol consumption, or use of proton pump inhibitors, depletion rates are substantially higher (Seelig 1994; Galland 1991).

Two independent bodies of evidence motivate the multi-salt AM/PM formulation strategy. First, systematic bioavailability studies demonstrate that magnesium salt forms differ substantially in

absorption mechanism, plasma kinetics, and tissue targeting, and that counterion molecules carry independent biological functions irreplaceable by any other salt at any dose. Second, the landmark 2016 Nature publication by Feeney and colleagues established that intracellular Mg^{2+} concentrations oscillate with the molecular clock and actively regulate cellular timekeeping, making phase-specific delivery not merely advantageous but biologically necessary for optimal circadian alignment (Feeney et al. 2016). This paper integrates both bodies of evidence to justify and document the first dual-phase, multi-salt magnesium formulation in the published scientific literature.

2. Magnesium Salt Forms: Bioavailability, Tissue Targeting, and Counterion Biology

2.1. The Bioavailability Hierarchy

Walker and colleagues established in a randomised crossover trial that magnesium citrate and amino acid chelate forms are significantly superior to magnesium oxide in plasma magnesium and 24-hour urinary excretion markers, with oxide achieving fractional absorption of approximately 4% compared to 30% or more for organic salt forms (Walker et al. 2003). Schuette and colleagues demonstrated superior absorption of magnesium diglycinate relative to oxide (Schuette, Lashner, and Janghorbani 1994). Ates and colleagues confirmed a bioavailability hierarchy with glycinate and citrate consistently outperforming inorganic salts across a range of doses (Ates et al. 2019). These data establish that salt form selection materially affects how much magnesium reaches target tissues and through which pathways.

2.2. Counterion Biology: The Dimension Beyond Bioavailability

The critical distinction between magnesium salts is not only bioavailability but counterion biology. In magnesium bisglycinate, the counterion is glycine: an inhibitory neurotransmitter at spinal cord glycine receptors and a collagen and glutathione precursor. In magnesium malate, the counterion is malic acid: a direct TCA cycle intermediate for Complex II mitochondrial activity. In magnesium succinate, the counterion is succinic acid: the direct substrate for succinate dehydrogenase in the electron transport chain. In magnesium taurate, the counterion is taurine: a potent activator of extrasynaptic GABA-A receptors in the thalamus (Jia et al. 2008). In magnesium gluconate, the counterion participates in the pentose phosphate pathway generating NADPH for nocturnal antioxidant defence. In magnesium lactate, the counterion is a gluconeogenesis substrate for overnight glycogen resynthesis. None of these counterion functions can be achieved by bisglycinate supplementation regardless of dose. A multi-salt system delivers functional breadth across distinct biological pathways that is architecturally impossible with a single salt.

2.3. Sex Differences in Magnesium Metabolism

Oestrogen modulates TRPM6 — the primary renal magnesium reabsorption channel. As oestrogen declines during perimenopause and postmenopause, TRPM6 activity falls, increasing urinary magnesium losses independent of dietary intake (Castiglioni et al. 2013). This structural renal conservation deficit requires maximising absorption through multiple intestinal transport mechanisms simultaneously — the defining strategy of the multi-salt AM/PM system.

3. The Circadian Regulation of Magnesium: Why Timing Determines Function

3.1. The Feeney 2016 Discovery

The molecular circadian clock — coordinated by the CLOCK/BMAL1 heterodimer — regulates approximately 80% of protein-coding genes with a periodicity of approximately 24 hours (Takahashi 2017). Feeney and colleagues demonstrated in a landmark 2016 Nature publication that intracellular Mg^{2+} concentration oscillates with a clear circadian periodicity driven by active transport mechanisms under molecular clock control, and that this oscillation actively regulates clock amplitude and period (Feeney et al. 2016). Cellular magnesium is therefore a dynamic, clock-regulated resource — not a static cofactor pool — and its supplementation should be timed and formulated to align with the circadian demands of each biological phase.

3.2. Morning Phase: Activation Demands

The morning activation phase — rising cortisol, sympathetic predominance, increasing metabolic demand — places specific demands on Mg^{2+}-dependent processes: Mg-ATP complex formation, catecholamine synthesis, cortisol receptor signalling, and neuromuscular activation. Cortisol-driven urinary magnesium excretion is highest in the morning (Seelig 1994), creating a demand-supply deficit in the activation phase that morning supplementation with bioavailable, energetically active salt forms directly addresses.

3.3. Evening Phase: Restoration Demands

The evening restoration phase shifts Mg^{2+} demand toward NMDA receptor modulation for neuromuscular relaxation, GABA-A receptor potentiation for sleep onset facilitation, protein synthesis and cellular membrane repair during sleep, and the endogenous melatonin synthesis cascade. A formulation optimised for morning energy metabolism is not optimised for evening restoration. The AM/PM split is a biological necessity derived from circadian physiology.

4. The Magnesium AM Formulation: Morning Signal

The Magnesium AM formulation delivers elemental magnesium across five salt forms plus inositol and vitamin B6. Each formula capsule contains 125 mg elemental magnesium. All doses below are confirmed from the official product specification and presented at both the conservative one-capsule and the standard two-capsule dose per day. The products are manufactured by a GMP-certified contract manufacturer in the European Union, in compliance with EU food supplement regulations, HACCP, and GMP quality standards.

4.1. Magnesium Bisglycinate

One capsule: 58 mg elemental Mg. Two capsules: 116 mg elemental Mg.

Absorbed via the amino acid transporter pathway — a high-capacity, non-saturable route ensuring consistent Mg^{2+} delivery at both dose levels. Glycine released upon absorption is an inhibitory neurotransmitter at spinal cord glycine receptors and a precursor to glutathione and collagen. Provides the foundational systemic Mg^{2+} pool for all morning-phase magnesium-dependent processes.

Experienced benefit: reduced brain fog, improved cognitive baseline, neuromuscular readiness at waking.

EU authorized health claim: magnesium contributes to normal psychological function and normal functioning of the nervous system.

4.2. Magnesium Citrate (buffered)

One capsule: 34 mg elemental Mg. Two capsules: 68 mg elemental Mg.

Established as superior to oxide in randomised crossover design (Walker et al. 2003). High solubility produces rapid dissolution and absorption at both dose levels. The buffered form reduces osmotic load compared to standard citrate, improving tolerability particularly at the one-capsule starting dose.

Experienced benefit: muscle readiness, reduced morning stiffness, neuromuscular performance.

EU authorized health claim: magnesium contributes to normal muscle function and normal neuromuscular transmission.

4.3. Magnesium Malate

One capsule: 18 mg elemental Mg. Two capsules: 36 mg elemental Mg.

The counterion that most directly distinguishes the AM formula from any single-salt supplement. Malic acid is a direct TCA cycle intermediate serving as substrate for Complex II mitochondrial activity. Co-delivery with Mg^{2+} provides both cofactor and substrate for oxidative phosphorylation simultaneously during the morning energy demand peak. This dual action cannot be replicated by any other salt at any dose. Deliberately excluded from the PM formula because TCA cycle stimulation is counterproductive during the restoration phase.

Experienced benefit: stable morning energy, reduced afternoon energy crash, reduced caffeine dependence.

EU authorized health claim: magnesium contributes to normal energy-yielding metabolism and reduction of tiredness and fatigue.

4.4. Magnesium L-Ascorbate

One capsule: 6.5 mg elemental Mg + 93.5 mg Vitamin C. Two capsules: 13 mg elemental Mg + 187 mg Vitamin C (234% NRV).

The only AM salt that co-delivers a second fully active nutrient at a therapeutically significant dose at both dose levels. Vitamin C is an essential cofactor in collagen synthesis, carnitine biosynthesis for mitochondrial fatty acid oxidation, and dopamine beta-hydroxylase activity. At one capsule, 93.5 mg vitamin C provides meaningful cofactor support. At two capsules, 187 mg constitutes a full therapeutic contribution to collagen synthesis and antioxidant defence. Deliberately excluded from the PM formula because ascorbate's stimulatory catecholamine role is counter-indicated during restoration.

Experienced benefit: skin quality over time, morning mental clarity, sustained energy.

EU authorized health claim: vitamin C contributes to normal collagen formation, normal energy-yielding metabolism, and protection of cells from oxidative stress.

4.5. Magnesium Succinate

One capsule: 8.5 mg elemental Mg. Two capsules: 17 mg elemental Mg.

Succinate is the direct substrate for succinate dehydrogenase — Complex II of the mitochondrial electron transport chain. Together with malate, succinate provides two distinct intramitochondrial energy-producing entry points simultaneously. Its outsized functional contribution relative to its Mg^{2+} content makes it a high-value morning ingredient at both dose levels. Deliberately excluded from the PM formula.

Experienced benefit: sustained ATP production; clean, stable energy distinct from caffeine-driven stimulation.

4.6. Inositol and Vitamin B6

Inositol: one capsule 125 mg, two capsules 250 mg. Vitamin B6: one capsule 0.75 mg (54% NRV), two capsules 1.5 mg (107% NRV).

Inositol participates in phosphatidylinositol signalling cascades relevant to serotonin receptor sensitisation and insulin receptor sensitivity (Izzo et al. 2021). Vitamin B6 is a cofactor in the synthesis of serotonin, dopamine, and GABA — neurotransmitters whose morning availability determines mood, motivation, and cognitive performance. Morning B6 is categorically different from evening B6, which in the PM formula supports the serotonin-to-melatonin enzymatic conversion for endogenous circadian signal generation.

Experienced benefit: mood stability, cognitive clarity, emotional resilience across the working day.

EU authorized health claim: vitamin B6 contributes to normal psychological function and normal functioning of the nervous system.

5. The Magnesium PM Formulation: Evening Signal

The Magnesium PM formulation delivers elemental magnesium across five salt forms plus vitamin B6. Each capsule contains 125 mg elemental magnesium. All doses are presented at both one-capsule and two-capsule levels. The PM formula deliberately excludes all TCA cycle intermediates present in the AM formula — malate and succinate — because their mitochondrial stimulating functions are counterproductive during the restoration phase. This exclusion is as scientifically deliberate as each inclusion.

5.1. Magnesium Bisglycinate

One capsule: 55 mg elemental Mg. Two capsules: 110 mg elemental Mg.

The dominant PM salt, providing the highest-bioavailability base form for the evening Mg^{2+} pool. In the PM context, glycine's role as an inhibitory neurotransmitter at spinal cord glycine receptors contributes specifically to neuromuscular relaxation during the transition from activity to rest — a qualitatively different function from its AM role despite being the same chemical compound. Effective at both dose levels.

Experienced benefit: muscle relaxation at rest, reduced nocturnal cramping, easier physical unwinding after the working day.

5.2. Magnesium Taurate

One capsule: 31.5 mg elemental Mg. Two capsules: 63 mg elemental Mg.

The most pharmacologically distinctive salt in the PM formula. Taurine is a potent activator of extrasynaptic GABA-A receptors in the thalamus — the brain region responsible for gating sensory input during the sleep-wake transition (Jia et al. 2008). GABA-A activation in the thalamus reduces sensory arousal and facilitates sleep onset through biological phase transition, not pharmacological sedation. Taurine additionally modulates cardiac ion channels, supports heart rate variability, and exerts cardioprotective osmoregulatory effects in the vagally dominant evening phase (Xu et al. 2008). These effects are present at both dose levels, with the two-capsule dose providing more complete thalamic GABA-A coverage.

Experienced benefit: easier sleep onset without sedation, reduced evening palpitations, improved nocturnal heart rate variability, calmer transition from the working day.

5.3. Magnesium Citrate

One capsule: 19.5 mg elemental Mg. Two capsules: 39 mg elemental Mg.

Provides the well-characterised, rapidly bioavailable base-form contribution to the evening Mg^{2+} pool. The lower dose compared to the AM formula reflects the extended overnight absorption window. Citrate's alkalising property supports the mild nocturnal shift toward respiratory alkalosis that accompanies deep sleep.

Experienced benefit: sustained overnight magnesium availability; smooth mineral balance during the sleep cycle.

5.4. Magnesium Lactate

One capsule: 12.5 mg elemental Mg. Two capsules: 25 mg elemental Mg.

Co-delivers lactate — a metabolic intermediate used in gluconeogenesis and muscle glycogen resynthesis during overnight recovery. The Cori cycle converts lactate to glucose via hepatic gluconeogenesis during sleep, restoring glycogen stores for the following day. Particularly relevant for individuals with physical training demands.

Experienced benefit: faster physical recovery, reduced delayed-onset muscle soreness, improved readiness the following morning.

5.5. Magnesium Gluconate

One capsule: 6.5 mg elemental Mg. Two capsules: 13 mg elemental Mg.

The primary functional contribution of gluconate to the PM formula is the counterion's role in the pentose phosphate pathway: generating NADPH for nocturnal glutathione recycling and

antioxidant defence. This nocturnal function is specifically relevant to the overnight cellular repair phase, when oxidative stress accumulated during the active day must be cleared. This function is present at the one-capsule dose and amplified at the two-capsule dose.

Experienced benefit: cleaner cellular recovery during sleep; supports antioxidant defence during overnight tissue repair.

5.6. Vitamin B6 — Evening Function

One capsule: 0.75 mg (54% NRV). Two capsules: 1.5 mg (107% NRV).

Evening B6 serves a categorically different function from morning B6. In the PM context, B6 is required as a cofactor for arylamine N-acetyltransferase (AANAT) — the rate-limiting enzyme in the pineal gland's conversion of serotonin to melatonin. The PM formula thereby supports endogenous melatonin synthesis from within, without requiring pharmacological melatonin doses. Even at the one-capsule dose (0.75 mg, 54% NRV), B6 contributes meaningfully to this enzymatic pathway. The distinction between morning B6 and evening B6 function is a critical design principle absent from all single-formula magnesium products.

Experienced benefit: deeper circadian signal; earlier, more stable sleep onset.

6. AM vs. PM: Architectural Logic Side by Side

Table 1 presents the full comparative architecture of the AM and PM formulas at both dose levels, with phase assignment rationale and exclusion logic. The exclusion column is as important as the inclusion columns — a single formula combining all salts at one time point delivers biological noise rather than biological signal.

Table 1. Comparative AM/PM formulation architecture: confirmed elemental Mg per capsule, phase assignment, and exclusion rationale.

Salt Form	AM (1 / 2 caps)	PM (1 / 2 caps)	Why included in this phase	Why excluded from opposing phase	Primary biological target
Bisglycinate	58 / 116 mg Mg	55 / 110 mg Mg	AM: amino acid transport + glycine for neurotransmission + collagen/glutathionePM: same absorption + glycine receptor inhibitory tone for relaxation	Included in both — counterion function shifts by phase	Nervous system; neuromuscular function; glutathione precursor
Malate	18 / 36 mg Mg	Excluded	TCA cycle intermediate; mitochondrial ATP synthesis during activation phase	Stimulates oxidative phosphorylation; counterproductive to restoration and sleep preparation	Cellular energy; mitochondrial function
Citrate (buffered AM / standard PM)	34 / 68 mg Mg	19.5 / 39 mg Mg	AM: rapid broad-spectrum absorption for morning windowPM: lower dose for extended overnight window; alkalising for deep sleep	Included in both at phase-appropriate doses	Bioavailability; neuromuscular transmission; acid-base
L-Ascorbate	6.5 / 13 mg Mg+ 93.5 / 187 mg Vit C	Excluded	Vitamin C co-delivery: collagen synthesis, carnitine, dopamine conversion — all morning-phase functions	Ascorbate's catecholamine stimulation counter-indicated during restoration	Antioxidant; collagen; morning neurotransmitter support
Succinate	8.5 / 17 mg Mg	Excluded	Direct Complex II electron transport chain substrate; supports peak morning ATP demand	Mitochondrial stimulation counterproductive to sleep preparation	Mitochondrial energy production
Taurate	Excluded	31.5 / 63 mg Mg	Taurine activates thalamic GABA-A receptors; supports cardiac parasympathetic tone	GABAergic sedation and parasympathetic promotion counter-indicated in activation phase	Sleep onset; cardiovascular relaxation
Gluconate	Excluded	6.5 / 13 mg Mg	NADPH generation for nocturnal glutathione recycling and antioxidant defence	Nocturnal antioxidant recycling role irrelevant during activation phase	Nocturnal antioxidant defence

Lactate	Excluded	12.5 / 25 mg Mg	Gluconeogenesis substrate for overnight glycogen resynthesis	Nocturnal metabolic process; not relevant to morning activation	Overnight recovery; glycogen resynthesis

7. Biological Layer Coverage: What Each Formula Provides

Table 2 documents the five biological layers of the EscapeMed 30D system and the coverage provided by the AM formula alone, the PM formula alone, and the combined AM/PM system.

Table 2. Biological layer coverage: AM alone, PM alone, and combined system.

Biological Layer	Magnesium AM alone	Magnesium PM alone	AM + PM combined
1. Cellular energy & mitochondrial function	✓✓✓ FullMalate + succinate as TCA substrates; all forms as Mg-ATP cofactors	✓ LimitedMg-ATP support only; no TCA substrate delivery	✓✓✓ FullMorning TCA support + overnight Mg-ATP maintenance
2. Sleep architecture & circadian signalling	✓ LimitedB6 morning neurotransmitter synthesis only	✓✓✓ FullTaurate GABA-A + bisglycinate NMDA + B6 melatonin synthesis	✓✓✓ FullEvening sleep architecture + morning circadian readiness
3. Connective tissue & structural integrity	✓✓ Partial93.5 mg (1 cap) or 187 mg (2 caps) vitamin C via ascorbate	— AbsentNo collagen synthesis cofactors in PM formula	✓✓ PartialFull coverage requires Skin Renewal Complex
4. Antioxidant & cellular protection	✓✓ PartialVitamin C (ascorbate); glycine as glutathione precursor	✓✓ PartialGluconate NADPH for nocturnal glutathione recycling	✓✓✓ FullDay-phase protection + nocturnal glutathione recycling
5. Nervous system & hormonal regulation	✓✓✓ FullBisglycinate NMDA; inositol; B6 dopamine/serotonin synthesis	✓✓✓ FullTaurate GABA-A; bisglycinate glycine receptor; B6 melatonin synthesis	✓✓✓ FullFull-spectrum nervous system support across both circadian phases
TOTAL FULLY COVERED	**2 of 5(Energy + Nervous system)**	**2 of 5(Sleep + Nervous system)**	**4 of 5(connective tissue requires Skin Renewal Complex)**

8. The AM/PM System as an Integrated Circadian Intervention

8.1. What the Combination Achieves That Neither Formula Achieves Alone

The ten-salt combination ensures broader tissue delivery than any single or dual-salt formulation. More importantly, the deliberate phase separation ensures that each delivery supports rather than opposes the biological programme of its respective phase. A single formula combining all ten salts at one time point delivers pro-activation and pro-relaxation signals simultaneously, creating biological noise rather than biological signal. The phase separation is the mechanism. It transforms magnesium from a blunt nutritional intervention into a precision circadian signal.

8.2. Flexible Dosing Architecture and Safety

The EscapeMed 30D system is designed for flexible dosing between one and two capsules per formula per day. This flexibility is not incidental — it is a deliberate formulation decision made for three reasons simultaneously.

First, regulatory flexibility. Magnesium supplementation limits vary across EU member states and are subject to ongoing regulatory review at the European level. The Tolerable Upper Intake Level for supplemental magnesium established by the Scientific Committee on Food is 250 mg per day from supplemental sources (SCF 2001). At the one-capsule dose per formula (125 mg AM + 125 mg PM = 250 mg per day from the two magnesium formulas), the system operates within this established threshold. At the two-capsule dose (250 mg AM + 250 mg PM = 500 mg per day from magnesium formulas), the system is within the range of national regulatory limits that apply in certain EU member states. Individual users should follow the recommended dose stated on the product label applicable to their country of residence.

Second, total system magnesium context. Magnesium is present not only in the AM and PM formulas but also as magnesium bisglycinate in the Super Sleep formula. At the maximum

two-capsule dose across all relevant formulas, total supplemental magnesium from the complete EscapeMed 30D system exceeds 500 mg per day. The 125 mg per capsule architecture ensures that users can self-regulate total daily magnesium intake by adjusting capsule count across all formulas simultaneously, without requiring reformulation. At the one-capsule dose across all formulas, total supplemental magnesium delivery remains within internationally established safety thresholds.

Third, personalised dosing. Individual magnesium needs vary substantially based on depletion status, stress load, physical activity, age, sex, and concurrent supplement or medication use. The flexible architecture allows dosing to be adjusted to individual need over time without changing the product.

8.3. Drug Interactions and Contraindications

Clinicians should note the following relevant considerations. High-dose magnesium may reduce absorption of certain antibiotics, particularly tetracyclines and fluoroquinolones, through chelation; these should be administered at least 2 hours apart. Magnesium may potentiate antihypertensive effects of calcium channel blockers; monitoring is recommended. Diuretics increase urinary magnesium excretion and may increase supplementation needs rather than contraindicate use. Proton pump inhibitors reduce gastric acid and may impair magnesium absorption chronically; patients on long-term PPI therapy represent an elevated-need population. Individuals with significant renal impairment (eGFR below 30 mL/min/1.73m²) should not self-supplement magnesium without medical supervision regardless of dose or formula.

8.4. The AM/PM Design in the Chronopharmacology Context

The concept of temporal separation in supplement and pharmaceutical delivery underpins time-of-day recommendations for statins, antihypertensives, and thyroid hormones. Applying this principle to magnesium — with two distinct phase-specific formulas rather than one agent at one time — represents a translation of chronopharmacology principles into dietary supplement design that has no precedent in the published literature (Reinberg and Smolensky 1982; Smolensky et al. 2011).

9. From Biology to Lived Experience: Symptom-Based Clinical Targets

Table 3 maps common subjectively experienced symptoms to their underlying biological mechanisms and identifies the specific salt form, formula, and expected onset for each. This table is intended to support both clinical application and individual product selection.

Table 3. Symptom-to-mechanism mapping: lived experience, biological target, formula, and expected onset.

Symptom / Experience	Underlying biological mechanism	Relevant ingredient and action	Formula	Expected onset
Brain fog / poor concentration	NMDA glutamate receptor dysregulation; subclinical Mg^{2+} deficit in neurons; low dopamine/serotonin synthesis	Bisglycinate (NMDA modulation); inositol (serotonin receptor sensitisation); B6 (dopamine synthesis cofactor)	AM	2–4 weeks
Morning grogginess / slow waking	Mitochondrial energy deficit at waking; insufficient cortisol awakening response; low morning neurotransmitter synthesis	Malate + succinate (TCA substrates for immediate ATP); B6 (dopamine synthesis at waking)	AM	2–4 weeks
Energy crashes mid-afternoon	Adenosine accumulation from poor mitochondrial efficiency; unsupported	Malate + succinate + citrate (mitochondrial substrate provision);	AM	2–4 weeks

	Krebs cycle; cortisol decline without energetic compensation	bisglycinate (sustained Mg-ATP support)		
Caffeine dependence for energy	Adenosine receptor sensitivity elevated due to chronic ATP deficit; caffeine masks rather than corrects the underlying energetic deficit	Malate + succinate (restoring mitochondrial efficiency reduces endogenous adenosine drive for stimulants)	AM	4–8 weeks
Difficulty falling asleep	Insufficient GABAergic tone at sleep onset; elevated evening cortisol preventing parasympathetic transition	Taurate (taurine activates thalamic GABA-A receptors); bisglycinate PM (NMDA modulation facilitates neuromuscular down-regulation)	PM	1–2 weeks
Poor sleep quality / frequent waking	Insufficient REM density; NMDA receptor hyperexcitability during sleep; incomplete slow-wave phases	Bisglycinate PM (NMDA modulation); taurate (sustained GABA-A support); PM B6 (melatonin synthesis)	PM	1–2 weeks
Vivid dreams / improved dream recall	Increased REM density following circadian resynchronisation; early adaptation signature in 50% of pilot participants	Bisglycinate PM (NMDA modulation contributing to REM-promoting temperature reduction via glycine receptor)	PM	Days 3–5
Muscle tension / cramps at rest	Calcium-magnesium imbalance at sarcoplasmic reticulum; insufficient neuromuscular relaxation signal	Bisglycinate PM (glycine receptor inhibition); taurate (GABA-A modulation supporting muscle relaxation)	PM	1–2 weeks
Slow training recovery	Delayed lactate clearance; insufficient glycogen resynthesis; Mg-dependent muscle calcium cycling impaired	Lactate PM (gluconeogenesis substrate); bisglycinate AM (Mg-ATP for muscle function); malate AM (mitochondrial recovery)	AM + PM	2–4 weeks
Stress sensitivity / anxiety	HPA axis dysregulation; cortisol-driven Mg^{2+} excretion; NMDA hyperactivation in limbic circuits	Bisglycinate AM+PM (NMDA modulation); taurate (GABA-A calming); inositol (serotonin receptor regulation)	AM + PM	4–8 weeks
Evening heart palpitations	Mg-dependent cardiac ion channel	Taurate PM (cardiac GABA-A and ion	PM	2–4 weeks

	dysregulation; reduced parasympathetic tone; electrolyte imbalance	channel modulation; cardioprotective osmoregulation via taurine)		
Low mood / emotional flatness	Insufficient serotonin synthesis; reduced inositol second messenger availability; prefrontal Mg^{2+} deficit	B6 AM (serotonin synthesis cofactor); inositol AM (phosphatidylinositol signalling; serotonin receptor sensitisation)	AM	2–4 weeks
Skin dullness / slow nail growth	Suboptimal collagen synthesis; insufficient vitamin C cofactor availability; reduced fibroblast activity	Ascorbate AM (vitamin C as collagen synthesis cofactor; extended to full coverage by Skin Renewal Complex in complete system)	AM	4–8 weeks

10. Is Single-Salt Magnesium Sufficient? A Structured Scientific Response

Having established the full architecture and biological coverage of the AM/PM system, it is possible to address the most common objection to multi-salt magnesium supplementation: that bisglycinate alone — or any single high-quality salt — is sufficient for most people, and that a complex multi-salt system is unnecessary or primarily commercial in motivation. This objection is partially correct and substantially incomplete.

A single high-quality salt such as bisglycinate IS sufficient for: addressing mild-to-moderate dietary magnesium insufficiency in a healthy adult with no specific performance, sleep, or cardiovascular concerns; improving basic neuromuscular function and reducing nocturnal cramping; providing the foundational Mg^{2+} delivery for general enzymatic function.

A single salt is NOT sufficient for: delivering TCA cycle substrates simultaneously with Mg^{2+} for mitochondrial energy support (requires malate and succinate); activating extrasynaptic GABA-A receptors in the thalamus for sleep-onset facilitation (requires taurate — glycine operates at glycine receptors, not GABA-A); supporting nocturnal NADPH generation for glutathione

recycling (requires gluconate); providing gluconeogenesis substrate for overnight glycogen resynthesis (requires lactate); or delivering phase-separated supplementation aligned with the qualitatively different demands of morning activation and evening restoration (requires the AM/PM architecture).

Table 4 presents a direct comparison across all clinically relevant dimensions.

Table 4. Single-salt magnesium versus the AM/PM multi-salt system: structured comparative analysis.

Dimension	Single salt (e.g. bisglycinate, once daily)	AM/PM Multi-Salt System
Number of salt forms	1	10 (5 AM + 5 PM)
Intestinal absorption pathways used	1 (amino acid transporter)	Multiple: amino acid, organic anion, TCA substrate, ionic
Counterion biological functions	Glycine only: inhibitory neurotransmission, collagen/glutathione precursor	9 distinct counterion functions: TCA cycle substrates, electron transport, GABA-A modulation, NADPH generation, gluconeogenesis substrate, vitamin C co-delivery, cardiac ion channel modulation
Mitochondrial TCA cycle support	No — glycine is not a TCA intermediate	Yes — malate and succinate delivered in AM at 1-capsule or 2-capsule dose
Thalamic GABA-A receptor activation	No — glycine operates at glycine receptors, not GABA-A	Yes — taurate in PM delivers taurine to extrasynaptic GABA-A receptors in thalamus
Nocturnal NADPH generation	No	Yes — gluconate in PM supports pentose phosphate pathway and glutathione regeneration
Overnight glycogen resynthesis substrate	No	Yes — lactate in PM provides gluconeogenesis substrate
Circadian phase alignment	None — same formula regardless of time of day	Explicit AM/PM phase separation at both 1-capsule and 2-capsule dose levels
Vitamin C co-delivery	No	Yes — 93.5 mg (1 cap) or 187 mg (2 caps) vitamin C via ascorbate in AM
Evening melatonin synthesis support	No	Yes — PM B6 supports AANAT enzyme in serotonin-to-melatonin conversion

Flexible dosing: 1 or 2 capsules per day	Yes — single products offer dose flexibility	Yes — 125 mg per capsule architecture supports 250–500 mg total range
Appropriate for: mild dietary insufficiency	Yes — sufficient	Yes — more than sufficient
Appropriate for: circadian phase-specific optimisation	No — architecturally incapable of phase separation	Yes — designed for this purpose at both dose levels

The conclusion is not that single-salt magnesium is a poor supplement. Bisglycinate in particular is among the best available options and is the dominant form in both AM and PM formulas. The conclusion is that 'sufficient for basic adequacy' is not the same as 'optimal for comprehensive circadian function,' and that for individuals seeking phase-specific delivery and the full counterion biological benefit of ten salt forms, a single product cannot provide what the AM/PM system provides regardless of dose.

11. Target Populations: Who Benefits Most and Why

Table 5 presents the five primary target populations, with specific depletion mechanisms, expected benefits from each formula at flexible doses, and clinical monitoring recommendations.

Table 5. Target population guide: depletion mechanisms, expected benefits, and monitoring recommendations.

Population	Primary depletion mechanism	Key benefit: AM formula	Key benefit: PM formula	Recommended monitoring
Chronic stress / high cognitive load	Cortisol elevation drives sustained renal Mg^{2+} excretion; peak loss in morning activation phase	Malate + succinate restore mitochondrial efficiency; bisglycinate + inositol support cognitive function under stress; start 1	Taurate GABA-A supports parasympathetic transition; B6 melatonin synthesis restores circadian amplitude	Salivary cortisol awakening response; RBC Mg^{2+} at 8–12 weeks; nocturnal HRV

		cap, adjust to 2 caps as needed		
Athletes (recreational and competitive)	Sweat losses proportional to intensity; Mg-ATP demand elevated; post-exercise recovery deficit	Malate + succinate support training energetics; 2-capsule dose recommended for active training phases; reduce to 1-cap during recovery periods	Lactate supports overnight glycogen resynthesis; bisglycinate supports muscle relaxation-contraction cycling	RBC Mg^{2+}; subjective recovery time; actigraphy sleep quality
Perimenopausal & postmenopausal women	TRPM6 downregulation with oestrogen decline; structural renal conservation deficit; sleep architecture disruption	Multi-pathway absorption compensates for TRPM6 deficit; vitamin C co-delivery supports collagen synthesis; 1- or 2-cap dose based on individual tolerance	Taurate sleep onset support; bisglycinate neuromuscular relaxation; B6 melatonin synthesis for circadian phase support	RBC Mg^{2+}; actigraphy sleep staging; self-reported sleep onset latency
Adults over 50	Age-related decline in intestinal absorption and renal conservation; progressive intracellular depletion despite normal serum values	Multiple transport pathways maximise absorption despite declining single-pathway efficiency; begin at 1 cap and adjust	Taurate + bisglycinate support sleep architecture that fragments with age; B6 supports age-related melatonin decline	RBC Mg^{2+} at baseline and 12 weeks; Pittsburgh Sleep Quality Index
Cognitive workers / sustained mental load	Neurological Mg^{2+} demand elevated by sustained cognitive activity; subclinical deficit associated with cognitive fatigue	Bisglycinate NMDA modulation; inositol serotonin receptor sensitisation; B6 dopamine/serotonin synthesis; 1- or 2-cap dose based on cognitive demand intensity	Taurate calms evening nervous system activation; B6 supports overnight neural repair via melatonin cycle	Validated attention battery; energy and focus diary; nocturnal HRV

12. Clinical Decision Framework: Formula Selection and Dosing

Table 6 provides a rational framework for formula selection and initial dose based on primary presenting concern. The one-capsule starting dose is recommended for all individuals initiating

the system, with adjustment to the two-capsule dose based on response, tolerance, and clinical context.

Table 6. Clinical decision framework: single formula versus combined system, and dosing guidance.

Primary concern	AM formula alone	PM formula alone	AM + PM combined	Starting dose
Daytime energy and fatigue	✓✓✓ RecommendedMalate + succinate address mitochondrial deficit	— Not primary	✓✓✓ OptimalAM activates; PM maintains overnight recovery	1 cap AM; adjust to 2 caps based on response
Brain fog and concentration	✓✓✓ RecommendedBisglycinate + inositol + B6	✓ PartialNMDA present but no morning neurotransmitter support	✓✓✓ OptimalFull cognitive support across both phases	1 cap AM; add 1 cap PM if sleep is also an issue
Sleep onset and quality	— Not primary	✓✓✓ RecommendedTaurate GABA-A + bisglycinate NMDA + B6 melatonin	✓✓✓ OptimalSleep architecture + morning circadian readiness	1 cap PM; adjust to 2 caps if insufficient response at 2 weeks
Muscle tension and recovery	✓ PartialSome NMDA support only	✓✓✓ RecommendedTaurate + bisglycinate + lactate	✓✓✓ OptimalAM performance + PM recovery	1 cap PM to start; add 1 cap AM for training phases
Cardiovascular / HRV support	— LimitedNo taurate in AM	✓✓✓ RecommendedTaurate cardiac ion channel modulation	✓✓✓ Optimal	1 cap PM; adjust based on HRV response
Comprehensive circadian optimisation	— Insufficient alone	— Insufficient alone	✓✓✓ The only optionPhase completeness requires both	1 cap AM + 1 cap PM; adjust to 2+2 based on response and regulatory context
Budget-limited starting point	✓✓ If primary complaint is daytime energy	✓✓ If primary complaint is sleep	✓✓✓ Recommended for full benefit	Begin at 1+1; the system is the mechanism at any dose

13. Preliminary Observational Support

Preliminary observational support for the biological plausibility of the AM/PM magnesium formulation comes from a recently submitted pilot study (Samarin 2026, under review) in which 20 participants using the complete EscapeMed 30D four-formula system for 30 days at the standard two-capsule dose reported improvement in energy levels in 80% of cases, sleep quality improvement in 75%, and overall wellbeing improvement in 90%. These outcomes are mechanistically consistent with the magnesium salt selection and circadian timing rationale described in this paper.

A notable informal observation was reported in approximately 50% of participants: increased dream vividness and transient afternoon fatigue during days 3–5, followed by improved sleep efficiency, reduced total sleep duration, stable daytime energy, and absence of morning grogginess. The PM formula is a primary mechanistic contributor: taurate GABA-A modulation deepens slow-wave sleep; bisglycinate NMDA modulation supports neuromuscular relaxation; evening B6 strengthens endogenous melatonin synthesis; and the intracellular magnesium oscillation restoration documented by Feeney et al. (2016) strengthens circadian amplitude. The AM formula contributes to the post-adaptation state through malate and succinate mitochondrial efficiency gains, inositol-mediated daytime serotonin stabilisation, and B6-supported morning neurotransmitter synthesis.

Expanded observational studies targeting perimenopausal women, recreational athletes, and cognitive workers are currently in progress, with planned outcome measures including red blood cell magnesium, salivary cortisol awakening response, heart rate variability, and actigraphy-based sleep staging. These studies will include participants using the one-capsule dose to document the biological response profile at the conservative dosing level.

14. The EscapeMed 30D System: Historical Context and Architectural Novelty

The Magnesium AM and Magnesium PM formulas are two of four products in the EscapeMed 30D system — a 30-ingredient, four-formula, five-biological-layer chronobiological supplement architecture designed and formulated by the author. To the authors' knowledge, EscapeMed 30D is the first dietary supplement system to: (1) explicitly separate the same mineral into two phase-specific formulas using different salt forms selected for circadian phase alignment; (2) coordinate four distinct timed formulas across the full 24-hour cycle; (3) structure 30 active ingredients across five defined biological layers with explicit formulation rationale for each; and (4) document this rationale in peer-reviewed literature. All four formulas are manufactured by a GMP-certified contract manufacturer in the European Union, in compliance with EU food supplement regulations, HACCP, and GMP quality standards.

The two additional formulas address biological functions that the magnesium formulas alone cannot cover. Skin Renewal Complex, administered in the late morning post-cortisol-decline window of peak fibroblast responsiveness (approximately 8–11 a.m.), delivers 14 active ingredients across the connective tissue synthesis and cellular protection layers. Super Sleep, administered approximately 30 minutes before sleep, delivers 8 active ingredients across the sleep architecture and circadian signalling layers, including melatonin at 0.1 mg per capsule — a physiological circadian signal below both EU authorized health claim thresholds of 0.5 mg for jet lag alleviation and 1 mg for sleep onset reduction. Super Sleep also contains magnesium bisglycinate, which contributes to the total system magnesium pool and is accounted for in the flexible dosing safety framework described in section 8.2.

CoQ10 and glutathione from Skin Renewal Complex improve mitochondrial recovery efficiency during sleep, augmenting sleep restoration quality. Glycine from Super Sleep extends the NMDA modulation initiated by PM bisglycinate. L-tryptophan in Super Sleep provides the serotonin precursor that evening B6 in Magnesium PM converts toward melatonin synthesis. The formulas are designed to be synergistic, not merely additive.

14.1. Why This System Cannot Be Replicated Through Individual Supplement Purchase

The practical replication of the AM/PM magnesium system through individual supplement purchase is not achievable with equivalent biological precision. The ten magnesium salt forms required are available as single-ingredient products, but each is sold at doses designed for standalone use. Achieving the specific elemental magnesium doses confirmed in the official product specification through individual products requires purchasing a minimum of eight to ten separate supplements. Several less common forms — magnesium ascorbate, magnesium succinate, magnesium gluconate, magnesium lactate — are not widely available in pharmacies or standard supplement retailers and must be sourced from specialist suppliers. The estimated monthly cost of these individual products at equivalent quality and appropriate elemental magnesium doses, sourced from reputable European suppliers, ranges from approximately €150 to €250 per month — substantially exceeding the cost of the integrated system.

Beyond cost, the DIY approach faces a more fundamental barrier: the formulation logic. The phase assignment of each salt — which forms belong in the morning, which in the evening, and which must be excluded from each phase and why — existed nowhere in the public scientific or consumer literature prior to this paper. A consumer assembling individual products without this documented rationale would have no basis for the phase separation that defines the system's

mechanism. The system is not difficult to replicate because of proprietary ingredients. It is difficult to replicate because the architecture — the combinatorial logic, the phase assignment, the dose rationale at both one and two capsule levels, the exclusion principles, and the counterion selection reasoning — existed only in the author's formulation decisions until the publication of this paper.

15. Future Research Directions

The primary testable hypothesis is that phase-separated multi-salt magnesium delivery produces superior tissue saturation and functional outcomes compared to single-salt, single-dose supplementation at equivalent elemental doses. The ideal study design is a three-arm randomised controlled trial: (1) EscapeMed 30D AM/PM system at two-capsule dose; (2) equivalent elemental magnesium as bisglycinate once daily; (3) placebo. A fourth arm at the one-capsule dose would allow direct comparison of conservative versus standard dosing within the phase-specific architecture. Primary outcomes: red blood cell magnesium at 8 and 12 weeks; sleep quality via actigraphy; cognitive performance via validated attention battery; energy levels via validated fatigue scale. Minimum study duration: 12 weeks. Recommended sample size: 60 participants per arm.

A secondary study of particular interest is the formal prospective characterisation of the early adaptation phase observed in approximately 50% of pilot participants taking the complete system at the two-capsule dose. A prospective study should determine whether this adaptation signature is present, attenuated, or absent at the one-capsule dose — providing direct evidence for the dose-response relationship within the phase-specific architecture.

Subgroup studies in perimenopausal women, recreational athletes, and cognitive workers are planned and in preparation, including one-capsule dosing arms to characterise the minimum effective dose for each population.

16. Conclusions

The EscapeMed 30D system — a four-formula, 30-ingredient, five-biological-layer chronobiological supplement architecture — represents, to our knowledge, the first integrated supplement system to coordinate phase-specific ingredient delivery across the full 24-hour biological cycle with documented scientific rationale for each component. The Magnesium AM and Magnesium PM formulas form one foundational layer of that system, and this paper represents the first peer-reviewed documentation of a dual-phase, multi-salt magnesium formulation designed according to circadian biology principles. The system is designed for flexible dosing between one and two capsules per formula per day, enabling use across a range of individual needs and regulatory contexts without reformulation.

The scientific case rests on three pillars. First, magnesium salt forms differ in absorption mechanism, tissue targeting, and the independent biological functions of their counterion molecules — making a multi-salt system functionally superior to any single-salt approach regardless of dose. Second, intracellular magnesium is a circadian-regulated resource — established by the landmark 2016 Nature publication of Feeney and colleagues — whose supplementation should be timed and formulated to align with phase-specific physiological demands. Third, the qualitative difference between morning activation demands and evening

restoration demands makes a single formula at any dose inherently incapable of serving both phases optimally.

The six tables provided operationalise these principles for clinical and individual use: the AM vs PM architectural comparison documents the science of phase assignment and exclusion; the biological layer coverage table shows what each formula provides alone and in combination; the symptom-to-mechanism table connects lived experience to biological targets; the single-salt comparison addresses the most common scientific objection to the multi-salt approach; the target population guide supports personalised application at either dose level; and the clinical decision framework supports rational formula and dose selection based on primary presenting concern.

This paper establishes the documented scientific foundation for a new category of circadian-informed magnesium supplementation. The formulation rationale is original, evidence-grounded, and publicly archived in peer-reviewed literature. It enters the permanent scientific record as the first description of its kind.

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Conflicts of Interest

The author is the founder and principal formulator of the EscapeMed supplement system investigated in this paper. The products are manufactured and distributed by EscapeMed d.o.o. This represents a potential conflict of interest, declared in full transparency in accordance with journal editorial policy. Escape Protocol Research is an independent research initiative. The

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