down predictive processing and related feedback connectivity, whilst theta and delta power is classically associated with REM sleep dreaming and related 'visionary' states. It is described that these results relate injection of DMT fumarate to the experience of feeling profoundly immersed in an entirely other world.

Silviera et al (Molecules, 2020, 25, 2072) discuss the stability profile of ayahuasca. Piries et al (Phytochem. Anal. 2009, 20, 149-153) discuss a method for simultaneous determination of the main active constituents found in samples of ayahuasca tea.

According to the Human Metabolome Database (HMDB), N,N-dimethyltryptamine degrades relatively quickly in solution (see specifically http://www.hmdb.ca/metabolites/HMDB0005973). Consequently, there is a need in the art for injectable solutions of DMT that are stable over longer periods of time, and are clinically acceptable, and are formulated in a manner that minimises discomfort and costs associated with administering dimethyltryptamine-based medicines. The present disclosure addresses this need.

SUMMARY OF THE INVENTION

The invention is defined in the independent claims. Some optional features of the invention are defined in the dependent claims.

The present disclosure generally relates to aqueous pharmaceutical formulations suitable for both intramuscular injection and nebulised inhalation, comprising about 10 mg/ml or greater (as freebase equivalent) of a salt of an optionally substituted dimethyltryptamine compound, and water, wherein the formulations have pH values of from 5 to 6.5 and typical osmolalities of from about 250 to about 350 mOsm/Kg. The formulations may have a pH of from about 5 to about 6, or a pH of from 5 to 6. These formulations are capable of delivering an effective dose of an optionally substituted dimethyltryptamine compound for use in psychedelic assisted therapy (pharmacological-assisted psychotherapy) within a volume of 5 ml or less, making them particularly suitable for both intramuscular injection and nebulised inhalation. Preferably, the formulations are capable of delivering an effective dose of an optionally substituted dimethyltryptamine compound for use in psychedelic assisted therapy within a volume of 4 ml or less, 3 ml or less, 2.5 ml or less, 2 ml or less, 1 ml or less, or 0.5 ml or less.

The present disclosure addresses the problem of providing pharmaceutical formulations suitable for intramuscular injection or nebulised inhalation with substantially reduced degradation products compared with known formulations when stored under standard or stressed conditions. This is indicative of improved shelf-life over such known

pharmaceutical formulations. Moreover, deuterated optionally substituted dimethyltryptamine compounds, such as deuterated compounds of Formula IA or IB, show significantly improved exposure and Cmax by intramuscular injection, compared with their undeuterated analogues (see Figures 1A and 1B). Thus, the present disclosure provides for the first time an aqueous pharmaceutical formulation with an effective dose (for at least an average weight human) of an optionally substituted dimethyltryptamine compound via intramuscular injection or nebulised inhalation with a volume of 5 ml or less, preferably 4 ml or less, or 3 ml or less, or 2.5 ml or less, or 2 ml or less, or 1 ml or less, or 0.5 ml or less.

Accordingly, viewed from a first aspect, the disclosure provides a pharmaceutical formulation suitable for both intramuscular injection and nebulised inhalation, comprising a salt of an optionally substituted dimethyltryptamine compound, a base agent, water; and optionally a buffer which is separate to the salt; wherein the formulation has a pH of from about 5 to about 6.5, a concentration of about 10 mg/ml as freebase or greater, and an osmolality of from about 250 to about 350 mOsm/Kg. The formulation may have a pH of from about 5 to about 6, or a pH of from 5 to 6.

In some embodiments of the first aspect of the disclosure , the formulation comprises from about 10 mg/ml to about 150 mg/ml, from about 10 mg/ml to about 100 mg/ml, from about 10 mg/ml to about 80 mg/ml, from about 15 mg/ml to about 70 mg/ml, from about 15 mg/ml to about 50 mg/ml, or from about 20 mg/ml to about 40 mg/ml (as freebase equivalent) of a salt of an optionally substituted dimethyltryptamine compound. Typically, the formulation comprises about 25 mg/ml (as freebase equivalent) of a salt of an optionally substituted dimethyltryptamine compound.

In preferred embodiments of the first aspect of the present disclosure , the pharmaceutical formulation comprises an effective dose of an optionally substituted dimethyltryptamine compound for use in psychedelic assisted therapy within a volume of 5 ml or less, preferably within a volume of 4 ml or less, 3 ml or less, 2.5 ml or less, 2 ml or less, 1 ml or less, or 0.5 ml or less.

Viewed from a second aspect, the disclosure provides a kit suitable for preparing a formulation of the first aspect, said kit comprising a salt of an optionally substituted dimethyltryptamine compound; a base agent, optionally a buffer which is separate to the salt, and optionally a tonicity agent and/or pH adjuster. In preferred embodiments of the second aspect of the present disclosure, the kit comprises an effective dose of an optionally substituted dimethyltryptamine compound for use in psychedelic assisted therapy within a volume of 5 ml or less, preferably within a volume of 4 ml or less, 3 ml or less, 2.5 ml or less, 2 ml or less, 1 ml or less, or 0.5 ml or less.

Viewed from a third aspect, the disclosure provides a method of preparing a pharmaceutical formulation of the first aspect, comprising contacting the salt, water, a base agent, optionally a buffer which is separate to the salt, and optionally a tonicity agent and/or pH adjuster. In preferred embodiments of the third aspect of the present disclosure, the formulation comprises an effective dose of an optionally substituted dimethyltryptamine compound for use in psychedelic assisted therapy within a volume of 5 ml or less, preferably within a volume of 4 ml or less, 3 ml or less, 2.5 ml or less, 2 ml or less, 1 ml or less, or 0.5 ml or less.

In some embodiments, the formulation or kit of the first and second aspect comprises a tonicity agent. In some embodiments, the formulation or kit of the first and second aspect comprises a pH adjuster. In some embodiments, the formulation or kit of the first and second aspect comprises a buffer. In some embodiments, the formulation or kit of the first and second aspect comprises a buffer and a tonicity agent. In some embodiments, the formulation or kit of the first and second aspect comprises a buffer and a pH adjuster. In some embodiments, the formulation or kit of the first and second aspect comprises a buffer, a tonicity agent and a pH adjuster.

Owing to the known instability of the free base of N,N-dimethyltryptamine in solution, solutions comprising optionally substituted dimethyltryptamine compounds are generally prepared immediately before or close to the time of use, i.e. storage of solutions of optionally substituted dimethyltryptamine compounds is avoided. Alternatively, solutions of optionally substituted dimethyltryptamine compounds are frozen. The inventors have found that when a buffer, which is separate to the salt, is used, the resultant formulations are more stable than formulations prepared without a buffer separate to the salt. In addition, when a container adapted to prevent penetration of ultraviolet light is used, the resultant formulations are more stable than those stored in containers that allow for ultraviolet light penetration.

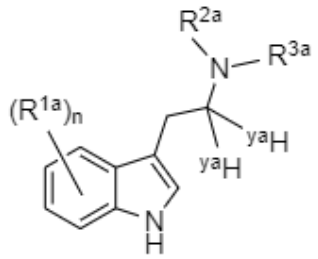
Viewed from a fourth aspect, the disclosure provides a formulation of the first aspect or kit of the second aspect for use as a medicament or for use in combination with psychotherapy.

Viewed from a fifth aspect, the disclosure provides a formulation of the first aspect or kit of the second aspect for use in a method of treating a psychiatric or neurological disorder in a patient.

Viewed from a sixth aspect, the disclosure provides a method of treating a psychiatric or neurological disorder comprising administering to a patient in need thereof a formulation of the first aspect.

Viewed from a seventh aspect, the disclosure provides a method of treating a psychiatric disorder comprising administering to a patient in need thereof a formulation of the first aspect in combination with psychotherapy.

Viewed from an eighth aspect, the disclosure provides an aqueous pharmaceutical formulation comprising a salt comprising a Brønsted acid having a pKa at 25 °C of from about 3 to about 5, and a compound of Formula IA



Formula IA

wherein:

R^{1a} is independently selected from $–R^{4a}$, -OH, $-OR^{4a}$, $-O(CO)R^{4a}$, monohydrogen phosphate, -F, -Cl, -Br and –I;

n is selected from 0, 1, 2, 3 or 4;

R^{2a} is $C(^{xa}H)_3$;

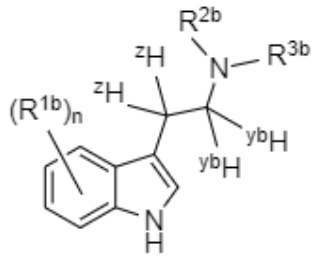
R^{3a} is $C(^{xa}H)_3$;

each R^{4a} is independently selected from C_1-C_4alkyl; and

each ^{xa}H and ^{ya}H is independently selected from protium or deuterium;

and water, with a pH from about 5 to about 6.5, and a concentration of the compound of Formula IA of about 10 mg/ml or greater as the freebase equivalent salt. Preferably, the formulation may have a pH of from about 5 to about 6, or a pH of from 5 to 6. In preferred embodiments of the eighth aspect of the present disclosure, the pharmaceutical formulation comprises an effective dose of a compound of Formula IA for use in psychedelic assisted therapy within a volume of 5 ml or less, preferably within a volume of 4 ml or less, 3 ml or less, 2.5 ml or less, 2 ml or less, 1 ml or less, or 0.5 ml or less.

Viewed from a ninth aspect, the disclosure provides an aqueous pharmaceutical formulation comprising a salt comprising a Brønsted acid having a pKa at 25 °C of from about 3 to about 5, and a compound of Formula IB



Formula IB

wherein:

R^{1b} is independently selected from $–R^{4b}$, -OH, $-OR^{4b}$, $-O(CO)R^{4b}$, monohydrogen phosphate, -F, -Cl, -Br and –I;

n is selected from 0, 1, 2, 3 or 4;

R^{2b} is $C(^{xb}H)_3$;

R^{3b} is $C(^{xb}H)_3$;

each R^{4b} is independently selected from C_1-C_4alkyl; and

each ^{xb}H, ^{yb}H and ^{z}H is independently selected from protium or deuterium:

and water, with a pH from about 5 to about 6.5, and a concentration of the compound of Formula IB of about 10 mg/ml or greater as the freebase equivalent salt. Preferably, the formulation may have a pH of from about 5 to about 6, or a pH of from 5 to 6. In preferred embodiments of the ninth aspect of the present disclosure, the pharmaceutical formulation comprises an effective dose of a compound of Formula IB for use in psychedelic assisted therapy within a volume of 5 ml or less, preferably within a volume of 4 ml or less, 3 ml or less, 2.5 ml or less, 2 ml or less, 1 ml or less, or 0.5 ml or less. For the avoidance of doubt, embodiments of the eighth aspect of the disclosure apply *mutatis mutandis* to the ninth aspect of the disclosure.

Viewed from a tenth aspect, the disclosure provides a lyophilised powder formulation comprising a formulation as defined in the first aspect of the disclosure which has been lyophilised.

Viewed from an eleventh aspect, the disclosure provides a method of preparing a lyophilised powder formulation comprising drying the formulation as defined in the first aspect of the disclosure by lyophilisation.

Viewed from a twelfth aspect, the disclosure provides a method of preparing an aqueous formulation comprising mixing the lyophilised powder formulation as defined in

the tenth aspect or as prepared in the method of the eleventh aspect into water to provide a formulation comprising the salt of an optionally substituted dimethyltryptamine compound, the base agent, water, and optionally the buffer which is separate to the salt to provide a formulation having a pH of from about 5 to about 6.5, a concentration of about 10 mg/ml as freebase or greater, and an osmolality of from about 250 to about 350 mOsm/Kg. Preferably, the formulation may have a pH of from about 5 to about 6, or a pH of from 5 to 6.

For the avoidance of doubt, embodiments of the first aspect of the disclosure apply *mutatis mutandis* to the tenth, eleventh and twelfth aspects of the disclosure.

For the avoidance of doubt, embodiments related to each aspect of the disclosure apply *mutatis mutandis* to the other aspects of the disclosure.

Further aspects and embodiments of the present disclosure will be evident from the discussion that follows below.

BRIEF DESCRIPTION OF THE FIGURES

The invention will now be described, by way of example only, and with reference to the accompanying figures in which:

Figure 1: Figure 1A and 1B show plots of the mean plasma N,N-Dimethyltryptamine (SPL026), d_2- N,N-Dimethyltryptamine (SPL028i) and d_8- N,N-Dimethyltryptamine (SPL028viii) concentration over time following 3.5mg/kg (as fumarate) IM dose; added as a cassette *in vivo*. Figure 1A – Linear plot, Figure 1B – Semi-log plot. All three drug substances achieve a Cmax greater than 50 ng/ml, indicative of a therapeutically relevant dose. SPL028i and SPL028viii each demonstrate significantly higher plasma levels at 30 mins compared with undeuterated DMT.

Figure 2A and 2B show plots of the mean plasma d_2-DMT (SPL028i) concentration over time following 3.5mg/kg and 10mg/kg (as fumarate) IM doses *in vivo*. Figure 2A – Linear plot, Figure 2B – Semi-log plot, SEM error bars.

Figure 3 shows the pH-solubility curve for N,N-dimethyltryptamine from pH 4 to pH 10.

DETAILED DESCRIPTION OF THE INVENTION

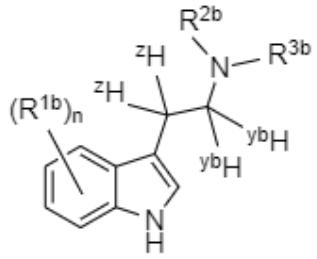
Throughout this specification, one or more aspects of the invention may be combined with one or more features described in the specification to define distinct embodiments of the invention.

Unless otherwise mentioned, measurements are carried out at room temperature and pressure, i.e. 20 °C (293.15 K, 68 °F) and 1 atm (14.696 psi, 101.325 kPa), respectively. Unless otherwise stated, ambient conditions refer to room temperature and pressure.

In the discussion that follows, reference is made to a number of terms, which are to be understood to have the meanings provided below, unless a context expressly

CLAIMS

1. A pharmaceutical formulation suitable for intramuscular injection, comprising a salt of a compound of Formula IB:



Formula IB

wherein:

n is 0;

R^{1b} is independently selected from $–R^{4b}$, -OH, $-OR^{4b}$, $-O(CO)R^{4b}$, monohydrogen phosphate, -F, -Cl, -Br or –I;

R^{2b} is $C(^{xb}H)_3$;

R^{3b} is $C(^{xb}H)_3$;

each R^{4b} is independently selected from C_1-C_4alkyl; and

each ^{xb}H, ^{yb}H and ^{z}H is independently selected from protium or deuterium;

and a Brønsted acid having a pKa of from about 3 to about 5;

a base agent, water, and optionally a buffer which is separate to the salt;

wherein the formulation has a pH of from about 5 to about 6.5, a concentration of the compound of Formula IB of about 10 mg/ml or greater as the freebase equivalent, and an osmolality of from about 250 to about 350 mOsm/Kg; and

wherein the formulation comprises a dose of the compound of Formula IB within a volume of 5 ml or less.

2. The formulation of claim 1, wherein the formulation has a pH of from about 5 to about 6.

3. The formulation of claim 1, wherein the formulation comprises a dose of the compound of Formula IB within a volume of 3 ml or less.

4. The formulation of claim 1, wherein R^{2b} is CD_3 and R^{3b} is CD_3; and/or wherein each ^{yb}H is D.

5. The formulation of claim 1, wherein the compound of Formula IB is N,N-dimethyltryptamine.

6. The formulation of claim 1, wherein the compound of Formula IB is selected from the group consisting of α,α-dideutero-N,N-dimethyltryptamine, α,α-dideutero-N,N-di(trideuteromethyl)tryptamine, α,α,β,β-tetradeutero-N,N-dimethyltryptamine, and α,α,β,β-tetradeutero-N,N-di(trideuteromethyl)tryptamine.

7. The formulation of claim 1, wherein the Brønsted acid is selected from the group consisting of fumaric acid, tartaric acid, citric acid, acetic acid, lactic acid and gluconic acid.

8. The formulation of claim 1, wherein the concentration of the compound of Formula IB is from about 20 mg/mL to about 40 mg/mL (as the freebase equivalent).

9. The formulation of claim 1, wherein the formulation comprises the buffer which is separate to the salt, optionally wherein the buffer comprises an acetate salt and acetic acid; or a citrate salt and citric acid; or a phosphate salt and phosphoric acid; or the buffer comprises an acetate salt, a citrate salt, or a phosphate salt.

10. The formulation of claim 1, wherein the formulation further comprises a tonicity agent and/or a pH adjuster.

11. The formulation of claim 1, wherein the formulation consists of the salt of the compound of Formula IB, water, the base agent and optionally the buffer and/or a tonicity agent and/or pH adjuster.

12. The formulation of claim 1, having an oxygen content of less than 5 ppm, or less than 2 ppm.

13. The formulation of claim 1, comprising the salt of the compound of Formula IB, the base agent, water, the buffer which is separate to the salt, and a tonicity agent or pH adjuster.

14. The formulation of claim 13, comprising a salt of the compound of Formula IB; the base agent which is selected from potassium hydroxide or sodium hydroxide; water; the buffer which is a citrate salt; and the tonicity agent or pH adjuster which is an acid.

15. A kit suitable for preparing the formulation of claim 1, said kit comprising the salt of the compound of Formula IB; optionally a tonicity agent and/or a pH adjuster; the base agent and optionally the buffer which is separate to the salt.

16. A lyophilised powder formulation comprising the formulation according to claim 1 which has been lyophilised.

17. The formulation of claim 1, wherein the concentration of the compound of Formula IB is about 25 mg/mL (as the freebase equivalent).

18. The formulation of claim 1, wherein the compound of Formula IB is a deuterated N,N-dimethyltryptamine.

19. The formulation of claim 18, wherein the deuterated N,N-dimethyltryptamine is selected from the group consisting of α,α-dideutero-N,N-dimethyltryptamine, α,α-dideutero-N,N-di(trideuteromethyl)tryptamine, α,α,β,β-tetradeutero-N,N-dimethyltryptamine, and α,α,β,β-tetradeutero-N,N-di(trideuteromethyl)tryptamine.

20. A pharmaceutical formulation suitable for intramuscular injection, comprising:

a fumarate salt of deuterated N,N-dimethyltryptamine selected from the group consisting of α,α-dideutero-N,N-dimethyltryptamine, α,α-dideutero-N,N-di(trideuteromethyl)tryptamine, α,α,β,β-tetradeutero-N,N-dimethyltryptamine, and α,α,β,β-tetradeutero-N,N-di(trideuteromethyl)tryptamine;

a base agent selected from potassium hydroxide and sodium hydroxide;

water; and

a buffer which comprises an acetate salt, a citrate salt, or a phosphate salt;

wherein the formulation has a pH of from about 5 to about 6.5, a concentration of the deuterated N,N-dimethyltryptamine from about 20 mg/mL to about 40 mg/mL as the freebase equivalent, and an osmolality of from about 250 to about 350 mOsm/Kg; and

wherein the formulation comprises a dose of the deuterated N,N-dimethyltryptamine within a volume of 5 ml or less.

21. A formulation according claim 20, comprising a fumarate salt of α,α,β,β-tetradeutero-N,N-di(trideuteromethyl)tryptamine.