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.

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.

SUMMARY

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.

In one aspect, the present disclosure refers to a controlled-release melatonin mini-tablet comprising: a therapeutically effective amount of melatonin; and one or more pharmaceutically acceptable carriers; wherein the mini-tablet has a diameter of less than or equal to 4 mm and, 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 about 1:1.1-5.9:0.8-8.3:1.8-8.8.

In another aspect, the present disclosure refers to a method of manufacturing a controlled-release melatonin mini-tablet, the method comprising: combining a therapeutically effective amount of melatonin and pharmaceutically acceptable carriers to produce a mixture; and compressing the mixture into mini-tablets that each have 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 about 1:1.1-5.9:0.8-8.3:1.8-8.8.

In another aspect, the present disclosure refers to a controlled release melatonin mini-tablet, produced by the method as disclosure herein.

In another aspect, the present disclosure refers to a Use of the controlled release melatonin mini-tablet of any one of claims 1-7 or 11: a. in a method of inducing sleep in a patient in need thereof, the method comprising: administering the controlled-release mini-tablet of claim 1 to the

patient, wherein sleep is induced in the patient; b. in a method of administering melatonin to a patient who has difficulty swallowing tablets or capsules, the method comprising administering the controlled-release mini-tablet to the patient; or c. in a method of inducing a phase shift of the circadian rhythm of a patient in need thereof, the method comprising administering the controlled-release mini-tablet to the patient, wherein a phase shift in the patient's circadian rhythm is induced.

In another aspect, the present disclosure refers to a method of safely inducing and maintaining sleep in a patient in need thereof, the method comprising: a. providing a pharmaceutical product comprising one or more melatonin mini-tablets capable of inducing sleep in a patient and achieving a minimal blood level of about 60 to about 200 picograms melatonin per milliliter over at least four hours following the administration without inducing unacceptable side effects in a human; and b. administering the one or more mini-tablets to the patient, wherein said pharmaceutical product is manufactured by combining a therapeutically effective amount of melatonin and pharmaceutically acceptable carriers to produce a mixture, and compressing the mixture into one or more mini-tablets that each have a diameter of less than or equal to 4 mm; and 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 about 1:1.1-5.9:0.8-8.3:1.8-8.8.

In another aspect, the present disclosure refers to a pharmaceutical mini-tablet formulation comprising melatonin in combination with pharmaceutical carriers, wherein, upon administration to a patient, the mini-tablet 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, and 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 about 1:1.1-5.9:0.8-8.3:1.8-8.8.

In one example, the present disclosure relates to a melatonin mini-tablet that contains a therapeutically effective amount of melatonin and one or more pharmaceutically acceptable carriers, wherein the mini-tablet has a diameter of less than or equal to 4 mm.

Another example of the disclosure relates to a method of manufacturing a melatonin mini-tablet, the method comprising combining a therapeutically effective amount of melatonin and one or more pharmaceutically acceptable carriers to produce a mixture, and compressing the mixture into mini-tablets that each have a diameter of less than or equal to 4mm.

The instant disclosure also relates to a method of inducing sleep in a patient in need thereof, the method comprising orally administering to the patient a pharmaceutical mini-tablet comprising a therapeutically effective amount of melatonin, wherein sleep is induced in the patient. Additionally, the disclosure relates to a method of orally administering melatonin to a patient who has difficulty swallowing tablets, the method comprising orally administering to the patient a pharmaceutical mini-tablet comprising a therapeutically effective amount of melatonin.

The disclosure further relates to a pharmaceutical mini-tablet formulation comprising melatonin in combination with at least one pharmaceutical carrier, diluent or coating, wherein, upon administration to a human, the formulation releases melatonin over time such that the person's melatonin plasma profile substantially simulates the melatonin plasma profile of a human having a normal endogenous melatonin profile.

In certain examples, the disclosure further relates to a pharmaceutical formulation containing a plurality of mini-tablets containing melatonin. In certain examples, the plurality of mini-tablets in the pharmaceutical formulation is a combination of immediate release and controlled-release mini-tablets. In other examples, each of the plurality of mini-tablets in the pharmaceutical formulation is a controlled-release mini-tablet. In other examples, each of the plurality of mini-tablets in the pharmaceutical formulation is an immediate-release mini-tablet provided in the form of a pharmaceutical formulation that has a controlled-release profile, e.g., in a controlled release capsule.

Further examples of the disclosure comprise a method of inducing sleep in a patient in need thereof, the method comprising manufacturing a melatonin mini-tablet, and orally administering to the patient a pharmaceutical mini-tablet comprising a therapeutically effective amount of melatonin.

These and other examples of the disclosure will be described in further detail below.

BRIEF DESCRIPTION OF THE DRAWINGS

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

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

CLAIMS

1. A controlled-release melatonin mini-tablet comprising:

   a therapeutically effective amount of melatonin; and

   pharmaceutically acceptable carriers;

   wherein the mini-tablet has a diameter of less than or equal to 4 mm and, 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 about 1:1.1-5.9:0.8-8.3:1.8-8.8.

2. The controlled-release melatonin mini-tablet of claim 1, wherein the mini-tablet is formulated such that it produces a minimal blood level of about 60 to about 200 picograms melatonin per milliliter over at least four hours after oral ingestion of the controlled-release melatonin mini-tablet by a human patient.

3. The controlled-release melatonin mini-tablet of claim 1 or claim 2, wherein the mini-tablet is formulated such that it produces a minimal blood level of about 100 to about 200 picograms melatonin per milliliter over at least four hours after oral ingestion of the controlled-release melatonin mini-tablet by a human patient.

4. The controlled-release melatonin mini-tablet of any one of claims 1 to 3, wherein the ammonio methacrylate copolymer is ammonio methacrylate copolymer type A.

5. The controlled-release melatonin mini-tablet of any one of claims 1 to 3, wherein the ammonio methacrylate copolymer is ammonio methacrylate copolymer type B.

6. The controlled-release melatonin mini-tablet of any one of claims 1 to 5, wherein the mini-tablet and /or the one or more pharmaceutically acceptable carriers comprise a fast dissolving sugar or alcohol that is not lactose.

7. The controlled-release melatonin mini-tablet of any one of claims 1 to 6, wherein the mini-tablet is coated with a pharmaceutically acceptable coating.

8. A method of manufacturing a controlled-release melatonin mini-tablet, the method comprising:

combining a therapeutically effective amount of melatonin and pharmaceutically acceptable carriers to produce a mixture; and

compressing the mixture into mini-tablets that each have 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 about 1:1.1-5.9:0.8-8.3:1.8-8.8.

9. The method of claim 8, further comprising a step of coating the tablets with a pharmaceutically acceptable coating.

10. The method of claim 8 or claim 9, wherein the combining step comprises dry blending the therapeutically effective amount of melatonin and the one or more pharmaceutically acceptable carriers.

11. A controlled release melatonin mini-tablet, produced by the method of any one of claims 8 to 10.

12. Use of the controlled release melatonin mini-tablet of any one of claims 1-7 or 11: a. in a method of inducing sleep in a patient in need thereof, the method comprising:

administering the controlled-release mini-tablet of claim 1 to the patient,

wherein sleep is induced in the patient,

b. in a method of administering melatonin to a patient who has difficulty swallowing tablets or capsules, the method comprising administering the controlled-release mini-tablet to the patient, or

c. in a method of inducing a phase shift of the circadian rhythm of a patient in need thereof, the method comprising administering the controlled-release mini-tablet to the patient, wherein a phase shift in the patient's circadian rhythm is induced.

13. The use of claim 12, wherein the patient is a pediatric patient.

14. The use of claim 12, wherein the patient is a geriatric patient.

15. The use of any one of claims 12 to 14, wherein the mini-tablet is administered before sleep.

16. The use of any one of claims 12 to 14, wherein the mini-tablet is administered between a first sleep period and a second sleep period.

17. The controlled release melatonin mini-tablet of any one of claims 1-7, 11, the method of any one of claims 8 to 10, or the use of any one of claims 12 to 16, wherein the therapeutically effective amount is 1mg, 2mg, 3mg, 4mg or 5mg.

18. A method of safely inducing and maintaining sleep in a patient in need thereof, the method comprising:
    a. providing a pharmaceutical product comprising one or more melatonin mini-tablets capable of inducing sleep in a patient and achieving a minimal blood level of about 60 to about 200 picograms melatonin per milliliter over at least four hours following the administration without inducing unacceptable side effects in a human, and
    b. administering the one or more mini-tablets to the patient, wherein said pharmaceutical product is manufactured by combining a therapeutically effective amount of melatonin and pharmaceutically acceptable carriers to produce a mixture, and compressing the mixture into one or more mini-tablets that each have a diameter of less than or equal to 4 mm; and 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 about 1:1.1-5.9:0.8-8.3:1.8-8.8.

19. A pharmaceutical mini-tablet formulation comprising melatonin in combination with pharmaceutical carriers, wherein, upon administration to a patient, the mini-tablet 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, and 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 about 1:1.1-5.9:0.8-8.3:1.8-8.8.