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Nanoparticles targeting the central circadian clock: Potential applications for neurological disorders☆

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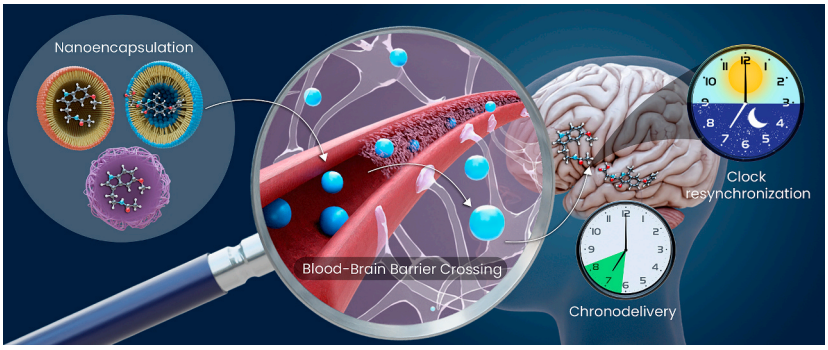
HIGHLIGHTS

- Circadian clock dysfunctions impact various diseases, including neurological ones.
- Circadian clock pharmacological resynchronization faces delivery challenges.
- Novel drug formulations are needed to improve targeting of the circadian clock.
- Nanoparticles could improve drug brain distribution and release profiles.
- Chronodelivery with nanoparticles could enable dose timing for optimal effects.

GRAPHICAL ABSTRACT



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ABSTRACT

Circadian rhythms and their involvement with various human diseases, including neurological disorders, have become an intense area of research for the development of new pharmacological treatments. The location of the circadian clock machinery in the central nervous system makes it challenging to reach molecular targets at therapeutic concentrations. In addition, a timely administration of the therapeutic agents is necessary to efficiently modulate the circadian clock. Thus, the use of nanoparticles in circadian clock dysfunctions may accelerate their clinical translation by addressing these two key challenges: enhancing brain penetration and/or enabling their formulation in chronodelivery systems. This review describes the implications of the circadian clock in neurological pathologies, reviews potential molecular targets and their modulators and suggests how the

Abbreviations: Aβ, amyloid beta; AD, Alzheimer's disease; BBB, blood–brain barrier; BD, bipolar disorder; CC, circadian clock; CNS, central nervous system; DDS, drug delivery system; GIT, gastrointestinal tract; MDD, major depressive disorder; NP, nanoparticle; PD, Parkinson's disease; PDDS, pulsatile drug delivery system; PK, pharmacokinetics; PNDDS, pulsatile nano-drug delivery system; SCN, suprachiasmatic nucleus.

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use of nanoparticle-based formulations could improve their clinical success. Finally, the potential integration of nanoparticles into chronopharmaceutical drug delivery systems will be described.

1. Introduction

In adaptation to the 24 h rhythm of days and nights, living organisms have evolved by developing circadian clocks (CCs) that control and regulate a wide range of biological processes in accordance to entrainment signals, the most dominant among them being light [1,2]. As a consequence, CCs offered evolutive advantages by modulating the behavior of individuals between day and night. In particular, circadian rhythmicity regulates systemic metabolic functions [3], such as temperature [4], blood pressure [5], hormone secretion [6,7] or glucose levels [8] (Fig. 1).

The identification of the first clock gene in 1984 revolutionized the understanding of mammalian CC [20]. Clock genes are expressed in nearly all cells and enable circadian oscillations that regulate physiological processes across major tissues and organs. These tissues host cell-autonomous peripheral clocks, where interconnected feedback loops drive signaling pathways (Fig. 2) [21]. In mammals, the central pacemaker of the CC, located in the supra-chiasmatic nucleus (SCN) of the anterior hypothalamus, synchronizes peripheral clocks, orchestrating systemic physiological rhythms (Fig. 1) [2]. It also governs the sleep-wake cycle through complex feedback loops involving proteins and neurotransmitters. Morning light activates signaling pathways that induce the circadian protein expression which together establish a 24-hour cycle. As night falls, melatonin levels rise to promote sleep, while with the onset of morning light melatonin levels decrease and orexin signalling stimulates wakefulness. The discovery of this intricate system that aligns physiological functions with the 24-hour day-night cycle earned Michael W. Young, Jeffrey C. Hall and Michael Rosbash the Nobel Prize in Physiology or Medicine in 2017 [22].

Morning light is detected by intrinsically photosensitive retinal ganglion cells, which send signals through the retino-hypothalamic tract to the SCN. This triggers the release of glutamate and pituitary adenylate

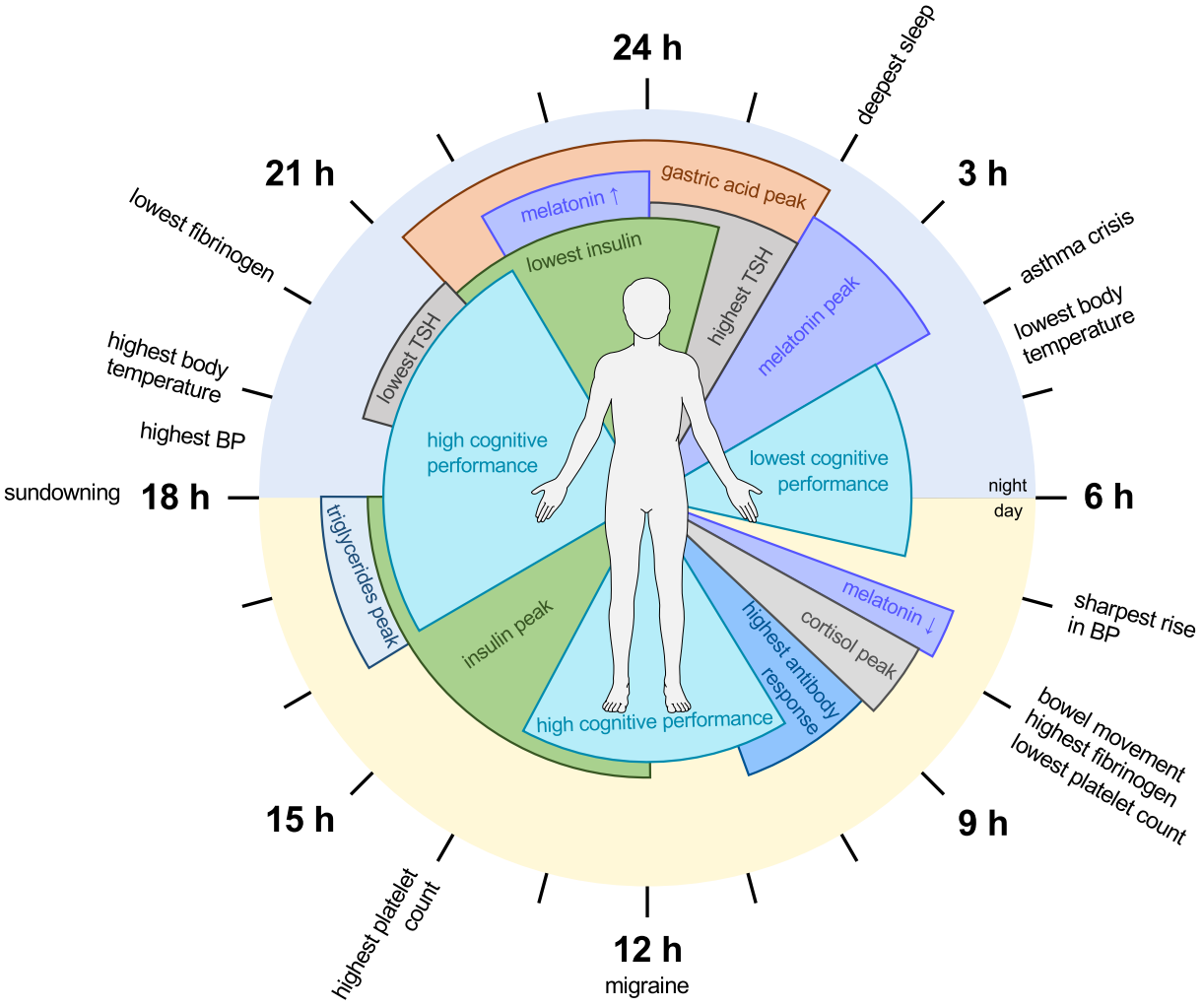

Fig. 1. Biological functions controlled by circadian rhythms. Variations of TSH levels promote patterns of rest and activity [9]. Peaks in levels of insulin and triglycerides follow feeding and fasting schedules [10,11]. Melatonin secretion begins during the evening to promote sleep onset and ceases with daylight. High melatonin levels at night exacerbate asthma and inflammation, and low levels trigger sundowning in dementia [2]. Inflammation markers are therefore more concentrated in the morning, exacerbating pain caused by chronic inflammation such as arthritis [12]. Antibody response is also the highest in the morning, making it the preferred moment for vaccination [13]. The sharp increase of blood pressure in the morning associated with high fibrinogen concentration is related to the high incidence of strokes and myocardial infarctions in early morning [14–16]. Gastric acidity peaks at night, provoking heartburn [17]. Cognitive performance is the highest between 10 am and 2 pm, and 4 pm and 10 pm [18,19].

cyclase-activating polypeptide (PACAP), leading to the activation of the cAMP response element-binding protein (CREB). These factors modulate the circadian rhythm through gene expression, together with a complex that binds to the E-box element. This complex is composed of circadian locomotor output cycles kaput (CLOCK) and aryl hydrocarbon receptor nuclear translocator-like protein 1 (BMAL1). Period circadian protein (PER) and cryptochrome (CRY) accumulate throughout the day and their complex formed with casein kinase 1 (CK1) eventually inhibits CLOCK/BMAL1, creating a negative feedback loop. The complex is eventually degraded, completing a 24-hour cycle, the core loop of the CC [2].

In a secondary loop, RAR-related orphan receptor (ROR) promotes BMAL1 expression, while REV-ERB inhibits it [23]. In addition, the REV-ERB and PER complex increases γ-aminobutyric acid (GABA) and vasoactive intestinal peptide (VIP), which inhibit the paraventricular nucleus (PVN), and in so doing control melatonin production in the pineal gland [24]. As GABA and VIP levels decrease, melatonin levels rise, peaking in the middle of the night, promoting sleep by inhibiting SCN neurons; as the morning light reactivates GABA and VIP levels, melatonin levels decrease [21]. In the early morning, SCN activity stimulates orexin neurons in the lateral hypothalamus (LH), helping maintain wakefulness and regulate sleep and feeding behaviors [2,25].

Growing evidence from the past decades has shown that dysfunction in the central CC pacemaker is a risk factor for a wide range of diseases and accelerate their progression, making the CC machinery a new promising therapeutic target [2]. While encouraging advances have been made in developing small molecules to treat CC dysfunction (melatonin receptor agonists, CK1 inhibitors, REV-ERB and ROR modulators), very few of them have shown effectiveness in clinical trials. The limited clinical translations could be attributed to lack of target specificity, poor brain penetration across the blood–brain barrier (BBB), and failure to address issues of dosing time.

Chronodelivery, the administration of treatments synchronized to a patient's biological rhythms, offers a promising approach for enhancing therapeutic outcomes. By aligning drug delivery with circadian phases, chronodelivery has demonstrated improved efficacy and safety in treating circadian-related disorders, such as asthma, myocardial infarction, hypertension, cancer, and others, as highlighted in various reviews [26,27]. This approach is particularly relevant for disorders where CC dysfunction intensifies disease severity [2]. Recent advances in nanotechnology, including nanoparticle (NP)-based drug delivery systems (DDSs), have further expanded the potential of chronodelivery. NPs can improve drug targeting, enhance BBB penetration, and optimize dosing schedules, offering a synergistic approach for treating circadian-related disorders more effectively. Despite these developments, chronodelivery of NP-based formulations remains underexplored but holds significant promise for future therapeutic innovation.

This review highlights how NP-based formulations could be used to enhance the brain distribution and SCN targeting of circadian resynchronizing molecules, and explores the potential of their combination in chrono-tailored DDSs to increase their clinical translation.

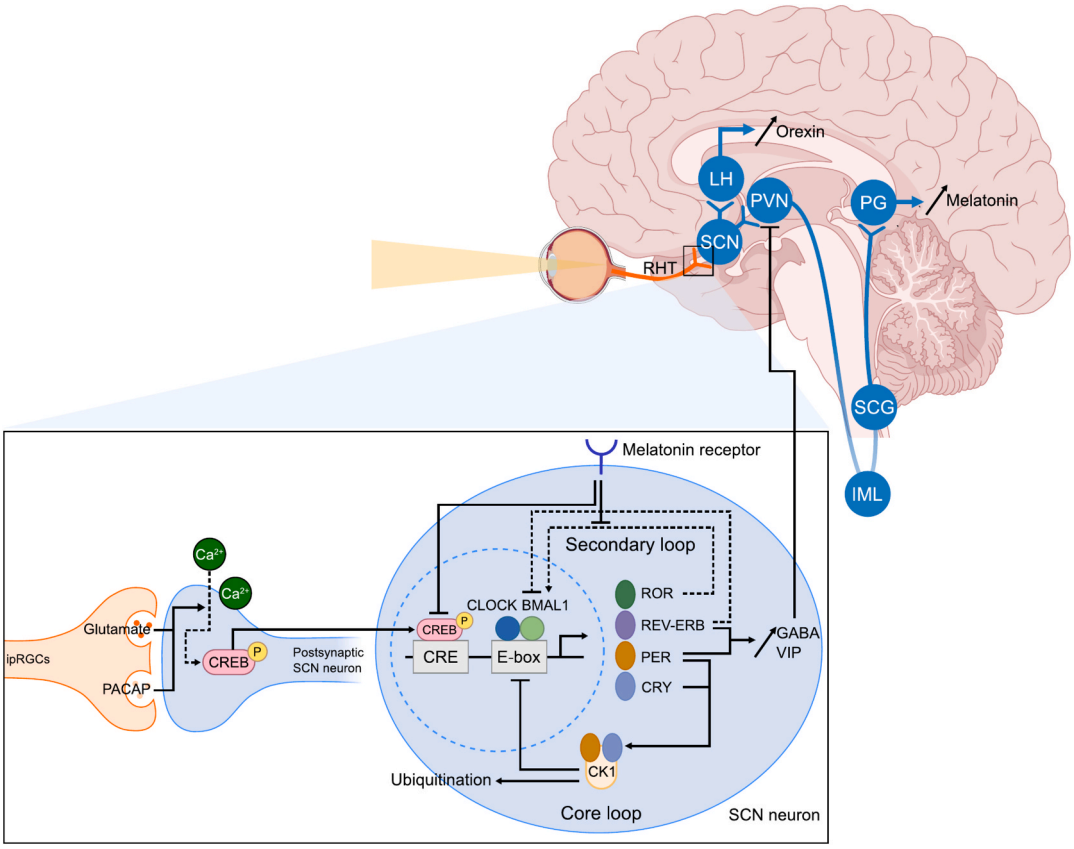

Fig. 2. Molecular signaling pathways governing the 24-hour cycle of the central circadian clock. CC regulation is initiated by morning light detection in which intrinsically photosensitive retinal ganglion cells (ipRGCs) transmit signals to the SCN through the retino-hypothalamic tract (RHT), releasing glutamate and PACAP, depolarizing SCN neurons. CREB is consequently phosphorylated and triggers clock gene expression of PER. The core loop consists of PER and CRY complexation with CK1, repressing CLOCK/BMAL1 activity. The complex is eliminated by ubiquitination [2]. The secondary feedback loop is composed of ROR, which increases BMAL1 expression while REV-ERB decreases it [23]. REV-ERB and PER increase GABA and VIP production, inhibiting Paraventricular Nucleus (PVN) activation by the SCN, and decreasing melatonin release. Melatonin secretion starts when daylight levels decrease, binding to melatonin receptors (MT) to inhibit SCN firing for sleep onset [21,24]. When daylight levels increase and melatonin levels decrease, SCN firing activates orexin neurons in the Lateral Hypothalamus (LH) promoting wakefulness [25].

2. Central circadian clock dysfunctions

Circadian rhythm is characterized by a phase, an amplitude and a period. Patient rhythmicity is determined by monitoring activity and resting periods with a wrist-worn accelerometer and plotting the actogram (Fig. 3) [28,29].

Actograms reveal CC dysfunctions characterized by various perturbations [30]:

(i) *Circadian misalignment* occurs when an external cue (e.g., light/dark cycle) is misaligned with the SCN phase, or when the SCN phase itself is misaligned with a peripheral rhythm (e.g., glucose levels). This misalignment is identified by an abnormal phase angle between two biological phases.
(ii) *Circadian desynchrony* is marked by mismatched periods and abnormal phase angle between rhythms.
(iii) *Social jetlag* arises from differences in sleep patterns between workdays and free days, causing misalignment between social and biological time.
(iv) *Chronodisruption* occurs when biological nights overlap with working hours, resulting in misalignment between circadian rhythms and daily schedule.

Peripheral clocks can face similar disruptions, but since the SCN entrains and synchronizes them, it is a potential key target for treating circadian-related disorders systemically. The following section 2.1 explores the most important aspects of SCN dysfunctions in neurological disorders and the available treatments.

2.1. Central circadian clock dysfunctions in neurological disorders

Night work, jet lag and exposure to artificial light are extensively present in our modern lifestyles, and they increase the prevalence of chronodisruption, insomnia and circadian misalignment [31]. Recent evidence has shown that CC dysfunctions are encountered in several diseases, including neurological disorders such as mental disorders and neurodegenerative diseases (NDs).

2.1.1. Mental disorders

Circadian dysfunction plays a critical role in mental disorders such as major depressive disorders (MDDs), anxiety disorders and bipolar disorders (BDs) [32]. In MDD, 90% of patients experience sleep disturbances, often accompanied by diurnal variations in depressive symptoms, with severe cases showing a morning worsening of the symptoms [33,34]. This CC dysregulation observed in MDD includes abnormal gene expression and disrupted gene relationships, and contributes to recurrent episodes and treatment relapses. This dysfunction may explain the higher prevalence of anxiety and depression among night shift workers and jet lagged travelers [32]. Similarly, circadian dysfunction is observed in BDs, where a phase advancement is more likely to induce maniac episodes, and a phase delay tends to induce depressive episodes [35,36].

CC resynchronization has shown efficacy in managing these disorders. Non-pharmacological approaches, such as bright light therapy, social rhythm therapy, and physical exercise, as well as pharmacological treatments that bring about a phase advancement (including selective serotonin reuptake inhibitors, serotonin and norepinephrine reuptake inhibitors, and agomelatine), have been associated with amelioration of depressive symptoms in MDD and BD [34,37–41]. Lithium, the main mood stabilizer used in BD, is believed to stabilize circadian rhythmicity, which may explain its positive effects. However, additional evidence is required to confirm this hypothesis [42–45].

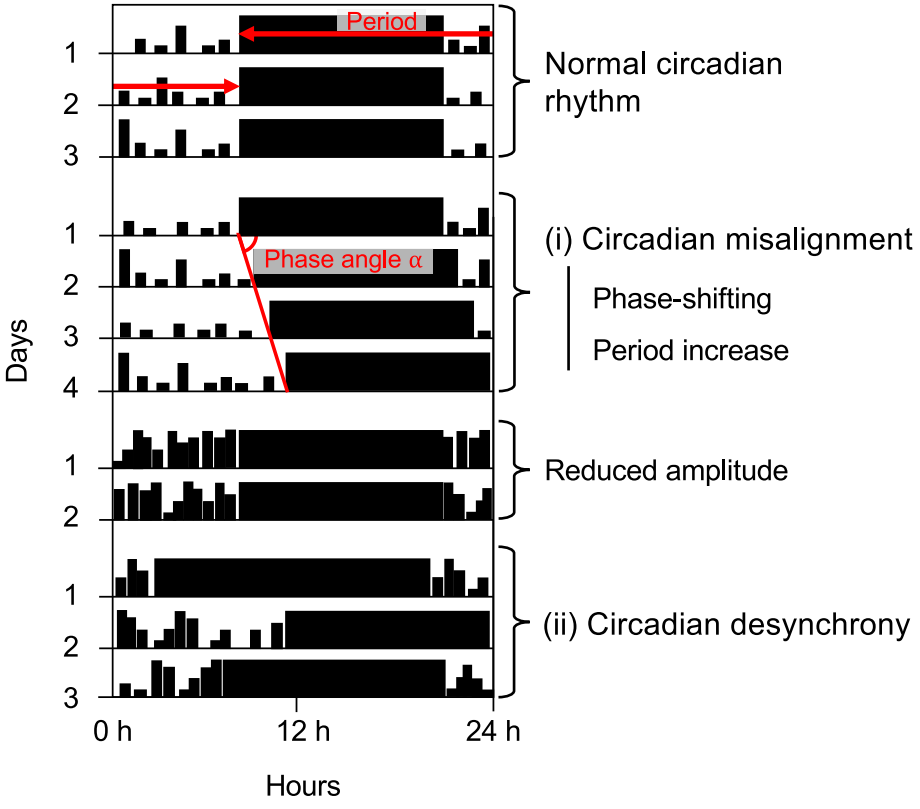

Fig. 3. Actogram displaying different types of circadian dysfunctions. Activity and resting periods are reported by dark and light phases respectively. Activity periods should onset at the same hour in a healthy circadian rhythm. Circadian misalignment is defined by a period alteration resulting in a phase-shifting characterized by an angle α. Circadian desynchrony consists of a loss of pattern in terms of period and phase angle.

2.1.2. Neurodegenerative diseases

NDs involve progressive loss of neuronal structure and function in the brain or peripheral nervous system, driven by multiple genetic and environmental factors. Aging is the primary risk factor for the development of NDs and is associated with circadian rhythm disruption. The elderly experience reduced sleep duration and efficiency, increased nighttime awakenings and sleep latency, and higher daytime sleepiness. These disruptions are attributed to decreased melatonin production, a loss of vasopressin-expressing cells in the SCN, and the age-related loss of phase coherence of the SCN; these three factors ultimately result in desynchronization and a reduced amplitude in biological rhythms, such as body temperature [46].

Sundowning, characterized by increased agitation and behavioral disturbances in late afternoon and evening in Alzheimer's (AD) or Parkinson's disease (PD), is worsened by CC phase delays and reduced amplitude [46,47]. Contributing factors are reduced exposition to light–dark entrainment signals, loss in rapid-eye-movement (REM) sleep and deterioration of SCN [46]. Therefore, a bidirectional relationship exists between the CC and NDs since CC dysfunction exacerbates ND symptoms and neurodegenerative processes disrupt circadian homeostasis [48,49].

Melatonin plays an important role in the physiopathology of NDs, not only through regulation of circadian rhythm, but also through its anti-inflammatory, cytoprotective and anti-oxidant properties [50]. Sleep disruption and insomnia, also marked by a decrease of melatonin secretion, are now believed to be risk factors for developing NDs [51]. Notably, the amplitude of melatonin rhythm is considerably reduced in individuals suffering from AD or PD compared to healthy aged population [46,52].

2.1.2.1. Alzheimer's disease. AD is the most common ND and is characterized by an accumulation of amyloid beta (Aß) plaques and hyperphosphorylated tau protein in the brain, leading to hippocampal, frontotemporal and cortical atrophy as well as ventricular enlargement. Age constitutes a direct risk factor of dementia; other risk factors for the development of dementia are CC dysfunction and fragmented circadian rhythms [46,50]. AD brains show a loss of neurons in the SCN correlating with a loss of motor activity amplitude. CC dysfunctions are quite common in AD patients, as up to 66% of them show sleep disruption, even before clinical diagnosis [50]. AD patients most commonly show a phase delay which is also a predictor of sundown syndrome, presented by 20 to 25% of them [53]. In a recent review article Ta-Wei Guu et al. highlighted that insufficient natural light exposure is associated with worsening sundown syndrome [47]. Finally, genetic variations in the clock genes such as *CLOCK* and *BMAL1* have been associated with an increased risk of AD [46,54,55].

In addition, several studies show that sleep apnea and insufficient sleep increase the risk of cognitive impairment. In fact, it has been shown that circadian rhythmicity controls the glymphatic system, the lymphatic system responsible for the clearance of metabolic waste from the brain. Impairment of the CC reduces the elimination of the protein Aß during the night [56]. Moreover, CC has been demonstrated to regulate Aß production through the *PSEN2* gene controlled by CLOCK/BMAL1. Aß accumulation is also responsible for the degradation of BMAL1, which ultimately leads to Aß plaque formation [57].

Current non-pharmacological interventions in AD, including natural light exposure, regular bed/wake times, physical exercise and limited caffeine and alcohol intake, are beneficial in restoring and maintaining a healthy circadian rhythm and reducing the severity of sundown syndrome [50]. Time-restricted feeding has been shown to increase Aß clearance, decrease amyloid deposition, improve sleep and memory, and reduce neuroinflammation and sundowning in an AD mouse model [58]. Unfortunately, drugs indicated for insomnia, such as melatonin receptor agonists and orexin receptor antagonists, have not shown significant effects in clinical trials for the treatment of CC dysfunctions in AD, nor any effect on AD endpoints, results that may be due to the complexity of the signaling pathways and the difficulty of conducting clinical trials in patients suffering from dementia [59].

2.1.2.2. Parkinson's disease. PD results from the degeneration of the dopaminergic neurons located in the substantia nigra, and is characterized by tremor, bradykinesia and muscle rigidity. Around 80% of PD patients display sleep-wake disturbances with changes in sleep timing, excessive daytime sleepiness, insomnia and restless legs syndrome, all of which contribute to a reduction of the amplitude [52,60]. PD is strongly associated with REM sleep behavior disorder and could even be used as diagnostic biomarker as 80% of people suffering from this disorder later develop PD or dementia [46].

Observation of the circadian rhythm in PD often highlights a reversed rhythm of blood pressure with high nocturnal blood pressure, no daytime variations of melatonin levels, reduced cortisol levels, reduced nocturnal BMAL1 levels and increased morning PER and REV-ERB levels [60]. Genetic variations in the gene clocks (e.g., *CLOCK*, *PER1* and *PER2)* are also significantly associated with PD [61].

Finally, both non-pharmacological treatments such as bright light therapy and pharmacological ones, such as melatonin receptor agonists, have been proven to improve sleep quality and motor PD symptoms in patients [62,63].

2.2. Targets and treatments of circadian clock dysfunctions

Several reviews have explored the impact of CC dysfunctions in specific systemic areas demonstrating that circadian rhythm monitors body function at several levels. In a 2018 review, Sulli et al. described 3 categories of CC dysfunction treatments [64]:

(i) training the clock by behavioral changes to restore a proper feeding/fasting or sleep/wake rhythm;
(ii) drugging the clock by targeting directly a CC component;
(iii) timing the drug administration by selecting a time for drug delivery to enhance the efficiency.

Even if training the clock has been proven to have a positive impact on the systemic level, this impact is limited in more severe and chronic pathologies (e.g., NDs) which explain the interest and necessity to develop agents to pharmacologically modulate the clock. However, despite the development of different pharmacological classes showing effects in preclinical studies, their clinical translation is limited (Table 1). This inconsistency can be explained by three main aspects.

First of all, the complexity of the CC signaling pathways makes the identification of optimal targets particularly challenging. While some developed compounds are available for CC dysfunction treatment, they can show a lack of specificity to target regulators of the SCN, compromising the therapeutic outcome in the treatment of CC-related NDs. In the case of REV-ERB agonists, GSK4112, SR9009 and SR9001 have shown limited efficacy in treating central CC dysfunctions in vivo, due to their lack of specificity and unintended binding to liver X receptor alpha [80]. Likewise, developed ROR modulators bind preferentially and/or selectively to RORα and/or γ, while RORβ is the subtype mainly expressed in the brain [2,80]. Due to this lack of specificity, certain drugs, such as antidepressants, cannot be used in the generic prevention and treatment of CC dysfunctions as they would generate too many side effects.

Another example of this lack of specificity is seen with vasoactive intestinal peptide receptor 2 (VPAC2) agonists and prolyl hydroxylase domain protein 2 (PDH2) inhibitors. VIP, produced by the SCN neurons, plays an important role in maintaining the synchronized circadian oscillations in the absence of an entraining cycle by inducing the expression of PER1 and PER2 through CREB phosphorylation [88,89]. PDH2 inhibitors reduce the degradation of the hypoxia-inducible factor-1α

Table 1
Examples of active pharmaceutical ingredients under study for the treatment of central circadian clock dysfunctions.

Molecular target	Mechanism of action	Commercially available drugs	Compounds in preclinical and clinical studies	Effects on pathologies related to SCN CC dysfunction	PK and delivery characteristics
Melatonin receptor	Agonists bind to melatonin receptors and phase-shift the circadian rhythm	Melatonin; tasimelteon, ramelteon; agomelatine; TIK-301	Piromelatine; GW117	Minimization of weight gain and dyslipidemia in rats models [65] GW117 and piromelatine show antidepressant and anxiolytic effects in rodents [66] Melatonin, agomelatine, ramelteon and tasimelteon show antidepressant and anxiolytic effects in depressive disorders [66] Melatonin shows antioxidant, antidepressant and neuroprotective effects, improves motor symptoms, cognition and sleep quality, decreases disease progression in NDs (e.g., ALS, AD, PD) in clinical trials [67,68] Melatonin is recommended for the treatment of primary headache disorders, effective in clinical trials compared to placebo [69] Melatonin receptor agonists are promising adjunctive treatment of bipolar mania [70]	Low oral bioavailability, high brain penetration [71] Phase-advancement when administered in late afternoon. Phase-delay when administered in early morning [2,72] Immediate release more effective than sustained release in some indications [69]
Orexin receptor	Antagonists block endogenous orexin binding and its effect on wakefulness and activity promotion	Suvorexant, lemborexant, daridorexant	Almorexant, filorexant; JNJ-48816274; SB-334867	Almorexant reduces Aβ plaques in mice [73] SB-334867 increases seizure threshold in mice [73] Precursor of suvorexant suppresses nocifensive response in the trigeminal ganglion in rats [73] Suvorexant reduces Aβ plaques and phosphorylated tau in healthy patients in clinical trials [73] Suvorexant and lemborexant increase sleep time in AD patients [73] Suvorexant improves sleep quality and shows antidepressant and anxiolytic effects in post-traumatic stress, MDDs and BDs [73] Suvorexant improves insomnia in schizophrenia [73]	Fast absorption and elimination Administration in late afternoon for sleep promotion [74]
CK1	Inhibitors lengthen the clock period by retention of PER2		PF-670462, PF-4800567, PF-05251749 [75]; LH846 [75]; NCC007, longdaysin [75]	PF-670462 entrains disrupted CC in mice [76] PF-670462 restores working memory, cognition and circadian rhythm and decreases the size of Aß plaques in AD mouse model [77,78]	Formulation of PF-670462 and PF-4800567 with cyclodextrins and/or cremophor needed to obtain brain-to-plasma ratio superior to 1 [79]
REV-ERB	Agonists bind to RORE motifs and repress BMAL1 transcription		GSK4112; SR9009, SR9011 [80]	SR9009 shows anxiolytic effect in rats [81] SR9009 induces wakefulness in mice [82] SR9009 and SR9011 regulate lipid and glucose metabolism homeostasis in obese mice [83] REV-ERB agonists may be used in the treatment of sleep disorders and jet lag [84]	High doses required in vivo due to high clearance [83] GSK4112, SR9009 and SR9011 lack selectivity due to liver receptor binding. However, selectivity improvement was achieved through modification of the chemical structure [85]
	Antagonists increase BMAL1 transcription		SR8278 [80]	SR8278 shows antidepressant and anxiolytic in PD mouse model [86] SR8278 decreases Aß plaques and neuroinflammation in AD mouse model [87]	Specific and optimal time of administration is needed to promote a response [82]

(*continued on next page*)

Table 1 (*continued*)

Molecular target	Mechanism of action	Commercially available drugs	Compounds in preclinical and clinical studies	Effects on pathologies related to SCN CC dysfunction	PK and delivery characteristics
				REV-ERB antagonists may be used in the treatment of sleep disorders and jet lag [84]	
ROR	Agonists bind to RORE motifs and promote BMAL1 transcription Increase amplitude and lengthen clock period		Nobiletin; neoruscogenin; SR1078	SR1078 regulates lipid and glucose metabolism homeostasis in obese and diabetic mice [83]	These compounds target preferentially or selectively RORα and/or RORγ while RORß is mainly found in the central nervous system, and reduce their activity towards the SCN [2,80]
	Inverse agonists repress BMAL1 transcription	Digoxin	SR1001 SR2211, SR1555, ursolic acid, ML209; SR3335	Lipid and glucose metabolism homeostasis in obese mice [83]	
VPAC2 receptor	Agonists activate CRE resulting in phase-delay and reduced amplitude [88,89]		VIP, PACAP; pemziviptadil; LBT-3627; BAY55-9837, DBAYL	Active VIP fragment enhances cognitive functions in AD in male Wistar rats [90]	Short half-life of VIP, PACAP and BAY55-9837 requiring continuous infusion [91]
					High peripheral effects due to multiple peripheral molecular targets [91]
PHD2	Inhibitors reduce the degradation of HIF-1α which increases the CC amplitude through expression of PER2 and CRY1 [92]	Roxadustat, daprodustat, enarodustat, desidustat, modulistat	IOX2, IOX3, IOX4	No studies of the effect on central CC [92]	High peripheral effects on cardiac, renal, endothelial tissues [94]
				Dimethyloxalylglycine, an HIF-hydroxylase inhibitor, resets peripheral clocks in chondrocytes, increasing the production of ECM [93]	Brain penetration needs to be improved [95]

(HIF-1α) by PDH2. HIF-1α form a complex with HIF-1β and translocate to the nucleus to express PER2 and CRY1, modulating the CC [92]. Used mostly as potential drugs for type 2 diabetes and commercialized for the treatment of anemia, respectively, both classes hold promising potential as repurposed modulators of the CC; unfortunately, they preferentially target peripheral tissues (e.g., liver, cardiac, renal tissue) and induce potentially serious side effects [91,94]. Reformulation into nanoparticles would help to target the CC and reduce off-site effects [96].

In addition, some of the compounds studied to treat CC dysfunctions show a poor pharmacokinetic (PK) profile with a short half-life and/or a poor brain penetration. Melatonin receptor agonists, for instance, suffer from a low oral bioavailability and require high dosage to achieve sufficient plasma exposure. Orexin receptors antagonists and REV-ERB and VPAC2 modulators show a fast elimination rate which require high doses and/or continuous infusion, limiting their clinical application and increasing their toxicity [74,83,91].

Finally, formulation of those compounds may face difficulties due to their physicochemical properties and/or time-dependent effect. For example, orexin receptors and REV-ERB modulators require specific time-of-day administrations to exercise their effect, and melatonin receptor modulators show opposite effects depending whether they are administered in early morning or late afternoon [2,72,74,82]. Thus, the need to address the time-dependent effect is an added challenge in designing experiments and defining dose regimens. For commercially available drugs, very limited data are available concerning the optimal time dependent effects. Further clinical data on dosing time-oriented administration are needed for each therapeutic class. Multiple dosing times reduce patient compliance, especially in polymedicated patients [97]. All these aspects could be improved by a tailored formulation of these compounds in chronopharmaceutical DDSs, eliminating the barriers to their clinical translation and increasing their clinical efficacy [98]. Table 1 reports a non-exhaustive list of the PK and delivery issues encountered for the compounds under study for CC dysfunction treatment.

3. Nanoparticles for enhanced brain delivery

Targeting the central CC is challenging due to its localization inside the brain, protected from the blood components by the BBB that plays a major role in hindering brain distribution of drugs. The BBB maintains brain homeostasis, controls the passage of nutrients, and prevents entry of pathogens and xenobiotics [99]. Most small molecules are effectively excluded from the brain parenchyma by the BBB or expelled by the active efflux [100].

Several reviews describe the role and functions of the BBB and drug delivery strategies to overcome it [99,101–104]. The following section 3.1 summarizes key BBB features relevant for brain drug delivery and NP-based approaches to enhance brain penetration.

3.1. Physiology of the blood–brain barrier

3.1.1. Brain translocation mechanisms

The BBB consists of endothelial cells forming a tight, continuous and non-fenestrated barrier restricting the free diffusion of molecules [104–107]; pericytes, regulating endothelial tight junction expression and the cerebral blood flow; and astrocyte endfeet, controlling waste clearance, brain blood flow and vascular function [104] (Fig. 4). There is a bidirectional communication between these components and the neurons and glia cells surrounding them, forming the neurovascular unit to adjust local brain circulation to meet energy demands [108,109].

Nutrients, endogenous molecules and xenobiotics can cross the BBB via 3 primary mechanisms (Fig. 4) [104]:

- Passive diffusion: small lipid-soluble compounds, ions, water and gases diffuse through (i) passive transcytosis, (ii) transcellular or (iii) paracellular diffusion [107].
- Active transport: large hydrophilic molecules use (iv) receptor and/or carrier mediated transcytosis [107].
- Efflux transporters (v): ATP-binding cassettes (ABC) transporters pump xenobiotics, ions, endogenous metabolites and nucleosides back into the blood circulation. Permeability-glycoprotein (P-gp), a

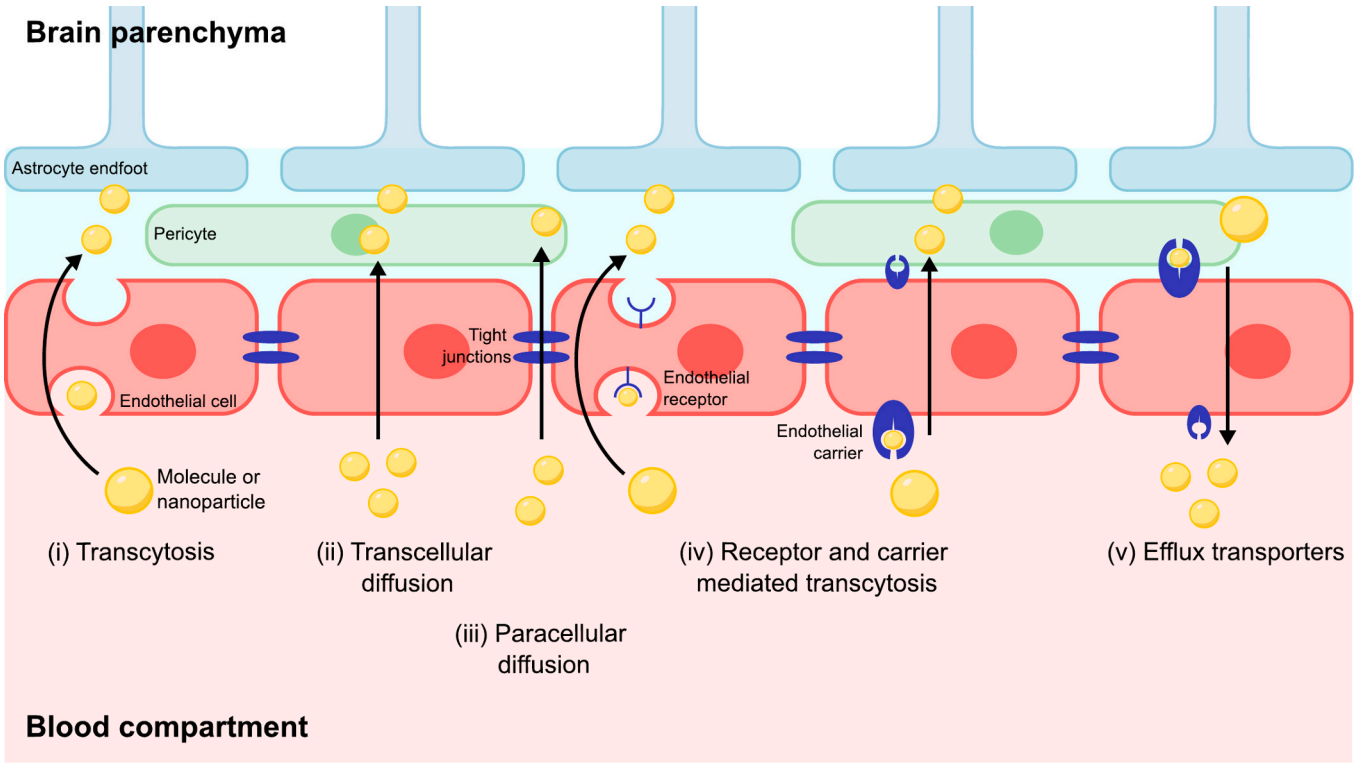

Fig. 4. Representation of the blood–brain barrier structure and exploitable translocation mechanisms. Passive diffusion of molecules or NPs occurs through (i) transcytosis, (ii) transcellular diffusion and (iii) paracellular diffusion, allowing the passage of water, ions, gases and lipid soluble compounds. Active transport of molecules or NPs is facilitated by (iv) receptor and carrier mediated transcytosis, which handles large molecules with high electrical charge, polarity and hydrophilicity. (v) Efflux transporters, such as ABC transporters, pump xenobiotics, ions, endogenous metabolites and nucleosides back into the bloodstream.

key ABC transporter, shows broad substrate specificity and is the main source of xenobiotic efflux [103].

3.1.2. *Blood-brain barrier circadian clock*

The BBB functions as a dynamic barrier that closely interacts with the CC, resulting in daily opening and closing patterns that are crucial for maintaining brain integrity and homeostasis [57,110]. These circadian influences are seen in the surface expression oscillations of tight junction proteins during the day in various epithelial tissues, including the BBB. Such oscillations impact tissue permeability based on the time of the day, with higher permeability during certain phases [111–113].

In addition, the expression of ABC transporters, key in maintaining neurochemical balance, generally decreases during the active phase, enabling efficient waste clearance during rest phases [57,110,114]. On the contrary, the expression of P-gp is reduced during resting phases, which allows for greater accumulation of P-gp substrates in the brain at these times [110]. This circadian-driven variation in BBB permeability opens opportunities to enhance drug delivery across the BBB. For example, in a mouse model of brain metastases of breast cancer, administration of paclitaxel in the middle of the dark phase resulted in an increase of paclitaxel concentrations by up to 47% compared to the beginning of the light phase [115]. Other endogenous and exogenous molecules, such as norepinephrine, leptin and daunorubicin, also exhibit time-dependent oscillations in their central nervous system (CNS) peak concentrations, a strong indicator that circadian timing influences neurochemical balance [110].

CC also regulates pericyte coverage of endothelial cells in the BBB. Nakazato et al. observed, in BMAL1-deficient mice, an age-dependent loss of pericytes leading to BBB hyperpermeability [116]. Disruptions in the CC therefore compromise BBB integrity, allowing more neurotoxic compounds to enter the brain and reducing the clearance of waste products, aggregates and plaques as observed in NDs [117]. Supporting this hypothesis, Kress et al. found that BMAL1-deficient mice experienced accelerated accumulation of Aß plaques [118]. Furthermore, sleep loss has also been associated with increased BBB permeability, underscoring the critical role of the CC in brain health [110]. These CC-related oscillations in BBB opening have often been overlooked when designing BBB penetrating drugs or delivery systems and could constitute a new axis of research in brain drug delivery.

3.2. *Overcoming the barrier*

The structure of the BBB restricts most drugs from penetrating the brain effectively. To address this, medicinal chemists modify drug structures to enhance diffusion, reduce efflux, and exploit carrier transporters [100]. For example, structural optimization of the PDH2 inhibitor IOX4 improved brain penetration and potency against HIFα in mice compared to IOX2 [95,119]. However, chemical modifications to enhance BBB permeability can compromise specificity, potency or elimination rate. Ideally, DDSs could enable the delivery of highly potent and specific drugs without requiring structural changes. Brain drug delivery strategies, reviewed in several articles [99,101,103,104,120], can be categorized as invasive or non-invasive:

(i) Invasive central brain drug delivery:
- Local drug delivery: includes intrathecal administration or intracranial implants, commonly used in life-threatening conditions (e.g., infections, cancer). This route of administration is painful, requires access to healthcare facilities, and carries risks such as cerebrospinal fluid leakage, infections, and bleeding, making it unsuitable for routine neurological treatments related to CC dysfunctions [121,122].
- BBB opening techniques: methods such as intra-arterial injection of a hypertonic solution [123], focused ultrasounds in combination with microbubbles [124], or hyperthermia [125] temporarily disrupt the BBB to enhance drug penetration. Some

of them have been approved (e.g., hypertonic solutions) with minimal adverse effects but lack long-term safety data [103,126–129]. The primary concern is neurotoxicity, especially in polymedicated patients, as BBB opening is non-selective [130].

(ii) Non-invasive brain drug delivery:
- Intranasal delivery: provides a direct nose-to-brain delivery, avoiding first-pass metabolism and enabling rapid drug absorption. Combining IN delivery with NPs enhances drug transport, achieving significantly higher brain concentrations [131,132]. For instance, IN delivery of melatonin NPs achieved brain concentrations around 10 times higher than those from oral administration [133]. However, challenges include enzymatic degradation, mucociliary clearance, and variability in drug absorption [134].
- Crossing the BBB from circulation: NPs improve biodistribution, tissue penetration and BBB crossing thanks to their small size (1–1000 nm). Their biocompatibility and tunability enable patient-friendly formulations, supporting better adherence [107].

3.3. Nanoparticles to reach the brain

NPs have attracted considerable interest for drug delivery due to their ability to non-invasively transport a wide range of molecules, from small molecules to biologics [135,136], and leverage biocompatible and biodegradable materials. They can cross the BBB via passive diffusion and active transport mechanisms when functionalized (Fig. 4). Additionally, they offer protection against efflux mechanisms, enhance drug concentrations in the brain, and improve the PK profile of encapsulated compounds [107]. For example, docetaxel-loaded liposomes demonstrated a 4.4-fold increase in brain concentrations compared to free docetaxel [137]. NPs used in drug delivery can be categorized into three main families:

(i) Polymeric and protein-based NPs are synthesized from natural or synthetic polymers or proteins. They can encapsulate a broad range of molecules (hydrophilic, hydrophobic, small molecules, biologics, macromolecules), are water-dispersible, and can be functionalized to trigger active transport across the BBB. [138]. Their good biocompatibility has led to the FDA approval of several of those formulations [138,139].

(ii) Lipid-based NPs are composed of different lipids tailored to the desired NP type, including nanoemulsions, liposomes, lipid-NPs, solid lipid NPs or nanostructured lipid carriers. They are biocompatible, exhibit high encapsulation efficiency, and their formulation can be easily scaled for industrial production. Due to these advantages, lipid-based NPs represent the most widely approved class of NPs by the FDA [138,139].

(iii) Inorganic NPs include iron oxide, gold and silica NPs, as well as quantum dots, and are used not only for drug delivery but also in diagnostics, imaging and photothermal therapies due to their unique physical, electrical, magnetic and optical properties. Their precise formulation techniques allow for control over size, structure and geometry. However, their toxicity and accumulation issues restrict their use [138].

3.3.1. Quality target product profile

The physicochemical characteristics of NPs can be fine-tuned to improve their biodistribution, particularly by enhancing circulation time, interaction with the BBB, and penetration into the brain parenchyma. Several key characteristics influence NP brain distribution, including (i) size, (ii) charge, (iii) shape, (iv) elasticity and (v) surface modifications.

NP size has a well-documented inverse relationship with BBB penetration [140–144]. NPs smaller than 10 nm are rapidly eliminated by the kidneys [145], whereas those larger than 200 nm trigger the complement system, leading to splenic filtration and sequestration [138,146]. NP size within the 50–100 nm range typically leads to liver accumulation and elimination [145]. However, NPs around 100 nm have been shown to exhibit extended circulation time, thereby increasing the likelihood of tissue extravasation [146]. Striking a balance between effective BBB penetration and minimized clearance by the liver and spleen is essential.

Regarding NP charge, given that cell membranes are negatively charged, positively charged NPs can undergo adsorptive-mediated transcytosis enhancing brain penetration [107,145]. However, several studies showed that NPs with neutral or slightly negative surface charges tend to exhibit reduced protein adsorption, thereby decreasing blood clearance and prolonging circulation time, achieving higher brain accumulation [146–148]. Although it is well established that surface charge influences NP biodistribution, the optimal balance must be individually determined to maximize BBB crossing.

Shape also dictates how NPs interact with vessel wall, influencing their biodistribution [149]. Spherical NPs tend to marginate less to vessel walls and have fewer binding contacts with the endothelial cells compared to discoidal and rod-shaped NPs which offer a larger contact area, enhancing endothelial accumulation and brain penetration [150,151]. However, the impact of the NP shape is size-dependent, as demonstrated by Nowak et al., highlighting the need for precise co-optimization of these parameters [142].

Elasticity influences NP deformability which impacts circulation time and cellular uptake. Soft NPs, being more deformable, exhibit prolonged circulation time in the bloodstream [152–154]. However, they require more energy for cellular internalization, leading to poor uptake by the endothelial cells [155]. Conversely, hard NPs typically exhibit higher cellular uptake [142,156]. Therefore, an optimization strategy is required to balance prolonged circulation time with effective endothelial penetration. The effect of elasticity might not be considered an independent parameter and should be evaluated alongside shape and size [141].

Surface modifications play a crucial role in overcoming opsonization – a process in which plasma proteins form a protein corona around the NPs, a major challenge in nanodelivery altering both biodistribution and elimination [157,158]. Polyethylene glycol (PEG) is widely used as a coating to reduce opsonization, thereby extending NP circulation time [138,159]. However, concerns regarding PEG immunogenicity and hypersensitivity reactions have led to the exploration of alternative stealth coatings to minimize adverse immune responses, such as poly(vinylpyrrolidone), hyperbranched poly(glycerol), polysorbate, and poloxamer [159–162].

In summary, rational design and optimization of NP physicochemical properties can significantly enhance BBB penetration and targeted delivery to the brain. However, each parameter must be systematically characterized and tailored to the specific therapeutic application.

3.3.2. Functionalization and bioconjugation techniques for nanoparticles

Even after optimizing the physicochemical properties of NPs, their ability to penetrate the BBB often remains insufficient to achieve therapeutic levels in vivo. NPs tend to distribute across various organs, which reduces the effective dose available for brain treatment. To address this issue, one of the most promising strategies is to functionalize the NP surfaces with ligands that bind to specific receptors or transporters located on the apical side of BBB endothelial cells. This approach triggers active transport mechanisms to enhance BBB crossing. The most commonly used moieties for NP functionalization aimed at brain targeting and penetration are outlined in Table 2.

Though the use of targeting strategies is increasingly common for in vitro optimization of NP brain distribution, no targeted-NP has been approved to date by the FDA, and active targeting has yet to be fully achieved. Key major challenges are:

Table 2
Common targeting strategies for nanoparticles brain delivery. ApoA, apolipoprotein A; ApoE, apolipoprotein E; g7, glycosylated heptapeptide; GABA, gamma-aminobutyric acid; LDL-R, low density lipoprotein receptor; LRP-1, low-density lipoprotein receptor related protein; nAChR, nicotinic acetylcholine receptor; RGD, arginylglycylaspartic acid; RVG, rabies virus glycoprotein; TAT, transactivator of transcription; TfR, transferrin receptor; TGN, threonylglycylasparagine.

Strategy	Target	Targeting protein or peptide	References
Active transport targeting	TfR	Transferrin	[163]
		B6-peptide	[164,165]
		Lactoferrin	[166]
	LDL-R	ApoE	[167,168]
		ApoA	
	LRP-1	Angiopep-2	[169]
		ApoE	[167]
	Insulin receptor	Insulin	[170]
	Integrins	RGD	[171]
BBB cell penetration enhancement	N/A	g7	[172,173]
	nAChR	RVG	[174]
	GABA receptor		
	N/A	TAT	[175,176]
		TGN	[177]

(i) Protein corona: upon their entry in blood, the NPs are immediately covered by plasma proteins that might cover the targeting moieties, and thus impairing their binding to targeted BBB receptors and their endocytosis [178,179].
(ii) Degradation of the targeting moieties: peptide-based targeting moieties are vulnerable to degradation by proteases in biological fluids, often losing their functionality before reaching their receptor [180].
(iii) Endogenous competition: targeted NPs have to compete with the endogenous ligands of those receptors [181]. For example, peptides targeting transferrin receptor need to compete with endogenous transferrin, which reduces their apparent affinity for TfR [163,182].
(iv) Industrial development: NP-based formulations already face major limitations due to scalability issues and functionalization with targeting moieties adds another layer of complexity [160,183].

The composition of the NPs can be optimized with PEG to reduce the protein corona, which cannot completely be avoided. This requires the assurance that the remaining protein layer does not mask the targeting moieties, preventing their binding to the BBB receptors [179,184]. Alternatively, researchers are exploring ways to control the composition of the protein corona to enhance brain targeting [158,178]. Surfactants, such as polysorbate 80 and poloxamer 188, increase and promote the adsorption of ApoE at the surface of the NPs, enhancing their BBB penetration efficiency via LPR-1 and LDR-mediated active transport [107,167,168].

Several targeting peptides stabilization strategies are being investigated, including N and C terminal modifications, cyclization and modifications of the backbone [180]. Retro-isomerization of targeting peptides – the peptide synthesized with D-amino acids and an inversed sequence – increases peptide stability in biological fluids by preventing their degradation by proteases [185–188]. The obtained retro-enantiomer has been shown to bind to a different binding site of the receptor, making *retro*-isomerization a potential strategy to limit endogenous competition [185]. Another potential solution to limit the competition between targeting moieties and endogenous proteins is to develop ligands binding to different sites of the targeted receptor. For example, monoclonal antibodies, such as OX26 and R17217 antibodies for TfR, and murine HIRMAb and 83–14 antibodies for the insulin receptor, can bind to epitopes that are different from endogenous ligand binding sites [189].

Finally, the market access of NPs already faces several challenges that may be exacerbated by the use of targeting moieties [160,183,190]. Manufacturing struggles with batch-to-batch reproducibility, requiring validated in vitro-in vivo correlation to ensure quality performance. Currently, limited data is available on critical parameters of NP quality control and no standardized regulation has been established. Regulatory agencies mainly focus on characterization and toxicity assessment of NP-based formulations without proposing standardized protocols [160,183]. As a result, only a few NP-based formulations have been approved by the European Medicine Agency (EMA) and the U.S. Food and Drug Administration (FDA) for CNS-related disorders (e.g., Focalin® XR and Ritalin LA® for attention deficit hyperactivity disorder, Invega® for schizophrenia), none of which use targeted NPs [139]. A recent review by Joyce et al. highlighted the lack of rigorous characterization of surface modifications, underscoring the need for robust analytical methods and stability assessments during production and storage, not only of the NPs, but of the targeting moieties themselves to ensure no loss of targeting properties [160]. To promote market access, manufacturing and characterization methods should be kept simple, reproducible and accurate. Development and validation of new characterization methods applicable at the industrial scale should be done while keeping in mind the cost of production, which may surge drastically after the synthesis and introduction of targeting moieties. In that regard, functionalization techniques should be reproducible, cost-effective, and compatible with large-scale production: click chemistry (e.g., thiol-maleimide, carboxyl-to-amine, aldehyde-based chemistries) or adsorption (e.g., electrostatic, hydrophobic interactions) [191].

Although targeted NPs are not yet clinically approved, advances in biomimetic strategies such as NP coating with extracellular vesicles lipid layer [192–195] and ligand engineering could represent alternative solutions to overcome those barriers. Optimizing NP functionalization while ensuring regulatory compliance will be key to translate brain-targeted NPs into clinical use.

3.3.3. *Outlook and challenges in the treatment of CC dysfunctions*

The ability of NPs to improve drug tissue penetration could resolve delivery and PK issues, and accelerate the clinical translation of circadian targeting drugs (Table 1). For example, the encapsulation of VPAC2 receptor agonists, such as VIP, PACAP and BAY55-9837, could increase their circulation time and thus allow for dose reduction. In the case of PHD2 inhibitors, the use of NPs could increase brain penetration, making it possible to reduce the therapeutic dose and limit peripheral side effects. Finally, some CK1 inhibitors such as PF-670462 may require cremophor for their formulation, which has been reported to cause an anaphylaxis response in other formulations, especially of paclitaxel and docetaxel [196]. The use of this excipient to increase drug apparent water solubility and bioavailability could be avoided by employing NP-based formulation instead. To our knowledge, no nanoencapsulation of any of these drugs has been attempted.

4. Chronopharmaceuticals

In treating CC dysfunctions, correct timing of the drug administration is crucial for achieving the desired therapeutic effect, whether it be phase advancement or phase delay [2]. Studies have demonstrated that drug absorption across several biological barriers is also influenced by the CC, in a phenomenon known as chronopharmacokinetics. In the gastrointestinal tract (GIT), for example, the expression of transporters and efflux transporters follows a diurnal pattern, leading to time-dependent variations in drug absorption [27,197,198]. This circadian influence on drug absorption is also observed in subcutaneous (SC), intramuscular, transdermal, nasal, ocular and intraperitoneal

administration. Other PK parameters such as drug distribution, metabolism and excretion, are similarly regulated by the CC [198].

Drug distribution within the CNS, governed by BBB permeability, also varies diurnally [198]. One of the functions of sleep is to clear metabolic waste accumulated in the cerebrospinal fluid during the day [199]. At night, BBB permeability increases by 60% to facilitate this waste elimination [200]. Research indicates that (i) P-gp activity is higher during the active phase [201], (ii) endocytosis peaks during the resting phase and (iii) the expression of claudin-5 is less than half of its active-phase level at night [110]. In a *Drosophilia* model, nighttime administration of an antiepileptic drug was more effective against mechanical seizure stimulation than daytime administration [201]. Similarly, in Wistar rats, the brain distribution of morphine exhibited fluctuations in the course of 24 h [202].

Timing the drug administration not only enhances the CC modulating effect, but also optimizes brain distribution, potentially limiting peripheral side effects, increasing specificity for the SCN and making it possible to reduce the required dose. When precise timing is needed, controlling the duration of drug release is equally important. The goal of therapy is to restore a normal circadian rhythm to treat the disease or alleviate symptoms. For example, a sharp peak of melatonin has been effective in treating jetlag, whereas a slow-release formulation showed no efficacy [72].

4.1. Timely administration

The most common approach to achieve chronodelivery is by administering the drug at a specific time. This strategy has been successfully applied in various CC related pathologies to optimize treatment efficacy (e.g., hypertension [203,204], inflammatory joint disease [205], cancer [23,206], hypercholesterolemia [207], and thyroid disorders [204]). Timely administration and time-dependent effectiveness across several indications has been observed for the oral route of administration, which is generally the preferred one, but also with parenteral, nasal, lung, skin, ocular, vaginal and rectal routes [198,208].

One of the biggest challenge with timely administration is poor patient compliance. Patient compliance is already problematic when DDSs are difficult to administer, for example, oral forms to young and elderly patients who have trouble swallowing, or inhalers to those with difficulties with hand/breath coordination. This is also the case with DDSs that cause discomfort, such as SC injection of insulin [27,198]. The additional challenge of timing further reduces overall compliance, particularly among polymedicated patients and those suffering from chronic illness and/or neurological disorders [209]. In addition, the logistics of timed delivery can be problematic in institutional care facilities, hospitals, and for outpatient chemotherapy scheduling [27].

In this context, the development and increased availability of oral chemotherapy and biological products, as well as nasal and skin DDSs, can improve patient adherence and make timely administration more feasible in community settings [209]. Educating patients through community health professionals is crucial to promote correct chronodelivery and thus enhance treatment efficacy.

NPs could have a positive impact on timely drug administration by enhancing drug absorption through various routes, thus increasing intracellular penetration and improving brain distribution [99,210–212]. NPs can also modulate the release profile of encapsulated molecules to achieve sustained drug release [210,211]. In the case of SCN related treatments, there is no conclusive evidence whether melatonin agonists are more effective when administered as immediate or sustained release formulations [213]. Further studies are needed to understand how the release profile affects the efficacy of SCN treatments and to identify the best formulation strategy.

Due to the challenges of timely nighttime drug administration, there has been increased focus on developing DDSs that can rapidly release a drug after a predetermined lag time. These systems, known as pulsatile DDSs (PDDSs), are designed to release medication at specific intervals, allowing for the delivery of multiple doses of one or several drugs at different times, effectively mimicking immediate administration and release of various treatments [209,214]. For the above reasons, the combination of NPs and PDDSs could offer a promising strategy to improve biodistribution and dosing time of CC targeting compounds, and will be discussed in the following section 4.2.

4.2. Pulsatile nano-drug delivery systems

PDDSs have been shown to optimize chronotherapy, as seen with products such as Covera® HS, which releases verapamil 4 h after bedtime administration to align with circadian rhythms and manage nighttime hypertension [215]. PDDSs can also mimic the body's natural circadian patterns, further enhancing therapeutic outcomes. Three main types of PDDSs can be identified, categorized according to the technology used to trigger rapid drug release: (i) PDDSs with predetermined lag times that are independent of external factors; (ii) PDDSs triggered by an endogenous physical or chemical signal; (iii) PDDSs triggered by an exogenous signal. These advanced DDSs offer a promising solution to improve the effectiveness of chronotherapy by ensuring precise drug delivery aligned with the body's natural rhythms.

To date, efforts have focused on achieving a pulsatile release profile for the drug itself. However, for brain and SCN targeting, it is essential that the drug remains encapsulated within the NPs in order to cross the BBB. Future efforts should seek to integrate NPs into PDDSs design to form pulsatile nano-DDSs (PNDDSs), thus combining a pulsatile release of the entire NP with the NP ability to achieve targeted brain delivery.

4.2.1. Pulsatile drug delivery systems independent from external signals

PDDSs with a predetermined lag time are designed to function independently of external factors. In these systems, the lag time is determined by the DDS itself. Most PDDSs are developed for oral administration of traditional drugs [214], but they could also be used for chronodelivery of NPs, thereby enhancing brain targeting and biodistribution. While some studies have shown that NPs can distribute within the brain after oral administration [216–218], it is crucial to ensure that NPs maintain their structure and ability to cross the BBB after passing through the GIT, especially if they are functionalized with targeting peptides or proteins.

Osmosis, reservoir, and matrix systems are three main technologies used to develop this type of PDDS, applicable for various routes of administration. Several technologies exploiting these techniques are already on the market (e.g., OROS®, PULSINCAP®, DIFFUCAPS®, CONTIN®), while others are currently under development. The osmosis system involves encapsulating the drug within a semi-permeable membrane that contains a small orifice. A separate compartment within the same system contains osmotic agents drawing water from the external environment, causing the compartment to swell and push the drug out through the orifice [219–222]. The reservoir technique encapsulates the drug within a polymer coating that erodes over time [223–225]. Finally, the matrix technique mixes the drug with a blend of hydrophilic and/or hydrophobic polymers controlling the drug diffusion at a predetermined rate [226,227].

To our knowledge, few studies have focused on developing PNDDSs, with even fewer exploring the incorporation of NPs into existing PDDSs. A system, called Particles Uniformly Liquified and Sealed to Encapsulate Drugs (PULSED), has been created using 3D-printed PLGA microstructures which are compatible with both small molecules and biologics. These microstructures were designed to release their cargo after predetermined lag times, and were able to do so for periods up to several months [223,228,229]. In the study by McHugh and Nguyen, this formulation induced a long-term antibody response to ovalbumin vaccination [223]. This example of PNDDS highlights the significant potential of micro and nanomaterials for precise chronodelivery of drugs and improved stabilization and efficacy in the delivery of biological molecules.

4.2.2. Pulsatile drug delivery systems dependent on endogenous signals

One of the main challenges with PDDSs that are independent of external factors is that the timing of administration is still crucial to ensure the drug is released at the correct moment after a specific lag time. Ideally, PDDSs should release their cargo at the optimal time, regardless of when they are administered. In this regard, DDSs triggered by endogenous signals hold significant potential. These systems can release drugs in response to biological signals associated with the disease, such as the release of insulin when glucose levels rise in diabetes treatment. This approach, which depends on the patient's biology, holds promise for a highly personalized therapy [27].

The incorporation of NPs in this type of PDDS is more common, as NPs provide a versatile platform that can be modified with molecular gates to achieve release triggered by physical or chemical signals. In a detailed review published in 2024, Ventura et al. described various techniques that could be used to synthesize and modify different types of chemically responsive NPs [230]. Although these techniques have not yet been applied to create circadian-responsive nano-platforms, they show great promise, especially as some are already used in other types of PDDSs, such as hydrogels.

Regarding physical endogenous signals, temperature could be a potential trigger, given its synchronization with the CC with the highest body temperature around 7 p.m. and the lowest between 4 and 5 am [4]. However, the temperature difference in humans between these points is only about 1 °C and body temperature can be influenced by physiological factors such as body mass, the menstrual cycle and infections, as well as environmental factors. Therefore, using circadian temperature variation as a trigger is not ideal [4]. Temperature-triggered PDDSs are typically controlled by external temperature sources and will be described in the next section 4.2.3 [231,232].

PDDSs triggered by chemical signals, such as pH, redox or molecular signals, could also be used to administer cargo according to CC time since, for example, the pH levels in the gastrointestinal tract, skin and urinary systems follow a circadian rhythm [27]. Coating drugs or NPs with pH-resistant polymers is a common strategy in oral delivery to release the drug at a specific site within the GIT [233]. This strategy aligned with circadian pH variations could be used for chronodelivery. Pramanik et al. applied this approach to develop pH-responsive NPs that release melatonin in the stomach in response to stress-induced gastric ulceration, and found its efficacy to be twice that of free melatonin treatment [234].

In cells undergoing intense oxidation such as tumor cells, spatiochronodelivery can be achieved using redox signals to release the drug when the PDDSs reach the target and only when the cell is damaged. For example, to limit post-surgical recurrence of glioblastoma, Erthal et al. developed responsive NPs loaded with paclitaxel, and incorporated them into a hydrogel containing free temozolomide. This hydrogel was placed in the surgery site after tumor resection in a mouse model to enable local sustained release of temozolomide and the paclitaxel-loaded NPs. The release of the paclitaxel was triggered by the reducing environment when the glioblastoma was recurrent. This formulation was able to delay the tumour recurrence in comparison with the sustained release of temozolomide alone [235].

Other successful examples of combining NPs in DDSs have been seen in diabetes treatment. These systems, commonly hydrogels or microneedles, respond to elevated glucose levels by releasing insulin in a pulsatile way [27,236,237]. In addition, the polymer composing them can be modified to achieve a lag time or a signal-triggered release and they can encapsulate NPs [27,238]. Volpatti et al. developed subcutaneous glucose-responsive NPs that provided glycemic control for 16 h using glucose oxidase [239].

In the future, PDDSs could be designed to respond to circadian signals, such as melatonin or cortisol levels. Such CC-responsive PNDDSs might open a new avenue of treatment modality. There remains a need for effective CC evaluation methods, because the CC can also be affected in several pathologies. It is necessary to develop methods to evaluate the circadian state of the patient, moving us closer to truly personalized medicine [26,27].

4.2.3. Pulsatile drug delivery systems dependent on exogenous signals

Externally triggered PDDSs offer precise control over drug release timing, as they are not dependent on the system's inherent properties or the patient's physiological conditions. NPs provide many opportunities to respond to external stimuli and deliver their cargo. Ventura et al. recently reviewed the most recent techniques in the formulation of complex NP systems capable of advanced communication. Some multiparticulate NP-based formulations can perform advanced coordinated tasks between them or communication directly with living systems. In those formulations, NPs are engineered to respond to a variety endogenous but also exogenous signals. These advanced systems may provide breakthroughs in the field of chronodelivery and several exogenous signals are currently being explored and utilized to trigger drug release [230].

Remote-controlled systems, managed by patients, offer a promising platform for chronodelivery, with the hope that on-demand administration will improve patient adherence. For instance, insulin pumps can be filled and programmed by patients to deliver both bolus and basal insulin at specific times and rates. These pumps could be adapted for programmable administration in other therapeutic areas [240,241]. Lee et al. developed an implantable pump system for the chronodelivery of bromocriptine in type 2 diabetes. In vivo tests on Zucker diabetic fatty rats demonstrated that evening administration resulted in reduced body weight gain, lower food intake, and improved postprandial glucose levels and insulin concentrations following an intraperitoneal glucose tolerance test [242]. Such systems can be programmed to respond to exogenous signals such as electrical stimuli and in the future may be adapted for thermal or light-triggered delivery [243]. Remotely controlled PDDSs hold great potential for improving chronodelivery strategies in patients with neurological disorders, particularly the elderly and those with multiple medications, enhancing compliance. Electrical signals are primarily used for topical drug administration via electroporation and iontophoresis to facilitate drug migration across biological membranes [240,244].

Thermally induced drug delivery offers a non-invasive approach to chronodelivery, enhancing NP distribution in target tissues, such as tumor sites [232], and the brain [125], while also triggering drug release. Widely employed in cancer treatment to specifically target tumor cells, localized hyperthermia can be generated through electromagnetic energy, high-intensity focused ultrasounds, ultrasounds or microwave. The combination with thermally induced NPs accumulating in tumor sites induces tumor specific hyperthermia enhancing the effectiveness of chemotherapy when administered at specific cure stages [232,245]. The NP type, composition, coverage and combination must be adapted to the desired thermal physical stimuli and response (e.g., magnetic NPs such as iron oxides, ferrites; thermoresponsive polymer systems; organic and inorganic photothermal material) [246–248]. Depending on the NP composition, hyperthermia can mechanically alter NP structures, prompting on-demand drug release [240]. For instance, Mirvakili et al. developed magnetic NPs coated with poly(lactic-co-glycolic) acid that exhibited a pulsatile release when exposed to a magnetic field [249]. Even when combined with NPs, localized hyperthermia poses risks, such as heat shock in surrounding tissues, which is particularly concerning in non-cancer therapeutic areas. To mitigate this, Purohit et al. developed liposomes capable of ultrasound-triggered drug release without inducing hyperthermia, thus increasing the clinical applicability of those PDDSs [250]. The main challenge to their applicability in chronodelivery is the development of portable devices or external signals that can be easily applied in home settings [232]. In that context, Kang et al. successfully synthesized temperature-triggered NPs for the treatment of osteoarthritis enabling an immediate release of diclofenac and a sustained release of kartogenin. The chronodelivery of both drugs was triggered by local cold therapy, a common method to

reduce inflammation, swelling and pain in osteoarthritis. This system addresses inflammation and cartilage regeneration only when the patient is experiencing pain, offering an optimal solution for ambulatory care [251].

Light-triggered PDDSs enable sequential, on-demand drug release. For instance, Rwei et al. developed infrared photoresponsive pulsatile liposomes for pain management. By controlling the timing, irradiance and duration of irradiation, they successfully regulated the timing, duration and intensity of anesthesia in rats [252]. Similarly, Zhan et al. created a DDS for pain management using a liposome-gold nanorod complex [253]. These light-responsive formulations offer a highly personalized platform, adaptable to a patient's specific pathology and symptom severity. However, most photoresponsive systems rely on UV light, which has limited tissue penetration and can damage biological molecules [240,254]. The eye, as the only organ that allows deep light penetration, is currently the preferred site for developing photoresponsive PDDSs. Moreover, these systems often face difficulties in achieving pulsatile release due to the irreversible changes induced by light exposure [254].

In summary, the integration of exogenous signals such as electrical, thermal and light stimuli into PNDDSs holds significant potential for enhancing drug delivery precision and patient adherence. However, challenges remain in adapting these technologies for broader clinical use, particularly in the development of portable, non-invasive systems suitable for home or ambulatory care.

Altogether, there are significant advantages of the use of NPs alone or in combination with PDDSs for the treatment of NDs related to CC dysfunction. Table 3 summarizes the potential advantages of the multiple and versatile strategies that NPs offer. Only future investigations will determine the potential of NPs to efficiently modulate the circadian rhythm for the treatment of neurological disorders.

5. Conclusion

Growing evidence highlights the connection between neurological disorders and CC dysfunctions, pointing to the need for new therapeutic approaches that target CC resynchronization. Despite their development these past decades and the market access of some classes, for example, melatonin receptor agonists and orexin receptor antagonists, none have shown significant therapeutic effects in neurological disorders modulated by the CC. Based on their promising results in preclinical studies, one possible explanation is the lack of advanced formulation strategies to enhance the PK profiles of these compounds, particularly their brain penetration, their biological half-life and their chronodelivery.

NPs have been successfully developed and approved to optimize the PK and brain penetration in other pharmaceutical classes. New strategies are emerging to further improve their brain targeting capabilities, particularly through active targeting mechanisms. NPs offer strong potential for encapsulating drugs that target the SCN, increasing their brain distribution and modulating their release profiles. However, this strategy remains largely unexplored and could be critical for increasing the clinical translation of CC targeting agents.

Integrating NPs into chronodelivery systems could further improve PK profiles and ensure that drugs are delivered within optimal therapeutic time windows. While preclinical studies have demonstrated the potential of chronodelivery, challenges remain in advancing pulsatile drug delivery systems for clinical use. Given the functionalization capabilities of NPs and their ability to modulate drug release, they offer a promising solution for overcoming these challenges.

Optimizing PK and chronodelivery, a major challenge in treating CC dysfunctions, will be crucial for improving clinical outcomes. However, the lack of research combining CC targeting agents, NPs, and chronodelivery, highlights the urgent need for innovation and further investigation in this area.

CRediT authorship contribution statement

Marion Le Meur: Conceptualization, Writing – review & editing. **Jaime Pignatelli:** Writing – review & editing. **Paolo Blasi:** Writing – review & editing. **Valle Palomo:** Conceptualization, Writing – review & editing.

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Table 3
Advantages of nanoparticles and their combination with chronodelivery systems for the treatment of circadian clock related neurological disorders.

Advantages	Possible modulations	Formulation strategies
Brain penetration	Optimization of NPs quality target product profile	Modulation of size, surface charge, shape, elasticity
		Surface coating to reduce protein corona formation
	Surface functionalization	Conjugation with active transport targeting, BBB cell penetration enhancement
Release profile	Immediate release	Small size for increased surface area
		Polymer composition and molecular weight control the release rate
		Drug loading at the surface of the particles
	Sustained release	Drug dispersion in a matrix system
		Polymer composition, crosslinking density and molecular weight control the diffusion rate
		Surface coating with polymers or lipids
	Lag time	Drug encapsulation in a reservoir system
		Polymer composition and molecular weight control the degradation rate
		Surface coating with polymers or lipids
Pulsatile delivery	Pulsatile lag times	Multilayer encapsulation
		Co-administration of NPs exhibiting different lag times
	Triggered by physical stimuli	Magnetic, lipid-based, thermoresponsive polymeric and photothermal NPs for hyperthermia and temperature-triggered delivery
		Photo-responsive polymeric NPs
		NP-based formulations with responsive polymers
	Triggered by chemical stimuli	NP-based formulations with responsive polymers (e.g., pH or redox signals)
		Polymer functionalization with communication systems detecting molecular levels

FSE “invierte en tu futuro”.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability

No data was used for the research described in the article.

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