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(54) Benævnelse: **Melatonin-minitabletter og fremgangsmåde til fremstilling deraf**

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DESCRIPTION

Description

FIELD OF THE INVENTION

[0001] The present invention is generally directed to a patient-friendly drug delivery system for targeted populations, such as pediatric and geriatric patients.

BACKGROUND OF THE INVENTION

[0002] The goal of any drug delivery system is to provide a therapeutic amount of drug to the proper site in the body to achieve and then maintain the desired drug concentration. The most convenient and commonly employed route of drug delivery has historically been by solid oral dosage forms, particularly tablets and capsules. However, conventional tablets and capsules are limited by their rigid dose content. Furthermore, difficulty swallowing tablets and capsules is a problem for many patients, and can lead to a variety of adverse events and patient noncompliance with treatment regimens.

[0003] Melatonin is an indole-derived hormone produced at night by the pineal gland, and it plays a major physiological role in the regulation of sleep. Melatonin is produced and secreted into the plasma in a circadian rhythm which parallels the sleep-wake cycle. Exogenous melatonin is often administered as a sleep-aid. Melatonin is also used to treat dependence on, tolerance of, or addiction to a benzodiazepine, as described in U.S. Pat. No. 6,469,044. Treatment with melatonin has been shown to produce positive effects on sleep induction, sleep quality, and most importantly, day-time-functioning as well as quality of life. Melatonin use is not associated with development of dependency.

[0004] Melatonin is available in several solid oral dosage forms, particularly tablets and capsules. Existing melatonin oral dosage forms include immediate-release dosage forms, useful for treating delayed sleep onset, and prolonged release forms, useful for sleep maintenance. Oral absorption of melatonin is rapid and peak plasma levels are achieved 20 to 60 min following ingestion.

[0005] Existing melatonin products suffer from disadvantages including poor patient compliance issues due to difficulty in swallowing tablets, e.g., prolonged-release Circadin® tablets, which are about 8.1 mm in diameter and 3-5 mm thick. Due to these difficulties, some patients break, crush, or chew the prolonged-release Circadin® tablets, which results in loss of

its prolonged-release profile. As such, when Circadin® tablets are broken, crushed or chewed, they exhibit a release profile that is close to immediate-release melatonin. European patent application EP 0 724 878 A discloses a tablet comprising 2 mg melatonin, EudragitRS 100, lactose and calcium hydrogen phosphate. The diameter of the tablet is 7 mm. Therefore, similar problems are encountered as observed for Circadin ® tablets.

[0006] There exists a need in the art for improved drug delivery systems for use in patient populations having an inability to swallow tablets and capsules, e.g., pediatric and geriatric populations. Specifically, there exists a need in the art for novel mini-tablet formulations. Even more specifically, there exists a need in the art for novel melatonin mini-tablet formulations having precise pharmacologic and pharmacokinetic properties.

BRIEF SUMMARY OF THE INVENTION

[0007] The scope of the invention is determined by the appended claims.

[0008] The present disclosure is generally directed to a patient-friendly drug delivery form and system for patients that have difficulty swallowing melatonin oral dosage forms intact.

[0009] In one embodiment defined in claims 1-7, the present disclosure relates to a prolonged-release melatonin mini-tablet comprising 1 mg, 2 mg, 3 mg, 4 mg, or 5 mg melatonin and pharmaceutically acceptable carriers comprising calcium hydrogen phosphate dihydrate, ammonio methacrylate copolymer and lactose monohydrate, wherein the ratio between melatonin, ammonio methacrylate copolymer, calcium hydrogen phosphate dihydrate and lactose monohydrate by weight is 1 : 1.1-5.9 : 0.8-8.3 : 1.8-8.8, and wherein the mini-tablet has a diameter of less than or equal to 4 mm.

[0010] Another embodiment of the invention defined in claims 8-12 relates to a method of manufacturing a prolonged-release melatonin mini-tablet, the method comprising combining melatonin and pharmaceutically acceptable carriers to produce a mixture, and compressing the mixture into a mini-tablet having a diameter of less than or equal to 4 mm, wherein the pharmaceutically acceptable carriers comprise calcium hydrogen phosphate dihydrate, ammonio methacrylate copolymer and lactose monohydrate, and wherein the ratio between melatonin, ammonio methacrylate copolymer, calcium hydrogen phosphate dihydrate and lactose monohydrate by weight is 1 : 1.1-5.9 : 0.8-8.3 : 1.8-8.8.

[0011] The instant invention also relates to a prolonged-release melatonin mini-tablet as defined above for use in a method of inducing sleep in a human subject in need thereof, as defined in claims 13-15, the method comprising orally administering prolonged-release melatonin mini-tablet to the human subject

[0012] These and other embodiments of the invention will be described in further detail below.

BRIEF DESCRIPTION OF THE DRAWINGS

[0013] FIG. 1 is a plot of endogenous melatonin plasma levels (adapted from Arendt et al, J Clin Endocrinol Metab. 1985; 60(6): 1166-73. 1985).

DETAILED DESCRIPTION OF THE INVENTION

[0014] Mini-tablets according to the present disclosure satisfy long-felt, but unmet therapeutic needs to provide effective melatonin therapy to a patient suffering from impaired swallowing and/or undergoing polypharmacy therapy. A problem with existing melatonin oral dosage, either immediate-release dosage forms or prolonged-release dosage forms, is that they are difficult to swallow for some patients. As such, existing melatonin products suffer from disadvantages including patient compliance issues due to difficulty in swallowing tablets, e.g., prolonged-release Circadin® tablets, which are about 8.1 mm in diameter and 3-5 mm thick. Due to these difficulties, some patients break, crush, or chew the prolonged-release Circadin® tablets, which results in loss of its prolonged-release profile. As such, when Circadin® tablets are broken, crushed or chewed, they exhibit a release profile that is close to immediate-release melatonin. Due to these problems, before the present invention, there was a long-felt, but unmet need for a prolonged-release dosage form of melatonin with improved swallowing, flexible dosing, and better patient compliance. The present disclosure satisfies the need in the field by providing melatonin mini-tablets having improved swallowing, flexible dosing, and better patient compliance, as well as a controlled-release profile that achieves the same minimal blood levels of melatonin present at night in the brain of a human with a normal endogenous melatonin profile, shown in Fig. 1, as well as an acceptable safety profile.

[0015] Mini-tablets according to the present disclosure provide pharmacokinetic and pharmacodynamics properties such that a patient achieves a minimal blood level of about 60 to about 200 picograms melatonin per milliliter over at least four hours following the administration without suffering unacceptable side effects. In certain embodiments, mini-tablets according to the present disclosure provide pharmacokinetic and pharmacodynamics properties such that a patient achieves a minimal blood level of about 100 to about 200 picograms melatonin per milliliter over at least four hours following the melatonin administration without suffering unacceptable side effects.

[0016] In certain embodiments, the mini-tablets will release less than 50% of the active pharmaceutical ingredient within 1 hour of oral administration. In certain embodiments, the mini-tablets will release about greater than 70% of the active pharmaceutical ingredient within 6 hours of oral administration.

[0017] Mini-tablets also offer therapeutic benefits such as dose flexibility. Mini-tablets are flat or

slightly curved tablets with a diameter less than 4.0 mm. Mini-tablets are particularly suitable for polypharmacy therapy and dose-flexibility because they may be filled into a capsule, thereby allowing administration of specifically tailored dosage amounts or drug cocktails for personalized patient therapy. Mini-tablets facilitate the simultaneous administration of non-compatible drugs (*i.e.* drugs that can't otherwise be formulated together). Mini-tablets may include immediate release, delayed release, and/or controlled release formulations. Due to increased surface area in relation to volume, a drug can be released more efficiently from mini-tablets compared to traditional tablets.

[0018] Mini-tablets are especially promising for use in pediatric populations because a smaller tablet is more likely to be acceptable to children. Studies have found that mini-tablets are a potential dosage form suitable for 2-6 year olds (based on placebo tablets 3 mm in diameter) (Thomson, S.A. et al., Pediatrics, 2009; 123: e235-e8.). Other studies have found that very young children (6-12 months) were fully capable of swallowing mini-tablets of 2 mm diameter and that they often preferred them to sweet liquid formulations. (Spomer, N., et al., Arch. Dis. Child., 2012; 97:283-86.) As used herein, a "pediatric patient" or "pediatric subject" means a human between 2 and 18 years of age.

[0019] The mini-tablets include an active pharmaceutical ingredient and pharmaceutically acceptable carriers that are formulated so as to provide controlled-release of the active pharmaceutical ingredient according to a desired pharmacokinetic and pharmacodynamics profile. As used herein, the term "mini-tablet" means a flat or slightly curved pharmaceutical tablet having a diameter ranging between about 1.0 and 4.0 mm.

[0020] According to the present invention, the mini-tablets contain melatonin as an active ingredient. The melatonin is present in an amount of 1 mg, 2 mg, 3 mg, 4 mg, or 5 mg. Melatonin analogs which substantially imitate the function of melatonin in the human body and their use in place of melatonin in the formulations and methods are also described. Such analogs include ramelteon, agomelatine, tasimelteon, β-methyl-6-chloromalatonin and TK-301. Other acceptable analogs are known to persons of skill in the art and include those listed in Depreux et al., J. Med. Chem. 37:3231-3239 (1994).

[0021] According to an embodiment of the present invention, the mini-tablets comprise pharmaceutically acceptable carriers comprising ammonio methacrylate copolymer, calcium hydrogen phosphate dihydrate, and lactose monohydrate. The ammonio methacrylate copolymer may be ammonio methacrylate copolymer type A (U.S. Pharmacopeia #1029909) or ammonio methacrylate copolymer type B (U.S. Pharmacopeia #1029910) or any other polymer providing the desired controlled release profile.

[0022] The ratio between melatonin, ammonio methacrylate copolymer, calcium hydrogen phosphate dihydrate, and lactose monohydrate in the mini-tablet is 1 : 1.1-5.9 : 0.8-8.3 : 1.8-8.8 by weight. In exemplary embodiments, the ratio between melatonin, ammonio methacrylate copolymer, calcium hydrogen phosphate dihydrate, and lactose monohydrate in the mini-tablet may be 1 : 1.175 : 0.85 : 1.865. In further embodiments, the ratio between melatonin,

ammonio methacrylate copolymer, calcium hydrogen phosphate dihydrate and lactose monohydrate in the mini-tablet may be 1 : 5.88 : 8.25 : 8.75 by weight.

[0023] The drug-release profile is strongly affected by formulation parameters. The type and amount of release-controlling agent (usually polymer) used in mini-tablets similarly determines the drug-release patterns mainly by diffusion. The instant inventors found that, in matrix mini-tablet studies, increasing the amount of rate-controlling compound led to slower drug release, which may be due to the increased hydrophobicity of the system. It was discovered that increasing water-insoluble compounds (e.g., lactose) provides faster drug release due to their water solubility and drug diffusion promotion.

[0024] Mini-tablet production is similar to the production of standard tablets, but requires excellent powder flow due to the small dies. Mini-tablet production also requires exact control of process parameters and special caution during tablet press assembly in order to avoid tool damage. The present inventors discovered that it was not possible to use known information about Circadin® tablets to make *a priori* assumptions or predictions about the resultant flowability, dissolution and release characteristics of mini-tablet formulations. In addition, the present inventors discovered that it was not possible to use known information about a developed mini-tablet dosage form, e.g., the first melatonin mini-tablet, to make *a priori* assumptions or predictions about the resultant flowability, dissolution and release characteristics of a mini-tablet having a different dosage amount, e.g., a second mini-tablet.

[0025] The mini-tablets of the instant invention may be provided as compressed tablets. The compressed mini-tablets may be prepared using the process of direct compression. In the direct compression method of tablet production, dry ingredients are thoroughly mixed and then compressed into tablets. The process of direct compression is convenient and cost-effective. However, the process is highly influenced by the characteristics of the active pharmaceutical ingredient (API) as well as the excipients, including flowability, compressibility and compatibility. Excipients must be selected carefully, because the raw materials must demonstrate good flowability and compaction properties for successful operation. Good powder flowability is necessary in terms of providing uniform die filling and for production of mini tablets with acceptable weight and content uniformity.

[0026] In order to improve flowability of the API/excipients powder, dry granulation via slugging or roller compaction can be employed. Dry granulation is used for increasing the bulk density of powders, whilst increasing the particle size, resulting in better flowing material, which is a prerequisite for manufacturing tablets on high speed production equipment. Bonding the particles of various substances together during the compaction process reduces the tendency for segregation of powder particles of different substances. This results in an improvement of the homogeneity of the active ingredients (API) within the powder blend, causing an improvement of dose uniformity of such dosage forms.

[0027] In some embodiments, the mini-tablets are coated. The type of coating process used usually depends on the type of coating material to be applied, whereas the durability of the

tablet core depends both on the coating material and application process. Generally, one of the following types of coating procedures are used in the pharmaceutical industry: sugar coating, film coating, compression coating, and enteric coating.

[0028] The mini-tablets of the instant invention may be provided as a pharmaceutical formulation wherein, upon administration to a patient, the formulation releases melatonin over time such that the patient's melatonin plasma profile substantially simulates the melatonin plasma profile of a human having a normal endogenous melatonin profile.

[0029] The mini-tablet may be provided for administration to a patient who has trouble sleeping, or who suffers from a melatonin deficiency or distortion in comparison to a person with a normal endogenous plasma melatonin profile. The patient may be, for example, a pediatric patient, a geriatric patient, a disabled patient, a patient who has an autism spectrum disorder, a patient who has a neurogenetic disease, or a patient who has been diagnosed with dysphagia (difficulty swallowing).

[0030] As used herein, a "geriatric patient" or "geriatric subject" means a human of greater than 65 years of age. It is understood, that methods of medical treatment are described for illustrating the invention only, but not meant to be encompassed by the scope of the invention. However, the invention provides melatonin mini-tablets for use in medical treatment, as defined in claims 13-15.

[0031] A melatonin mini-tablet of the instant invention can be provided for administration to a patient, for example, once or twice daily at preselected times, in order to raise the level of melatonin in the patient's blood to a desired level. In a preferred embodiment, the amount of melatonin in the patient's blood will substantially simulate the normal plasma melatonin night time profile, as shown in Fig. 1. Preferably, the mini-tablet will be provided for administration before sleep, so that the desired profile will be achieved while the patient sleeps. Optionally, the melatonin mini-tablet may be provided for administration between a first sleep period, such as before bedtime, and a second sleep period, such as during a period of waking in the middle of the night. In some embodiments, a first mini-tablet may be provided for administration before a first sleep period, and a second mini-tablet may be administered between the first sleep period and a second sleep period. The first mini-tablet and the second mini-tablet may contain different amounts of melatonin.

[0032] In other embodiments the melatonin mini-tablet may be provided for administration several hours before the desired bedtime to reset the biological clock in subjects suffering from transient or chronic circadian rhythms disorders (for example jet lag following trans meridian flight, sleep following night shift, clock resetting in totally blind individuals with non-24h sleep wake disorder, delayed sleep phase syndrome).

[0033] In certain embodiments, melatonin mini-tablets are provided for administration in combination with a substance which alters the phase position or shape of the patient's melatonin plasma profile, such as a melatonin receptor modifier or a melatonin profile modifier.

As melatonin is known to act at a specific time of day and be ineffective at other times of the day due to diurnal variations in melatonin receptors, it is important that melatonin and its receptors be present simultaneously. Melatonin receptor modifiers include short-acting benzodiazepines, such as oxazepam and triazolam; melatonin profile modifiers include benzodiazepines, such as alprazolam (McIntyre, et al., Chronobiology International, 10:205-213 [1993]), beta-blockers, such as propranolol (Brismar et al., Acta Medica Scandinavia, 223:525 [1988]), serotonin uptake inhibitors, such as desipramine (Franey et al., British J. Med. Pharmacol., 22:73 [1986]), acetylcholesterase inhibitors (Wong, C.W., Drugs Aging, 33(7):451-60 [2016]), and alpha antagonists, such as clonidine (Lewy et al., J. Pharmaceutics and Pharmacology, 38:55 [1986]).

[0034] In certain embodiments, the melatonin mini-tablets can be provided for administration in combination with light therapy. Light can be used to adjust a patient's biological clock. In addition, a patient who has insufficient exposure to light may have internal desynchronization of his bodily rhythms, which may result in melatonin being produced during the daytime rather than at night. In such cases, treatment only with melatonin will not be fully satisfactory, as the patient also will have melatonin in his blood during the daytime. Light is known to suppress melatonin production by the pineal gland, so in these circumstances light can be used to help blunt melatonin production during the day. Exposure to light during the daytime can be continued until the patient's biological clock stabilizes. Thus, in accordance with the present invention, it would be desirable to encourage exposure to light during the day and avoidance of light at night.

[0035] The present invention is illustrated by the following examples, which are not intended to be limiting.

EXAMPLES

Example 1 - Development of a first melatonin mini-tablet

[0036] The inventors sought to develop a first melatonin mini-tablet. 2 mg controlled-release melatonin tablets (about 8 mm diameter) were commercially available under the brand name Circadin®, and the inventors initially attempted to use the formulation of Circadin® to develop the first melatonin mini-tablets. The commercial Circadin® formulation contains a specific combination of ammonio methacrylate copolymer type B, calcium hydrogen phosphate dihydrate, and lactose monohydrate. The formulation of Circadin® is described in U.S. Pat. No. 6,469,044. The 2 mg Circadin® formulation is also shown in Table I, below.

[0037] The inventors initially attempted to prepare a melatonin mini tablet by direct compression using the same inactive ingredients as those used in commercial Circadin® 2 mg.

However, it was impossible to use the Circadin® formulation to produce a melatonin mini-tablet because an unacceptable difference in melatonin release rate was recognized. Specifically, decreasing the tablet size from the standard level (8 mm) to mini-level (≤ 4 mm) resulted in unacceptably fast drug release due to increased surface-to-volume ratio. Additionally, the Circadin® tablet was produced using wet granulation, and required the use of an organic solvent as a granulation liquid, causing health, safety, disposition and residual level issues. Accordingly, it was necessary to develop a completely novel formulation and manufacturing process in order to produce mini-tablets that could achieve the same pharmacokinetic and pharmacodynamic properties as the Circadin® tablet.

[0038] Various formulations for the melatonin mini-tablet were produced by dry blending. Initially, the tablets were formulated with decreased ratios of lactose monohydrate and an increased ratio of calcium hydrogen phosphate dihydrate when compared to Circadin® 2 mg. These mini-tablets demonstrated promising dissolution profiles, but were still outside the Circadin® 2 mg dissolution specification.

[0039] In subsequent studies, two additional lots were prepared using an increased amount of calcium hydrogen phosphate (55.5% by weight), and 12% or 15% by weight of ammonio methacrylate copolymer type B, respectively. These variations were made in an attempt to slow down the dissolution profile of the first melatonin formulation. Mini-tablets containing 35% lactose and about 33% of calcium hydrogen phosphate gave optimal results with a dissolution profile falling between the low and high limit dissolution specifications. Table I shows the ratio of ingredients (by weight) in the first melatonin mini-tablet formulation, in comparison to the Circadin® formulation.

Table I

	Melatonin	Calcium Hydrogen Phosphate Dihydrate	Ammonio Methacrylate Copolymer, Type B or A	Lactose
First Minitab	1	8.25	5.87	8.75
2mg Circadin	1	20	20	40

Example 2 - Development of a second melatonin mini-tablet

[0040] In order to produce an acceptable second melatonin mini-tablet, it was necessary to design, manufacture and test at least 10 different formulations. The initial formulations were based on the first mini-tablet formulation shown in Table I. Table II presents seven different tablet formulations (Ex. 1 - Ex. 7), for which the proportions of calcium hydrogen phosphate dihydrate, ammonio methacrylate copolymer, and lactose monohydrate were varied in order to obtain adequate physical mini-tablet properties, and to obtain acceptable dissolution profiles.

[0041] For the first formulation (Ex. 1), the increased amount of melatonin was compensated for by reducing the amount of calcium hydrogen phosphate. However, the compressed tablets revealed a dissolution profile which was too slow compared to the target profile.

[0042] Lactose monohydrate is a fast-release agent. Based on the assumption that the hydrophilic lactose will increase the dissolution rate, a second prototype (Ex. 2) was manufactured with an increased amount of lactose. In order to compensate for the increased lactose, the amount of ammonio methacrylate copolymer type B was decreased, while calcium hydrogen phosphate was kept the same as the first prototype. The dissolution profile of tablets of the second prototype was surprisingly too slow.

[0043] After the confirmation that higher lactose in the second prototype increased the dissolution rate, the third prototype (Ex. 3) was manufactured with a maximum amount of lactose. To compensate for the increased amount of lactose, the amount of ammonio methacrylate copolymer type B and calcium hydrogen phosphate was reduced. Testing of this third prototype revealed that the dissolution profile of the mean values complied with the target dissolution profile of the first mini-tablet formulation. However, there was an unacceptably high variability among the tested samples (8 tabs).

[0044] Assuming that the high variability of the third prototype was due to incomplete matrix formation, the fourth prototype (Ex. 4) was prepared with an increased amount of ammonio methacrylate copolymer type B. This increase was compensated for by a decrease in calcium hydrogen phosphate. Testing of this fourth prototype showed that the mean dissolution rate was unacceptably slow and did not meet the target specifications.

[0045] In an attempt to get a formulation with a faster dissolution rate, a fifth prototype (Ex. 5) was manufactured. While the component combinations were similar to the second formulation, a different quality of lactose, having a smaller particle size, was used. Testing the fifth prototype revealed that the particle size of lactose did not influence the dissolution of melatonin. Accordingly, it was necessary to design and test further prototypes. Sixth and seventh prototypes (Ex. 6 and Ex. 7) were manufactured using a more permeable grade of ammonio methacrylate copolymer (type A). The sixth and seventh prototypes were based on the first and second prototypes, respectively. The dissolution profiles of the sixth and seventh prototypes were acceptable.

Table II

	Ex. 1	Ex. 2	Ex 3	Ex. 4	Ex. 5	Ex. 6	Ex. 7
Melatonin	1	1	1	1	1	1	1
Type of Ammonium Methacrylate	B	B	B	B	B	A	A
Ammonio Methacrylate	1.17	0.78	0.6	0.8	0.8	1.18	0.78
Calcium Hydrogen Phosphate	0.85	0.85	0.6	0.4	0.4	0.85	0.85
Lactose Monohydrate	1.75	2.15	2.58	2.58	2.58	17.5	21.5

Example 3 - Human Clinical Trial

[0046] The effect of prolonged-release (PR) melatonin mini-tablets according to the present invention was determined in a study population consisting of randomized 125 Children with Autism Spectrum Disorder (ASD) and/or neurogenetic diseases. The children were screened and entered a 4 weeks sleep hygiene period, those who did not respond to the non-pharmacological treatment continued into a single blind placebo run-in for 2 weeks; those who were still eligible after these 2 weeks, were randomized to receive either 2 mg active treatment (2X 1mg PR melatonin mini-tablet) or placebo for 3 weeks. After these 3 weeks those who did not respond to the treatment were escalated to a dose of 5 mg (5X 1mg PR melatonin mini-tablet) in both treatment groups for another 10 weeks double blind period (altogether 13 weeks double blind treatment period). After this period, children continued for a 13 week open label period on the dose that they took up to that point.

[0047] Sleep parameters were measured by a Daily Sleep and Nap Diary that was completed by the parents 2 weeks before each visit. For each subject, the mean sleep variable was calculated as the mean of the last 14 days prior to each scheduled visit; the change from baseline in mean variable was analyzed using a mixed-effects model for repeated-measures (MMRM).

[0048] It was found that the PR melatonin mini-tablet significantly improved total sleep time over placebo after 3 months (SE= standard error) as shown in Table III.

Table III

	Adjusted treatment mean sleep variable (SE)		Treatment difference (SE)	p-value
	PR melatonin mini-tablets (N=58)	Placebo (N=61)		
Week 15	56.16 (10.46)	18.73 (10.82)	32.43 (15.10)	0.034

[0049] It was also found that PR melatonin MT significantly improved sleep initiation (SL) over placebo after 3 months as shown in Table IV.

Table IV

	Adjusted treatment mean sleep initiation (SE)		Treatment difference (SE)	p-value
	PR melatonin mini-tablets (N=58)	Placebo (N=61)		
Week 15	-37.88 (6.82)	-12.58 (7.00)	-25.30 (9.79)	0.011

[0050] Conclusion: PR melatonin mini-tablets treatment improves sleep in ASD children suffering from sleep disturbances by shortening sleep initiation and improving sleep maintenance.

[0051] While particular embodiments of the invention have been particularly described hereinabove, it will be appreciated that the present invention is defined in the claims.

REFERENCES CITED IN THE DESCRIPTION

Cited references

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Patentkrav

1. Melatonin-minitablet med forlænget frigivelse, omfattende:
1 mg, 2 mg, 3 mg, 4 mg eller 5 mg melatonin; og
hvor farmaceutisk acceptable bærere omfatter calciumhydrogenphosphatdihydrat, ammonio-methacrylatcopolymer og lactosemonohydrat,
hvor vægtforholdet mellem melatonin, ammonio-methacrylatcopolymer, calciumhydrogenphosphatdihydrat og lactosemonohydrat er 1 : 1,1-5,9 : 0,8-8,3 : 1,8-8,8; og
hvor minitabletten har en diameter på mindre end eller lig med 4 mm.

2. Melatonin-minitablet med forlænget frigivelse ifølge krav 1, hvor ammonio-methacrylatcopolymeren er ammonio-methacrylatcopolymer type A eller ammonio-methacrylatcopolymer type B.

3. Melatonin-minitablet med forlænget frigivelse ifølge et hvilket som helst af kravene 1-2, hvor minitabletten yderligere omfatter hurtigtopløsende sukker eller alkohol, som ikke er lactose.

4. Melatonin-minitablet med forlænget frigivelse ifølge et hvilket som helst af kravene 1-3, hvor minitabletten er coatet med en farmaceutisk acceptabel coating.

5. Minitablet med forlænget frigivelse af melatonin ifølge krav 4, hvor den farmaceutisk acceptable coating er valgt blandt sukkercoating, filmcoating, kompressionscoating og enterisk coating.

6. Melatonin-minitablet med forlænget frigivelse ifølge et hvilket som helst af kravene 1-5, hvor melatonin-minitabletten med forlænget frigivelse har en frigivelsesprofil med mindre end 50% melatoninfrigivelse inden for 1 time og ca. mere end 70% melatoninfrigivelse inden for 6 timer.

7. Melatonin-minitablet med forlænget frigivelse ifølge et hvilket som helst af kravene 1-6, hvor minitabletten er formuleret således, at den giver et minimalt blodniveau på ca. 60 til ca. 200 picogram, fortrinsvis ca. 100 til ca. 200 picogram melatonin pr. milliliter i løbet af mindst fire timer efter en menneskelig patients orale indtagelse af melatonin-minitabletten med forlænget frigivelse.

8. Fremgangsmåde til fremstilling af en melatonin-minitablet med forlænget frigivelse, hvilken fremgangsmåde omfatter:
kombinering af melatonin og farmaceutisk acceptable bærere til frembringelse af en blanding; og
komprimering af blandingen til en minitablet med en diameter på mindre end eller lig med 4 mm,
hvor de farmaceutisk acceptable bærere omfatter calciumhydrogenphosphatdihydrat, ammonio-methacrylatcopolymer og lactosemonohydrat, og
hvor vægtforholdet mellem melatonin, ammonio-methacrylatcopolymer, calciumhydrogenphosphatdihydrat og lactosemonohydrat er 1 : 1,1-5,9 : 0,8-8,3 : 1,8-8,8, hvor minitabletten omfatter 1 mg, 2 mg, 3 mg, 4 mg eller 5 mg melatonin.

9. Fremgangsmåde ifølge krav 8, endvidere omfattende et trin med coating af tabletterne med en farmaceutisk acceptabel coating.

10. Fremgangsmåde ifølge krav 9, hvor den farmaceutisk acceptable coating er valgt blandt sukkercoating, filmcoating, kompressionscoating og enterisk coating.

11. Fremgangsmåde ifølge et hvilket som helst af kravene 8-10, hvor minitabletten yderligere omfatter hurtigtopløsende sukker eller alkohol, som ikke er lactose.

12. Fremgangsmåde ifølge et hvilket som helst af kravene 8-11, hvor ammonio-methacrylatcopolymeren er ammonio-methacrylatcopolymer type A

eller ammonio-methacrylatcopolymer type B.

13. Minitablet med forlænget frigivelse ifølge et hvilket som helst af kravene 1-7 til anvendelse i en fremgangsmåde til inducering af søvn hos et menneskeligt individ med behov herfor, hvor fremgangsmåden omfatter oral indgivelse af minitabletten med forlænget frigivelse til det menneskelige individ.

14. Melatonin-minitablet med forlænget frigivelse til anvendelse ifølge krav 13, hvor det menneskelige individ er en pædiatrisk patient, en geriatrisk patient, en handicappet patient, en patient, der har en autismespektrumforstyrrelse, en patient, der har en neurogenetisk sygdom, eller en patient, der er blevet diagnosticeret med dysfagi.

15. Melatonin-minitablet med forlænget frigivelse til anvendelse ifølge krav 13 eller krav 14, hvor det menneskelige individ har en autismespektrumforstyrrelse.

DRAWINGS

Drawing

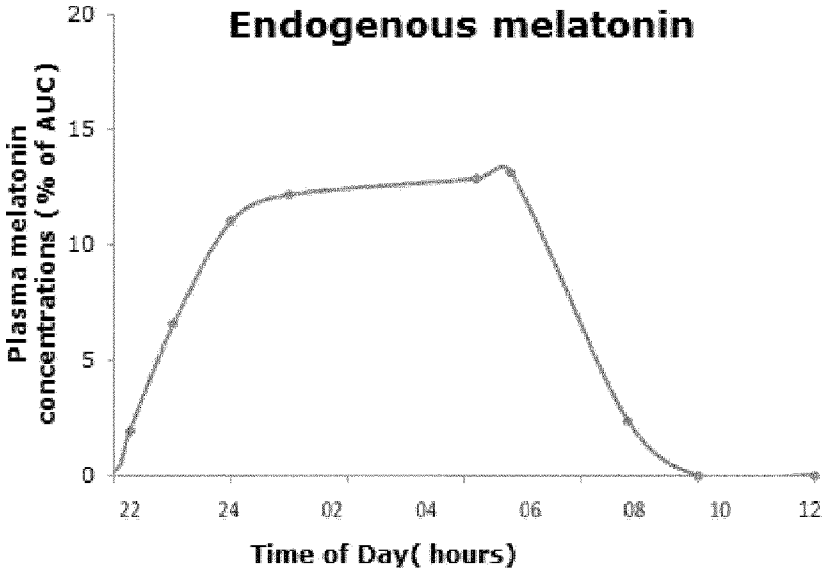

FIG. 1