



# Understanding Skin Chronobiology to Unveil and Transform Dermal Chronotherapeutics: Paving the Way for the Future

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All the organisms on earth spontaneously tend to exhibit certain inherent tendency that helps them to adapt to their respective environment, which is monitored by internal biological clock. The basic rudiments of skin circadian rhythm which varies with diurnal-nocturnal pattern as well as the seasonal pattern is explained. Correlation between sleep and dermatological ailment like psoriasis, eczema, and aging is described. The recent application of chronopharmacological studies in age prediction, wound healing, and fat metabolism is summarized. The diverse circadian activity of skin tends to affect pharmacodynamics and pharmacokinetics of drug providing a temporal link to drug and its effects.

**Key Words:** Circadian rhythm; Pharmacodynamics; Pharmacokinetics; Seasonal affective disorders; Wound healing

**Received:** December 6, 2020 **Revised:** January 18, 2021 **Accepted:** January 19, 2021

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## INTRODUCTION

Chrono pharmacology elaborates on how the outcomes of drug changes with biological timing and endogenous rhythm. It assists in optimization of drug action and accordingly lessens adverse effects by timing medication relative to biological periodicity [1]. Circadian rhythm is being stimulated by zeitgeber mechanisms like light–darkness, warmth–cold, eating–fasting, etc. Zeitgeber is a stimulus which tends to initiate as well as regulate all the circadian rhythms of our body [2]. Basically, the circadian clock consists of three components: an input, central clock, and an output. The major input of zeitgeber is light which is cascaded through the retino-hypothalamic tract and geniculo-hypothalamic tract through messengers like glutamate, pituitary adenyl cyclase-activating peptide, and substance P. Central clock or the pacemaker of the circadian rhythm is suprachiasmatic nucleus (SCN) which is located in basal hypothalamus [3]. SCN tends to control outputs via neural or humoral pathways [4]. SCN fibers target endocrine neurons—such as gonadotropin-releasing hormone, thyrotropin-releasing hormone, and corticotropin-releasing hormone—and autonomic neuron projecting preganglionic sympathetic as well as parasympathetic neurons in the spinal cord.

Being the pacemaker SCN synchronizes circadian oscillation according to zeitgeber, external and peripheral oscillation. Efferent or the output of SCN are confined and spare within the medial hypothalamus, projecting medial preoptic area, paraventricular nucleus of the hypothalamus or subparaventricular nucleus [5]. Circadian clock mechanism is being regulated by clock gene expression via CLOCK (circadian locomotor output cycles protein) and BMAIL (aryl hydrocarbon receptor in brain and muscles), they form dimers and play a key role in molecular clock regulation and thereby lead to activation of clock genes, per (period) and cry (cryptochrome). Post translation modification of per and cry activates phosphorylation and ubiquitination and hence contributes to length-period modulation [6]. If a certain change in our body is day-related then it is termed as diurnal and if it is night-related it is called as nocturnal, 1 day or 1 night connected behavioral change is coined as nycthermal while 24-h associated difference is titled as circadian [7].

## MELATONIN

Melatonin being first disengaged from the cow-like pineal organ in 1958 however, in people, it is the primary hormone inte-

grated and discharged by the pineal gland [8]. It is incorporated from a pathway which incorporates both tryptophan and serotonin. It is emitted around evening time and its levels are highest between 3 am to 4 am, a period which is set apart by vigorous circadian mood and greatest plasma levels of melatonin. There is a solid connection between the everyday ascent of melatonin discharge and resulting increment in rest inclination around 2 hours before the individual's customary sleep time. At the point when the melatonin discharge begins the "rest entryway" opens and the affinity to nod off likewise increments and rest is most drastically averse to happen at the time before the emission. The cadenced arrival of melatonin is directed by the focal circadian beat generator—the suprachiasmatic core (SCN) of the front hypothalamus [8].

It regularly gives the idea that melatonin is a "hormone of obscurity," as opposed to be the hormone of rest since it gives data about haziness. It is realized that it balances out different circadian rhythms in the body and consequently it is known as the "endogenous synchronizer." Its impact on rest shows up more charmed in the circadian musicality of rest wake guideline. Rest beginning is identified with MT1 receptor while MT2 receptor is connected with the stage moving impacts of melatonin. The chronobiotic and mesmerizing impacts of melatonin are interceded through 2 receptors: MT1 and MT2. SCN is found to have both of these receptors, yet they are additionally spread all through different locales in the mind and different organs, which shows that melatonin probably influences other natural frameworks as well. This far reaching dispersion shows that melatonin effectively affects human science that have not been completely explained, including going about as a neuroprotective and managing the rest wake cycle.

One of numerous circadian rhythms is the rest-wake cycle. The circadian time of rest/wake is around 24.2 hours, yet fluctuates between 23.8 to 27.1 hours. The inborn circadian inclination for evening time (extensive stretch) or daytime (brief period) is firmly identified with this period which can be controlled by estimating the circumstance of maximal emission of melatonin and resulting related center internal heat level (core body temperature, CBT). When CBT is at its most minimal and melatonin levels are at their most noteworthy, it demonstrates a time of greatest sleepiness [9].

### Melatonin and the circadian rhythm of sleep-wake cycle

Melatonin seems to have 2 extremely entrancing consequences for the rest-wake cycle. The primary impact included entraining and moving the circadian musicality (process C) in a chronobiotic work. Second result includes promoting sleep onset and continuity in a very hypnotic operate by increasing the physiological state drive to sleep (process S). These effects seem to be equal. Clinically, exogenous internal secretion given within the morning delays evening drowsiness by delaying the part of biological time. Each phase can be advanced if internal secretion is given within the evening. The use of exogenous internal secretion in primary sleep disorder reveals mixed results. One meta-analysis

showed effectivity trends of internal secretion [10]. In another study, though the results were reported as negative, it showed a statistically important positive result of a decrease in sleep latency by a median of 7.2 minutes for internal secretion [11]. The development in sleep latency is well inside the vary of different marketed pharmaceutical hypnotic agents however still for reasons unknown, the result was thought-about to be statistically insignificant [12].

The usage of 2 mg of extended-release internal secretion showed important improvement in primary sleep disorder, which was disclosed by studies that were disbursed in massive teams of old and senior patients. Positive results were primarily seen in patients aged 55 or older and effectivity was seen over a 6 months in the study that was conducted in more than 500 patients. Most likely the age-related decrease in internal secretion levels is to blame for the advantageous results of exogenous internal secretion in nursing older population [13]. Some potential causes of this embrace lightweight input that is a smaller amount effective, attenuate activity of the SCN, or calcification of the epiphysis. This mechanism is supported by the proof that comes from a study of patients of all ages with comparatively low internal secretion levels and World Health Organization showed advantageous response to the sleep effects of exogenous internal secretion.

### Internal secretion agonists

#### Ramelteon

Some of the intrinsic biological issues thought to be joined to the inconsistent findings of internal secretion on sleep area unit are solved by ramelteon, a more modern MT1/MT2 internal secretion receptor agonist approved by the FDA in 2005 for the treatment of insomnia [14-16]. It has a 3- to 16-fold bigger affinity for the MT1 and MT2 receptors. A lively matter is to blame for its action and its blessings over internal secretion clearly embrace its longer half-life, exaggerated tissue absorption and bigger lipotropic properties. It has no affinity for minor tranquilliser, opioid, dopamine, or 5-hydroxytryptamine receptor subtypes and it exerts its action principally on the SCN. The consequences area unit quickly seen inside per week and its effectivity last for six months. It targets sleep onset quite internal secretion itself that is proved by its MT1 receptor selectivity [17,18]. It is additionally shown part shifting skills of the biological time still as some mixed positive ends up in tiredness disorder. It is currently thought-about first-line treatment for primary sleep disorder, particularly if the patient is senior or has problems with rebound sleep disorder, next day effects, withdrawal, or components of biological time sleep disorders.

#### Circadin

First internal secretion receptor agonist accredited within the global organization (2007) indicated for the treatment of primary sleep disorder in patients aged 55 years or older is prolonged unharness internal secretion, i.e., circadin [19-21]. In patients aged 55 years or older who are suffering from poor sleep quality; inter-

nal secretion production is even under in healthy senior individuals while not such complaints and circadin is built to bit by bit unharness internal secretion over 8–10 hours [20,22,23]. It had been approved by the European Medicines Agency (EMA) 2007 in Europe as monotherapy for the short-run treatment of primary sleep disorder characterized by poor quality of sleep in patients World Health Organization area unit aged 55 or older and is presently commercialized in Europe and Asia-Pacific territories. It has been ascertained to be effective in rising sleep latency, quality of sleep, quality of life and morning alertness in primary sleep disorder patients, suggesting additional restorative sleep, while not withdrawal symptoms upon discontinuation [13,24,25]. In clinical trials, its safety and tolerability profile was adored placebo cluster, with no negative effects on memory or bodily property stability throughout the night. The treatment with it had been not restricted to 2–4 weeks as finished different classical sedative hypnotics sleep medication however allowed for up to three months while not interruption considering its safety and tolerability information.

#### Agomelatine

Agomelatine is an internal secretion MT1 and MT2 receptors agonist and a weak 5-HT<sub>2C</sub> antagonist. In depressive patients, agomelatine is understood to enhance sleep quality and cut back waking once sleep onset. The melatonergic activity is joined to its sleep promoting activity and 5-HT<sub>2C</sub> receptor antagonism is to blame for its anti-depressive action. However, there is some tilt on what extent 5-HT<sub>2C</sub> antagonism contributes to its therapeutic effect as a result of its short half-life and low 5-HT<sub>2C</sub> affinity [26].

#### Tasimelteon

Tasimelteon is a particular MT1 and MT2 receptors agonist. It has been developed for the treatment of unit of time rhythms sleep disorders and approved within the USA in 2014 for the treatment of non-24-hour sleep-wake disorder within the blind. Clinical Trial Phase III studies are conducted in transient sleep disorder related to shifted sleep and wake time and within the clinical trial study, sleep latency was reduced; sleep potency was exaggerated compared with placebo and there was a dose dependent advancement in plasma internal secretion rhythm with tasimelteon [27,28]. Improvement in sleep latency, sleep potency and also the wake once sleep onset was ascertained within the clinical test study. In each of the studies, the frequency of adverse events were as compared to placebo [29].

## SKIN AND ITS CIRCADIAN RHYTHM

Skin is the largest organ in our body and it plays a crucial role by acting as a barrier, protecting from external environment as well as synthesis of vitamins [30]. Skin consists of 3 major components, outermost layer is epidermis (50 cell layers to 100 cell layers), average thickness being 0.1 mm. Epidermis is further categorized into 5 horizontal layers—stratum corneum, stratum ba-

sale, stratum spinosum, stratum granulosum, and stratum lucidum [31]. Dermis lies below epidermis and is made up of fibrous network of tissue to provide resilience and structure to skin, its average thickness being 2 mm. It consists of blood, lymph vessel, and structural proteins [32]. Innermost layer is hypodermis which tends to refer fat tissues below dermis that basically provides shock absorption and insulates body from cold temperature. In response to discrepancy due to external stimuli, it tends to show varied reciprocation in the level of enzymes, texture and mediators because of 24-hour day-night cycle or seasonal cycles [33].

In various studies, it was found that epidermal layer of skin acts as a circadian biomarker and also foresees that many skin functions tends to follow circadian rhythm. Le Fur I et al. [34] carried out studies on 8 Caucasian women for a time period of 48 hours and determined parameters like, variation in skin temperature of forearm, facial skin as well as trans-epidermal water loss (TEWL) according to that of day–night cycle to which they concluded that skin temperature is at peak in late afternoon for forearm skin and highest in early morning for facial skin. They inferred that maximum TEWL for cheeks was observed at 8:00 and 12:00 and trough after 14:00. Similar studies were carried out by Yosipovitch et al. [35] where various parameters like TEWL, skin pH, and stratum corneum hydration was studied on forearm, upper back, and shin skin of men. Measurement of TEWL was carried out with Evaporimeter (Teavometer), stratum corneum hydration level was studied with corneometer, pH using pH meter and skin temperature using a digital infrared thermometer. In this statistical analysis, it was evident that parameters like TEWL, skin pH, and skin temperature showed time dependent rhythms while in stratum corneum hydration no time dependent rhythm was detected. TEWL was more prominently obtained in evening and trough level was observed in morning (8:00–10:00) on all sites except on shin where peak was noted around 12:00 and 04:00, 2 nadirs at 22:00 and 08:00 was seen. Skin pH which was studied on shin & forearm was at peak in afternoon around 14:00 and 16:00, while minimum was in evening around 20:00. Recently, in a comparative study of 38 Japanese volunteers, wrinkle analysis on human face was done using images of replicas acquired from different areas on face susceptible to wrinkling and it was found that on all areas of skin, wrinkles are more noticeable in afternoon than that in morning or night [36]. Rhythmic action of cutaneous blood flow was studied by Yosipovitch et al. [37] and they reported that in late afternoon and late evening there is high cutaneous blood flow whereas it is less in early day. Interestingly, time dependent croon of skin was also observed at cellular level where epidermal cell proliferation or the M-phase of the cell cycle of skin cells was studied using biopsies from healthy volunteers which showed proliferation at 23:00 and trough at noon (Table 1) [34–40].

#### Seasonal cycles

Not only the 24-hour biological clock but also the environmental seasonal pattern affects the histology of skin. It was eventually observed by Uter et al. [41] that skin is more hydrated in summer

because of increase in sweat secretion and comparatively dryer in winter. Therefore, the incidence of dermatitis is more likely to be observed in winter. In a study, Hellemans et al. [42] investigated that lipid peroxides present on the surface of skin are responsible for oxidation of lipids and thereby affect the strength of stratum corneum. In the beginning of spring there is increase in level of lipid peroxidase and they peak during summer, mainly due to exposure of solar irradiation and hence show gradual loss of catalase activity. Interestingly, on further studies it was observed that UV-A tends to downregulate but UV-B does not affect catalase activity. Melanin Index, TEWL as well as moisture level in skin was studied on 22 healthy Japanese volunteers by Gardner-Medwin et al. [43] where neck skin for 11 males and ventral forearm skin for 11 females were used as area for test. It was observed that melanin index was high in late spring and early winter whereas TEWL level and moisture level was maximum in rainy season. Moisture level and TEWL was found to be minimal in late spring. Seasonal variation pattern is also varied in male and female. It is also observed that skin variation is more pronounced in females than in males. Studies evidently focus light on the fact that at 15°C females need less cooling to attain same temperature of skin as men. The epidermis of men was found to be thicker in summer whereas for

women the epidermis was thickest in rainy season, the epidermis being thinnest in spring for both sexes [44-47]. Xerosis which leads to rough and dry skin, it found prominently in winter [46]. Studies done by Tupker et al. [48] found that there exists a rhythm for susceptibility to SLS-induced irritation in response to non-active agents like substance P, methacholine, and trypsin, and it was concluded that such irritation is high in November compared to July (Table 2).

## CHRONOTHERAPEUTICS

Chronotherapeutics is over a time (day/night) purposely delivering different medications in unequal amount as it takes circadian rhythm into account. It is useful to predict the optimized administration time or to reduce adverse effects [49]. In some conditions, chronotherapeutics is very essential to predict delivery pattern of drug, primarily in neuroendocrine analogues to enhance the therapeutic outcomes. It does not insist need of new medicine to improve biological outcomes but it involves improved drug dosing application schedules of the established drug [50]. Following is the application of chronotherapeutic studies (Table 3).

**Table 1. Twenty-four-hour cycle effecting skin parameters**

Study	Parameters	Instrument	Sites	Peak	Low
Le Fur I et al. [34]	Skin temperature	Thermometer	Forearm	Late afternoon	-
			Face	Early morning	-
Yosipouitch et al. [35]	TEWL	Tevameter	Cheek	08:00 and 12:00	14:00
			Upper back	20:00	08:00-10:00
			Forearm		
			Forehead		
			Shin	12:00 and 04:00	08:00 and 22:00
pH	pH meter	Forehead	14:00 and 16:00	20:00	
		Shin			
Tsukahara et al. [36]	Skin wrinkles	Images of replicas	Facial	More noticeable in afternoon	Less in morning or night
Yosipovitch et al. [37]	Cutaneous blood flow	-	-	Late afternoon and late evening	Early in morning
Latreille et al. [38]	Sebum production	Sebuntry	Forehead	Noon	-
Bjarnason and Jordan [39]	Epidermal cell proliferation	Cell biopsies	-	23:00	Noon
Denda et al. [40]	Barrier recovery rate	Tape stripping	Forearm skin	03:00	20:00 and 23:00

**Table 2. Seasonal cycle effects on skin**

Study	Parameters	Maximum level	Minimum level
Uter et al. [41]	Skin hydration	Summer	Winter
Hellemans et al. [42]	Lipid peroxides	Spring	Summer
Gardner-Medwin et al. [43]	Melanin index	Late spring and early winter	-
	Moisture level and TEWL	Rainy season	Late spring
Sandby-Møller et al. [44]	Epidermal thickness	Summer (thick) for men	Spring
		Rainy season for women	
Kodydková et al. [45]	Catalase activity	Summer	Winter or rainy
Roger et al. [46]	Xerosis	Winter	-
Nakagawa et al. [47]	Corneum stiffness	Winter	-
Tupker et al. [48]	Sodium lauryl sulfate (SLS)-induced irritation	November	July

**Table 3. Studies on chrono therapeutics**

Class	Dosage form	Drug	Clinical application	Chrono therapeutics	Reference
Vitamin	Cream	Maxacalcitol	Used in skin inflammation (psoriasis)	Drug effective from the period 12–18 hours and showed no effect when taken in 0–6 hours	Yoshioka et al. [52]
	Creams	Retinoids	Perifollicular inflammation and microdome formation Acne	Applied only in evening not in the morning	Smolensky and Peppas [53]
Steroids	Cream, Lotion, Ointment	Betamethasone dipropionate	Psoriasis, atopic dermatitis	Longest effect when applied at 16:00 than at 09:00	Debon et al. [55]
Anesthetics	Transdermal injections	Ropivacaine	Local anesthetics	Longer effect in diurnal period (morning and afternoon) than in nocturnal (evening and night)	van de Kerkhof [54] and Debon et al. [55]
Beta agonist	Transdermal patch	Tulobuterol	Asthma	Application of trans epidermal patch at night would show stabilizing effect for 24 hours	Turek et al. [57]

### Vitamins

Vitamin D analogue maxacalcitrol has shown a remarkable inhibition in proliferation of keratin cycle [51]. High proliferation of epidermis leads to chronic inflammatory diseases like psoriasis, dermatitis etc. It also tends to initiate differentiation process within skin and thereby stands out as a reliable therapeutic option for treatment of psoriasis. 1,25-dihydroxy vitamin D3 is an active metabolic of vitamin D and it is necessary that active metabolite bind with vitamin D receptor (VDR) to show its therapeutic effect, which means therapeutic responsiveness of vitamin D analogues depends upon level of expression of VDR in tissue. Studies project that nuclear expression of VDR in mice skin had daily variation, exhibiting peak at 16:00 or mid-day. Yoshioka et al. [52] concluded that treatment carried out between 12 to 18 hours after light onset (HALO), i.e., active phase of VDR expression and then from 0 to 6 HALO had varied result. Inflammatory mediators like IL-23 and IL-17 as well as IL-17 were the prominent variables responsible for psoriatic inflammation. It was analyzed that expression of these variables were decreased while dosing at activated phase, but not significantly for inactive. Hence it can be concluded that skin protection activity of maxacalcitrol is greater when dosing is done in activated period. Maxacalcitrol is mostly used twice a day for treatment of psoriasis so rather than twice a day application once a day (in activated period) would show similar effect.

Topical retinoids (vitamin A) stand out to be a major option for the treatment of acne vulgaris as it tends to reduce perifollicular inflammation and decrease microdome formation [53]. Earlier it was applied in evening just because of its unstable structure but with recent advances in vehicle formulation, UV light stable formulations are available which can be applied in morning. Studies evidence that in evening there is high cell proliferation of skin, hence it is more therapeutically efficient to apply it in evening. Also along with skin proliferation TEWL is also high in evening as compared to that in morning and thus it may add moisturizer to retinoid dose regimen. Hence, in case of retinoids there are

two factors that govern therapeutic efficacy they are UV stability and skin proliferation, in both cases evening topical application is efficacious

### Steroids

About 65% of patients suffering with atopic dermatitis, chronic urticaria, and psoriasis complained of elevation in pruritus during evening due to lower level of cortisol in evening [54]. Betamethasone dipropionate (0.05%) ointment is used as topical steroid for treatment of dermal pathological conditions like dermatitis, inflammation and psoriasis. Topical corticosteroids are basically used to suppress hyper proliferation and inflammatory response. Debon et al. [55] carried out study on 0.05% betamethasone propionate (BP) with different form of vehicle formulations in which skin blanching response was analyzed by using chromometer, maximal as well as duration of response was studied. The studied formulation vehicles were Diprosone ointment, Diprolene Af cream, Diprosone lotion, Diprolene-augmented cream and Diprosone cream. In vivo study concluded that 0.05% of BP has circadian variation linked up with therapeutic efficacy. When drug was applied at 09:00 (morning), decrease in chromometer was measured at 21:00 and 23:00, i.e., after 12–13 hours of application. Similarly when drug was applied at 16:00 (evening), maximal activity was found in midnight, which concluded that has maximal activity at night irrespective of the time of application. To get the optimal benefit 0.05% of BP is used for treatment for duration of 2–6 hours, data suggest that when BP is applied in late afternoon then it produce a greater activity for longer as compared to application in morning. Therefore 0.05% of BP irrespective of time of application shows maximal activity at midnight and to enhance the period of maximum activity it is preferable to apply in afternoon for duration of 2 to 6 hours.

### Anesthetics

Ropivacaine is a local anesthetic prominently used as labor anal-

gesia. Various human and animal trials have shown variation in drug kinetics. In case of local anesthetic especially for labor it is mandatory to use specific dose or else it switches from efficacy to toxicity. This study was carried out on 194 women between at least 36 weeks of gestation, enrolled as per American Society of Anesthesiologists [55]. Epidural administration of 14 mL ropivacaine was carried out for 4 phases (morning, noon, evening, and night). Assessment of intensity of pain was determined using visual linear analogues. It was extrapolated that administration of epidural ropivacaine during the first stage of Labor has significantly longer effect in the diurnal compared to nocturnal phase. The duration was 28% longer in case of diurnal period over nocturnal. Secondly, it was analyzed that not considering chronobiological parameters can create a statistical error of type 1. Thereby we can say chronobiological parameters should be included and more explored in studies of obstetrical anesthesia.

### Beta agonist

Hokunalin is the first branded beta agonist patch developed for long-term treatment of chronic obstructive pulmonary disorder disease and asthma in Korea, China, and Japan. With its prominent safety and efficacy established since 13 years in clinical trial launched in Japan, this part of patch of Tulobuterol tends to follow circadian rhythm. Studies had found that respiratory functions suppress from late night till early morning, which is termed as “morning dip.” Hokunalin tape is a crystal reservoir system with reducing size of formulation that tends to prolong the release of drug. In order to balance suppressed function at night oral beta adrenoagonist and Hokunalin tape was administered around 20:00 and it was projected that with sustained release profile effective therapeutic dose was released in morning dip period. As compared to oral beta adrenoagonist, no excessive or increase in blood concentration in blood was found and over long period of time also effective blood concentration was maintained. Maximum blood concentration was attained for 9–12 hours and effective concentration was maintained nearly for 24 hours of application [56]. Hence, when patch is applied before bedtime, maximum concentration is achieved during morning dip suppressing asthmatic attacks. With its minimal adverse reaction it was found useful for child asthma patient as well.

## RECENT ADVANCEMENT IN SKIN CHRONOBIOLOGICAL STUDIES

### Prognosis

As we have seen earlier that human circadian system is synchronized by internal biological clock, but with age almost all the circadian system loses its functionality [57]. Hofman and Swaab [58] justified that with age that there is impairment in input systems like pupillary myosis, which through crystalline lens hastens the transmission of blue light in retina, hence there is depletion of ipRGCs as well as atrophy of dendritic tree of ipRGCs. Also, the functionality of main pacemaker SCN is influenced by age-related dif-

ferent neuronal impairment [58]. Aging can also modify output preferences evening to morning. Furthermore, irregular vasoconstriction and vasodilation mechanism tends to swag thermoregulation. As a result of such thermoregulatory changes there is change in body temperature as well as the amplitude of core temperature rhythm is decreased [59]. Martinez-Nicolas et al. [60] carried out studies on 44 young and 44 aged volunteers where their distal skin temperature (DST) was constantly monitored. Compared to the young participants, aged volunteers had high DST during evening. In young volunteers lowest skin temperature was observed in late evening (22:00 to 22:00), while in aged volunteers it was lowest at day time in the morning (10:00 to 12:00).

### Healing aid

Wound healing is a self-repair process of skin due to internal or external injuries. Aquaporins (AQPs) are present on the skin which acts as a basic transporter. It is specifically involved in cell migration and proliferation [61]. AQPs are integral proteins which facilitate water transportation. Recently the role of all AQPs in cell migration and proliferation has been postulated, role of AQP1 in cell migration was put forth by Saadoun et al. [62] The activity of all the aquaporin channels AQP3 [63] and AQP4 [64] in the activation of cell events was explored in keratinocyte migration studies which were performed on mouse and human cells by Matsunaga et al., [65] hence the relevance of AQP3 in keratinocyte proliferation was found in wound healing. AQP3 is a glycerol specific porin channel which is used for transportation of water and glycerol between and within the cells, which on further metabolism by Krebs cycle and glycolysis leads to production of ATP. The relationship of circadian rhythm and AQP3 was studied by Matsunaga et al. [65] whereby they concluded that expression of AQP gene by mApq3 mRNA was seen prominently at 21:00, i.e., at night and the physiological function of mApq3 was controlled by CLOCK genes [65].

### Thermal regulation

Brown fat is generally found in infants and is characterized by presence of large number of mitochondria and existence of mitochondrial uncoupling protein 1 (UCP1) within fat cells contribute to its brown color [66]. It leads to breakdown of glucose and fats which thereby generated heat. Infants lack the ability to shiver when they become cold so brown fats shield as a protective mechanism against cold temperature [67]. Acosta et al. [68] carried out a study on the circadian rhythm of brown fats breakdown. There was a cross sectional study performed on 82 young healthy participants (out of which 27% were males) in which breakdown of brown fats was studied using DST which was measured by thermochrons wireless temperature sensor (Buton DS-1922.L) for about 7–8 days. It was found that there was a constant increase in temperature during night phase with deduction in core body temperature [68]. Earlier studies postulated that during night there is increase in DST which is associated with short sleep latency, Glotzbach and Heller [69] studied connecting links between sleep

center and thermo regulators which demonstrated that at night there is high breakdown of brown fats and hence there is increase in body temperature. Similarly, in morning skin temperature is at trough, i.e., low fats breakdown.

## CONCLUSION

Skin plays a crucial role in dermal and transdermal delivery system. Release of drug from various dosage form like gels, creams, films and patches depends on the barrier histology of skin. From above studies, we can infer that 24 hours (light/dark phase) as well as seasonal cycles lead to varied changes in skin temperature, TEWL, skin texture as well as epidermal thickness. So accordingly, it is very necessary to select proper dose as well as dose delivery pattern to get optimal biological actions which is evident from various chronotherapeutic studies of drugs. In certain conditions, improper timing of dosage may lead to unexpected reactions which is also termed as chrono toxicological conditions. Recent studies have confirmed that chronobiological studies can be used as age predictor, to study wound healing or to determine breakdown of brown fats. It was also found that there exists a direct relation between sleep and dermatological diseases like eczema, psoriasis, or skin aging which can also throw light on new avenues for the treatment.

## Acknowledgments

None

## Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

## Author Contributions

Conceptualization: Jagruti Thoke, Shivangi Patel. Data curation: Jagruti Thoke. Resources: Shivangi Patel. Supervision: Anuradha Majumdar. Visualization: Jagruti Thoke, Shivangi Patel, Anuradha Majumdar. Writing—original draft: Jagruti Thoke. Writing—review & editing: Jagruti Thoke, Shivangi Patel, Anuradha Majumdar.

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