Biomimetic rhythm programming and intelligent delivery: The BRIGHT transdermal patch revolutionizes chronotherapy for growth hormone treatment

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Circadian rhythms play a pivotal role in regulating biological homeostasis, particularly in the temporal encoding mechanisms of hormone secretion.[1,2] For example, human growth hormone (hGH), a 191-amino-acid secretory protein, not only governs longitudinal bone growth but also demonstrates a tightly coordinated relationship between its nocturnal triphasic pulsatile secretion and the spatiotemporal specificity of growth and development.[3-5] Multiple studies have demonstrated that pulsatile drug delivery strategies that mimic natural secretion profiles significantly enhance growth-promoting efficacy compared to continuous administration – a phenomenon validated in both murine models and clinical observations in children aged seven and above.[6,7] However, the present clinical standard of daily subcutaneous injections faces dual challenges: It fails to replicate endogenous secretory rhythms, and its invasive nature exacerbates patient non-compliance, particularly among pediatric populations.[8] These limitations underscore the urgent need for novel chrono-adaptive drug delivery systems.

In a groundbreaking study recently published in *Nature Materials*, the Gu's group reported the BRIGHT transdermal patch as an innovative solution to the challenge of rhythmic growth hormone delivery.[9] By employing a biomimetic strategy to construct a coordinated delivery system comprising multiple modules, the study achieved, for the 1st time, triphasic drug release synchronized with physiological rhythms (**Figure 1A**). The core innovation lies in the synergistic optimization of the material system and structural design. Specifically, the burst-release module utilizes a copolymer of *N*-vinylpyrrolidone (NVP) and ethylene glycol dimethacrylate (EGDMA) as the microneedle (MN) matrix – NVP's high biocompatibility and hydrophilicity ensure efficient loading of recombinant hGH (rhGH), while the photo-crosslinking properties of EGDMA impart superior mechanical strength. In conjunction with a 3% effervescent agent that generates CO_2 foaming effects, this design creates transient microporous channels within the interstitial fluid, achieving an initial release efficiency of 53.6% within 0.5 h. The dual delayed-release modules are based on a core-shell structure, incorporating a hydroxypropyl methylcellulose (HPMC) core layer and an ethylcellulose (EC)/polyethylene glycol (PEG) composite outer shell. Here, the HPMC core exhibits a pronounced concentration-dependent swelling rate – by employing HPMC swelling at 10 mg/mL for module 2 and 1 mg/mL for module 3, the system drives a delayed rupture of the EC/PEG outer shell, precisely controlling the lagged release of rhGH at 4 and 6 h. Moreover, the EC/PEG (93.75: 6.25) outer shell achieves spatiotemporal matching of the rupture threshold and the core's expansion rate by balancing PEG's pore-forming effect with EC's hydrophobicity (**Figure 1B**). This modular design not only overcomes the technical barrier of achieving multiphasic pulsatile release within hours but also establishes a programmable "time-dose-space" triaxial controlled-release paradigm. Animal studies in large animal models demonstrate that the patch significantly outperforms conventional high-dose injections and long-acting formulations in promoting bone growth, while selectively modulating lipid metabolism without affecting muscle mass – a finding that suggests its metabolic reprogramming potential. Notably, therapeutic efficacy observed in GH-knockout models confirms the platform's validity for hormone replacement therapy under pathological conditions.

As an emerging delivery technology, MN patches inherently achieve precision-controlled release while maintaining high patient compliance[10-12]; other periodic controlled-release platforms such as implantable micropumps,[13] osmotic pumps,[14] layered polymeric microspheres and stimuli-responsive hydrogel arrays[15] offer on-demand

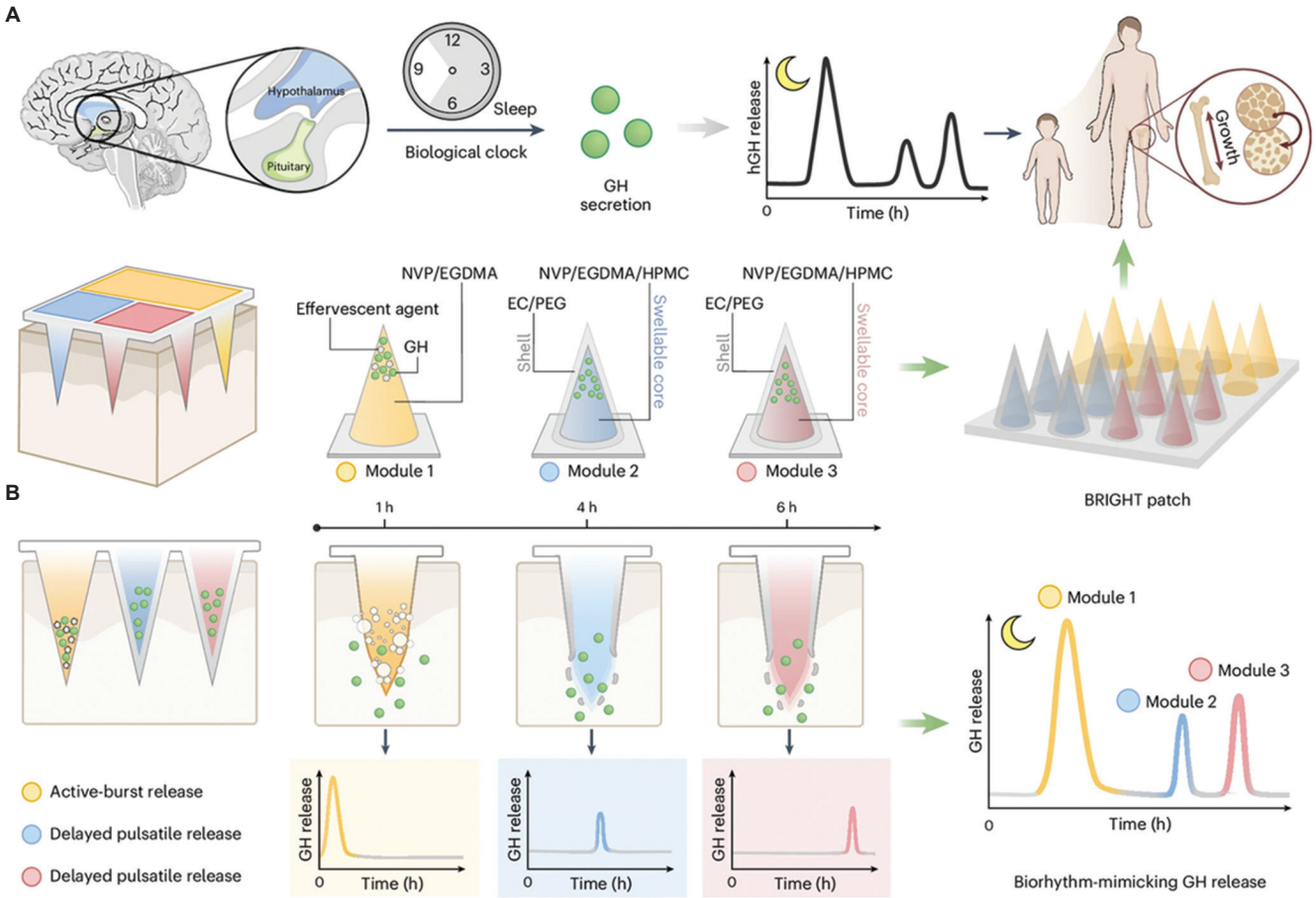

Figure 1. Bioinspired design and triphasic release mechanism of the BRIGHT microneedle patch. (A) The rhGH secretion is pulsatile, with three pulses at night. (B) The autonomous BRIGHT patch contains three modules, which are responsible for the three-stage pulsatile release pattern of GH *in vivo*. Due to the fast-disintegrating reactions of the effervescent agent in tissue fluid, rapid rhGH release is achieved (module 1). Modules 2 and 3 are core-shell MN structures. Through controlling the swelling rate of the MN core by adjusting the content of HPMC, delayed release of rhGH with pre-determined lag times is achieved due to the time-delayed rupturing of the MN shell. Reprinted by permission from Macmillan Publishers Ltd.: Han *et al.* (2025).[9]
Abbreviations: EGDMA: Ethylene glycol dimethacrylate; GH: Growth hormone; hGH: Human growth hormone; HPMC: Hydroxypropyl methylcellulose; MN: Microneedle; NVP: *N*-vinylpyrrolidone; PEG: Polyethylene glycol; rhGH: Recombinant human growth hormone.

or sequential release capabilities but suffer from drawbacks including the need for surgical implantation and external power sources, limited multistage control, manufacturing complexity and non-specific triggering under physiological conditions. The BRIGHT patch extends these advantages by integrating burst and delayed-release mechanisms, thereby transcending the temporal limitations of conventional systems and pioneering a chrono-bioinspired drug delivery paradigm. The research team established a comprehensive validation framework spanning multiple dimensions: biocompatibility with skin barriers and hepatorenal functions was confirmed through 2-month safety assessments; transcriptomic analyses revealed specific activation of ERK/MAPK and insulin-like growth factor 1 signaling axes; and cost-benefit evaluations demonstrated that raw material costs account for only 8.8% of those associated with long-acting formulations. Collectively, these findings construct an integrated evidence chain that bridges basic research and clinical translation. Moreover, the BRIGHT platform's modular chrono-adaptive design could be readily tailored to other circadian-dependent therapies. For corticosteroids – where morning dosing of prednisone aligns with the endogenous cortisol surge to maximize anti-inflammatory efficacy and minimize adrenal suppression – incorporating a burst-then-delayed release patch could deliver a high initial dose at dawn followed by tapering levels throughout the day to mimic physiological rhythms.[16] In insulin replacement, a MN array engineered to release basal insulin in synchrony with the dawn phenomenon and deliver prandial bursts could improve glycemic control by matching endogenous secretion profiles more closely than current pumps.[17] Beyond hormones, non-hormonal chronotherapeutics such as chronobiotic neuroprotectants (e.g., melatonin analogs administered at night to enhance sleep-dependent neurorecovery) or time-gated administration of anti-inflammatory agents in rheumatoid arthritis and cancer chemotherapy could leverage the same core-shell, effervescent and swellable modules to achieve precise multiphasic release aligned with disease-specific circadian vulnerabilities.[18]

Nevertheless, several limitations warrant attention. First, the secretion of GH is not only influenced by the circadian rhythm

but also closely associated with sleep-onset dynamics and sleep architecture. When an individual's sleep schedule is disrupted by external factors such as shift work or transmeridian travel, traditional secretion curves based on fixed circadian rhythms become inadequate to accurately reflect the true state of their physiological rhythm.[19,20] Consequently, there is a need to develop an intelligent feedback system with adjustable time parameters that can dynamically adapt to an individual's actual physiological state – such as alterations in sleep phases – to achieve personalized management. The development of an intelligent transdermal delivery system necessitates the integration of embedded biosensing mechanisms – such as flexible epidermal sensors for skin temperature/hydration monitoring, wearable actigraphy/electroencephalography for sleep-stage tracking, and on-patch biosensors for interstitial biomarker sampling – coupled with real-time control algorithms. Concurrently, this innovation must align with regulatory frameworks governing combination drug-device products, data privacy protocols, and clinical validation pathways. To address these translational challenges, strategic adoption of existing regulatory precedents is critical. The Food and Drug Administration's (FDA) 2017 Draft Guidance (Docket No. FDA-2017-D-4792) for MN devices clarifies classification criteria under the FD&C Act, while adaptive skin irritation grading scales – derived from the vaccine and transdermal patch guidelines – provide standardized local tolerability assessment protocols.[21] Furthermore, clinical paradigms validated in first-in-human trials of influenza vaccine microprojection arrays,[22] including pharmacokinetic frameworks for systemic exposure and localized tissue response monitoring, establish direct references for BRIGHT patch validation. Collectively, these elements construct a cohesive review roadmap spanning pre-clinical standards, quality system compliance, and adaptive clinical endpoint designs, thereby accelerating the translation of MN -based systems from bench to bedside.

Second, while exhibiting superior efficacy in rodent models, interspecies disparities in skin architecture (including stratum corneum thickness, lipid composition, and hydration level) and hormone metabolism between primates and humans demand validation in non-human primates such as cynomolgus macaques, as these variables can meaningfully alter MN penetration depth, interstitial fluid uptake, drug dissolution rates, and overall pharmacokinetics.[15] Furthermore, individual variability in skin properties – even within a single species – can significantly influence patch performance: thicker stratum corneum layers slow diffusion and require higher insertion forces, dry or poorly hydrated skin reduces microchannel formation and drug flux, and overly hydrated or lipid-rich skin may accelerate patch dissolution and lead to pre-mature release.[23,24] Accounting for these sources of variability will be critical for translating the BRIGHT platform into a universally effective therapy and may necessitate pre-application skin assessments (e.g., corneometry, Raman spectroscopy) along with adaptive patch designs featuring tunable MN lengths or hydration-modulating excipients.

Third, the study does not address the biodistribution and systemic pharmacokinetics of transdermally delivered growth hormone: as growth hormone exerts pleiotropic effects across multiple tissues and organs,[25] quantitative tracking of where – and how rapidly – the hormone diffuses after patch application is essential to predict both on-target efficacy and potential off-target exposure.[26] Future work should therefore incorporate *in vivo* pharmacokinetic profiling (e.g., serial blood sampling and pharmacokinetic modeling), imaging-based biodistribution studies (such as fluorescence or radiolabeling of rhGH) and microdialysis of peripheral tissues to map absorption kinetics, regional uptake and clearance pathways.[24,27] Fourth, laboratory-scale fabrication processes (≈5 patches/h) for core-shell MNs hinder industrial scalability. Overcoming technical bottlenecks in high-throughput manufacturing – while maintaining HPMC gradient concentrations and EC/PEG membrane homogeneity through microfluidics – remains critical for commercialization. Encouragingly, the researchers have outlined a roadmap for optimization: developing photo-responsive materials for external temporal control, establishing personalized chrono-databases for dosing guidance, and exploring 3D printing for MN array fabrication.

Having evolved over two decades from simple permeation enhancers to intelligent delivery platforms, MN technology has entered a new era of "chrono-adaptation" with the advent of the BRIGHT patch. Its innovation extends beyond merely addressing the temporal delivery challenges of growth hormone – it establishes a technological framework for decoding physiological temporal codes. This paradigm, which translates circadian biology into engineered solutions, offers methodological insights for fields that require precise temporal intervention. To guide future efforts, we propose five concrete directions: (i) systematic *in vivo* testing of chrono-adaptive patches in models, such as cancer chrono-immunotherapy and neurodegeneration, with longitudinal monitoring of circadian biomarkers and treatment outcomes; (ii) integration of flexible electronics and artificial intelligence-driven control algorithms to enable on-patch sensing of physiological signals (e.g., hormone levels, skin temperature, activity) and real-time adjustment of release profiles; (iii) development of novel stimuli-responsive matrices – such as photo- or ultrasound-activated polymers – to allow externally triggered, patient-specific dosing; (iv) optimization of high-throughput manufacturing through microfluidics or 3D printing that preserves precise gradient architectures at scale; and (v) creation of open-access chrono-databases linking individual circadian metrics to optimal dosing schedules across diverse therapeutic areas. By pursuing this roadmap, researchers can not only accelerate the clinical translation of BRIGHT-style systems but also catalyze the next generation of precision chronomedicine – delivering "the right dose, via the right method, at the right time."

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Conflicts of interest statement
The authors declare no conflicts of interest.

Author contributions

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Consent for publication

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