It is described that these results relate injection of DMT fumarate to the experience of feeling profoundly immersed in an entirely other world.

According to the Human Metabolome Database (HMDB), dimethyltryptamine degrades relatively quickly in solution (see specifically http://www.hmdb.ca/metabolites/HMDB0005973).

SUMMARY OF THE INVENTION

Aspects of the invention are defined in the independent claim. Some optional features of the invention are defined in the dependent claims. Accordingly, implementation of the invention may allow for injectable solutions of DMT that are stable over longer periods of time, and are clinically acceptable.

The present invention relates generally to pharmaceutical formulations, optionally suitable for injection, comprising a salt of an optionally substituted dimethyltryptamine compound, a buffer, which is separate to the salt, and water, wherein the formulations have pH values of from about 3.5 to about 6.5 and typical osmolalities of about 250 to about 350 mOsm/Kg. Human blood serum has a pH of about 7.4 (typically ranging between 7.35 to 7.45, see G. K. Shwalfenberg, *J. Environ. Public Health*, 2012; 2012:727630), and the obvious go-to formulation of salts of optionally substituted dimethyltryptamine compounds is isotonic with a pH of 7.4. It has now been found that formulations described in the prior art or adapted therefrom have non-optimal shelf-life when stored under ambient conditions. The present disclosure addresses this problem of providing pharmaceutical formulations, optionally suitable for injection, with substantially reduced degradation products compared with known formulations when stored under stressed conditions. This is indicative of improved shelf-life over such pharmaceutical formulations described in the prior art.

Accordingly, viewed from a first aspect, the disclosure provides a pharmaceutical formulation, optionally suitable for injection, comprising a salt of a dimethyltryptamine compound optionally substituted with deuterium and optionally substituted at position 4 or 5 with acetoxy or methoxy or position 4 with monohydrogen phosphate; a buffer which is separate to the salt; and water, wherein the formulation has a pH of about 3.5 to about 6.5 and an osmolality of about 250 to about 350 mOsm/Kg.

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 a dimethyltryptamine compound optionally substituted with deuterium and optionally substituted at position 4 or 5 with acetoxy or methoxy or position 4 with monohydrogen phosphate; and a buffer which is separate to the salt.

Viewed from a third aspect, the disclosure provides a method of preparing a pharmaceutical formulation of the first aspect, comprising contacting the salt, buffer, water and optionally a tonicity agent. In some embodiments, the formulation or composition of the first and second aspect comprises a tonicity agent.

Owing to the instability of dimethyltryptamine in solution, solutions comprising dimethyltryptamine are generally prepared immediately before or close to the time of use, i.e. storage of solutions of dimethyltryptamine is avoided. Alternatively, solutions of dimethyltryptamine 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, therefore, the present disclosure provides for the use of a buffer to ameliorate degradation of an injectable pharmaceutical formulation of a salt of a dimethyltryptamine compound optionally substituted with deuterium and optionally substituted at position 4 or 5 with acetoxy or methoxy or position 4 with monohydrogen phosphate.

Viewed from a fifth aspect, the disclosure provides a formulation of the first aspect for use in therapy.

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

Viewed from a seventh 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.

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

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.

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 indicates to the contrary. The nomenclature used herein for defining compounds, in particular the compounds described herein, is intended to be in accordance with the rules of the International Union of Pure and Applied Chemistry (IUPAC) for chemical

compounds, specifically the “IUPAC Compendium of Chemical Terminology (Gold Book)” (see A. D. Jenkins et al., Pure & Appl. Chem., 1996, 68, 2287-2311). For the

As used herein the term ‘obsessive-compulsive disorder’ (OCD) is defined by the presence of either obsessions or compulsions, but commonly both. The symptoms can cause significant functional impairment and/or distress. An obsession is defined as an unwanted intrusive thought, image or urge that repeatedly enters the person's mind. Compulsions are repetitive behaviours or mental acts that the person feels driven to perform. Typically, OCD manifests as one or more obsessions, which drive adoption of a compulsion. For example, an obsession with germs may drive a compulsion to clean or an obsession with food may drive a compulsion to overeat, eat too little or throw up after eating (i.e. an obsession with food may manifest itself as an eating disorder). A compulsion can either be overt and observable by others, such as checking that a door is locked, or a covert mental act that cannot be observed, such as repeating a certain phrase in one's mind.

The disclosure provides a formulation or kit according to the first and second aspect for use in a method of treating an eating disorder. The term “eating disorder” includes anorexia nervosa, bulimia and binge eating disorder (BED). The symptoms of anorexia nervosa include eating too little and/or exercising too much in order to keep weight as low as possible. The symptoms of bulimia include eating a lot of food in a very short amount of time (i.e. binging) and then being deliberately sick, using laxatives, eating too little and/or exercising too much to prevent weight gain. The symptoms of BED include regularly eating large portions of food until uncomfortably full, and consequently feeling upset or guilty.

As used herein the term ‘depressive disorder’ includes major depressive disorder, persistent depressive disorder, bipolar disorder, bipolar depression, and depression in terminally ill patients.

As used herein the term ‘major depressive disorder’ (MDD, also referred to as major depression or clinical depression) is defined as the presence of five or more of the following symptoms over a period of two-weeks or more (also referred to herein as a ‘major depressive episode’), most of the day, nearly every day:

- depressed mood, such as feeling sad, empty or tearful (in children and teens, depressed mood can appear as constant irritability);
- significantly reduced interest or feeling no pleasure in all or most activities;
- significant weight loss when not dieting, weight gain, or decrease or increase in appetite (in children, failure to gain weight as expected);
- insomnia or increased desire to sleep;
- either restlessness or slowed behaviour that can be observed by others;
- fatigue or loss of energy;

As used herein, the term ‘substance abuse’ means a patterned use of a drug in which the user consumes the substance in amounts or with methods that are harmful to themselves or others.

As used herein, the term ‘an avolition disorder’ refers to a disorder that includes as a symptom the decrease in motivation to initiate and perform self-directed purposeful activities.

The disclosure provides a pharmaceutical formulation, optionally suitable for injection, comprising a salt of a dimethyltryptamine (DMT) compound optionally substituted with deuterium and optionally substituted at position 4 or 5 with acetoxy or methoxy or position 4 with monohydrogen phosphate; a buffer which is separate to the salt; and water, wherein the formulation has a pH of about 3.5 to about 6.5 and an osmolality of about 250 to about 350 mOsm/Kg.

The inventors have found that the formulation is surprisingly more stable than formulations prepared at higher pH (specifically those prepared at a pH matching human blood serum, i.e. at a pH of about 7.4). The greater stability of the formulation of the invention relative to the go-to formulation is discussed in more detail in the Example section.

Osmolality is formally defined as the quotient of the negative natural logarithm of the rational activity of water and the molar mass of water, as represented by formula:

$$osmolality = \frac{-lna_w}{18.015};\ a_w = \frac{p}{p^*}$$

where p is the partial vapour pressure of water in the solution and p^* is the partial vapour pressure of pure water. In simpler terms, osmolality is the number of osmotically active particles (the number of solute particles) in 1 kg of a solution. Thus, osmolality is a function only of the number of particles, and is not related to particle molecular weight, size, shape, or charge (see D. K. Faria *et al.*, M. E. Mendes and N. M. Sumita, *J. Bras. Patol. Med. Lab.*, 53, 1, 38-45 (2017) for a review of the measurement of serum osmolality). For example, one mole of a nondissociating substance (e.g. DMT as a free base) dissolved in 1 kg of water has an osmolality of 1 Osm/kg (1000 mOsm/kg), whilst one mole of a substance that dissociates into two separate species in solution (e.g. DMT fumarate) dissolved in 1 kg of water has an osmolality of 2 Osm/kg (2000 mOsm/kg).

Where a first solution is defined herein to be isotonic with a second solution, the solutions have the same osmolality. For example, where a formulation is defined to be isotonic with human blood serum, the formulation has the same osmolality as human blood serum. Human blood serum typically has an osmolality of about 275 to about 300 mOsm/Kg (L. Hooper *et al.*, *BMJ Open*, 2015; 5(10): e008846).

of a buffer has more than one pKa value (i.e. each molecule of the acid is able to donate more than one proton), in order for the buffer to be suitable, at least one of the pKa values lies within the desired pH range.

The weak acid and conjugate base of the buffer are in equilibrium with one another. In accordance with Le Chatelier's principle (if a constraint (such as a change in concentration of a reactant) is applied to a system in equilibrium, the equilibrium will shift so as to counteract the effect of the constraint), addition of acid or base to the formulation shifts the position of equilibrium in favour of the conjugate base or weak acid, respectively. Consequently, the concentration of free protons in the formulation (and thus the pH) is relatively unchanged.

As described above, the disclosed formulation has a pH of from about 3.5 to about 6.5. In some embodiments, the buffer comprises an acetate salt and acetic acid (pKa = 4.75); a citrate salt and citric acid (pKa = 3.13, 4.76 and 6.40); an ascorbate salt and ascorbic acid (pKa = 4.17 and 11.6); a benzoate salt and benzoic acid (pKa = 4.20); a phosphate salt and phosphoric acid (pKa = 2.14, 7.20 and 12.37); an oxalate salt and oxalic acid (pKa = 1.25 and 4.14); or a formate salt and formic acid (pKa = 3.75). The pKa values cited herein are those reported at 25 °C in water. Typically, the buffer comprises only one of the pairs listed above, i.e. one acid and its conjugate base.

In some embodiments, the buffer comprises an acetate salt and acetic acid; a citrate salt and citric acid; an ascorbate salt and ascorbic acid; a benzoate salt and benzoic acid; or a phosphate salt and phosphoric acid.

In some embodiments, the pH of the formulation is from about 3.75 to about 6.5, such as from about 3.75 to about 5.75. Often, the pH of the formulation is from about 3.75 to about 4.25, typically about 4.0. In such embodiments, the buffer often comprises an acetate salt and acetic acid; a citrate salt and citric acid; an ascorbate salt and ascorbic acid; a benzoate salt and benzoic acid; an oxalate salt and oxalic acid; or a formate salt and formic acid. Sometimes, the buffer comprises an acetate salt and acetic acid; a citrate salt and citric acid; an ascorbate salt and ascorbic acid; or a benzoate salt and benzoic acid.

In some embodiments, the buffer comprises an acetate salt and acetic acid, often sodium acetate and acetic acid, or potassium acetate and acetic acid.

The concentration of buffer within the formulation is typically great enough to resist significant pH change of the formulation on storage of the formulation for two weeks (i.e. the pH typically fluctuates less than about 0.1 pH unit), and is small enough so that the osmolality of the formulation lies within the desired range. The skilled person is able to assess suitable buffer concentrations and to achieve this. Often, the

any one or a combination of 4-acetoxy-N,N-dimethyltryptamine, 4-acetoxy-α-monodeutero-N,N-dimethyltryptamine and 4-acetoxy- α,α-dideutero-N,N-dimethyltryptamine; or

any one or a combination of 5-methoxy-N,N-dimethyltryptamine, 5-methoxy-α-monodeutero-N,N-dimethyltryptamine and 5-methoxy- α,α-dideutero-N,N-dimethyltryptamine; and

an acid selected from the group consisting of fumaric acid, tartaric acid, citric acid, acetic acid, lactic acid and gluconic acid, typically fumaric acid.

In some embodiments, the salt is DMT fumarate, i.e. it comprises DMT and fumaric acid.

The DMT compound may have a purity of about 80 to 100 %. Sometimes, the purity is about 90 to 100 %, such as from about 95 to 100 %. Typically, the DMT compound has a purity of from about 99 to 100 %, i.e. a purity greater than or equal to 99%. Percentages of purity herein are as determined by HPLC.

It is particularly advantageous to prepare the formulations with a drug substance comprising the optionally substituted DMT compound or salt thereof with a purity of greater than 99%. By drug substance is meant, as is understood in the art, an active ingredient intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure or any function of the patient concerned, but does not include intermediates used in the synthesis of such ingredient. It will be understood that the drug substance may comprise one or more such active ingredients.

Formulations made with less pure drug substance show greater rates of related substances, which is indicative of inferior shelf-life. Accordingly, preferred embodiments of any aspect of the present invention comprise a drug substance comprising an optionally substituted dimethyltryptamine compound or salt thereof having a purity of greater than or equal to 99% when measured by HPLC. Particularly preferred embodiments comprise a drug substance comprising an optionally substituted dimethyltryptamine compound or salt thereof having a purity of greater than or equal to 99.5%, even more preferably 99.7%, and even more preferably 99.9%, when measured by HPLC. The concentration of the DMT compound within the formulation may be any desired concentration, provided that the osmolality of the formulation is about 250 to about 350 mOsm/Kg. The DMT compound may be at a concentration of about 0.001 to about 28 mg/mL, such as about 2.5 mg/mL to about 28 mg/mL. Accordingly, in some embodiments, the formulation of the invention comprises the DMT compound at a concentration of from 2.5 mg/mL to 28 mg/mL, including any integer value within this

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 a DMT compound optionally substituted with deuterium and optionally substituted at position 4 or 5 with acetoxy or methoxy or position 4 with monohydrogen phosphate; and a buffer, which is separate to the salt.

Also provided is a kit to generate a formulation of the first aspect, the kit comprising:

- a first composition comprising a salt of a DMT compound optionally substituted with deuterium and optionally substituted at position 4 or 5 with acetoxy or methoxy or position 4 with monohydrogen phosphate; and

- a second composition comprising a buffer, which is separate to the salt,

wherein the first and second compositions are mixed with water and optionally a tonicity agent, and the resulting mixture generates the formulation of the first aspect.

For the avoidance of doubt, embodiments related to the optionally substituted DMT salt and the buffer of the first aspect of the disclosure as defined herein apply *mutatis mutandis* to the second aspect. For example, the optionally substituted DMT salt of the kit may comprise a Brønsted acid having a pKa at 25 °C of from about 3 to about 5, and a compound of Formula I and/or the buffer may comprise an acetate salt and acetic acid.

The optionally substituted DMT salt within the kit may be a solid, e.g. in a powder or crystalline form. To ameliorate degradation of the optionally substituted DMT salt in the solid form, the salt may be lyophilised (freeze-dried) before incorporation into the kit. Lyophilising the salt comprises freezing it in the presence of solvent (typically water) and separating the solvent from the salt by sublimation.

The kit may further comprise a tonicity agent. When the kit further comprises a tonicity agent, the embodiments related to the optional tonicity agent of the first aspect of the disclosure as defined herein apply *mutatis mutandis* to the second aspect. For example, the tonicity agent may be any one or a combination selected from the group consisting of sodium chloride, potassium chloride, dextrose, glucose, mannitol, lactose, sorbitol and sucrose.

Viewed from a third aspect, the disclosure provides a method of preparing a pharmaceutical formulation of the first aspect, which is typically a solution. The method comprises contacting the optionally substituted DMT salt, buffer, water and optionally a tonicity agent. For the avoidance of doubt, the embodiments of the first aspect of the disclosure apply *mutatis mutandis* to the third aspect. For example, the salt may be

DMT, the buffer may comprise acetic acid and an acetate salt, and/or sodium chloride may be used as a tonicity agent.

It will be understood that the contacting of the method may be achieved in a variety of ways. Often, the optionally substituted DMT salt is dissolved in water to form a first solution to which the buffer is added and dissolved, forming a second solution. If a tonicity agent is used, it is often added to and dissolved in the second solution.

In some embodiments, an aqueous solution of the buffer is contacted with the salt, wherein the aqueous solution has a pH of about 3.5 to about 6.5, such as a pH from about 3.75 to about 6.5. Sometimes, the aqueous solution has a pH of about 3.75 to about 5.75, such as a pH from about 3.75 to about 4.25. In some embodiments, the aqueous solution has a pH of about 4.0.

The optionally substituted DMT salt within the formulation may be formed by contacting optionally substituted DMT as a free base with an aqueous solution comprising a quantity of buffer suitable to stabilise the pH and act as counterion to the optionally substituted DMT when protonated. Accordingly, the method of the disclosure may comprise contacting the optionally substituted dimethyltryptamine in free base form with the buffer, water and optionally a tonicity agent.

In some embodiments, the method further comprises adjusting the pH of the solution resultant from the contacting. Since the pH of the solution resultant from the contacting is usually low, pH adjustment often comprises contacting the solution with a suitable base. The skilled person is able to assess which bases are suitable to adjust the pH of the solution resultant from the contacting without risk of degradation of the optionally substituted DMT salt.

Often, the pH of the solution resultant from the contacting is adjusted with any one selected from the group consisting of sodium hydroxide, potassium hydroxide, sodium carbonate, ammonium hydroxide, calcium hydroxide and magnesium hydroxide. In some embodiments, the pH is adjusted with sodium hydroxide or potassium hydroxide.

As described above, to ameliorate degradation of the formulation further, it may be desirable to minimise the total oxygen content within the container in which the formulation is stored, the oxygen within the container equilibrating between the formulation and the headspace (if any) within the container. Accordingly, it may be desirable to store the formulation under an inert atmosphere for example by purging the headspace to reduce its oxygen content from about 20% typically found in air, to less than, for example, 0.5%. Additionally or alternatively, in some embodiments, the method further comprises sparging the solution resultant from the contacting with an inert gas, such as nitrogen or argon, typically nitrogen.

Viewed from a fourth aspect, there is provided use of a buffer to ameliorate degradation of an injectable pharmaceutical formulation of a salt of a dimethyltryptamine compound optionally substituted with deuterium and optionally substituted at position 4 or 5 with acetoxy or methoxy or position 4 with monohydrogen phosphate.

For the avoidance of doubt, the embodiments of the first aspect of the disclosure apply *mutatis mutandis* to the fourth aspect. Specifically, the embodiments of the first aspect relating to the buffer and the optionally substituted DMT salt apply *mutatis mutandis* to the fourth aspect. For example, the buffer of the fourth aspect may comprise an acetate salt and acetic acid; a phosphate salt and phosphoric acid; a citrate salt and citric acid; an ascorbate salt and ascorbic acid; or a benzoate salt and benzoic acid; and/or the optionally substituted DMT salt of the fourth aspect may comprise a Brønsted acid having a pKa at 25 °C of from about 3 to about 5.

As described above, DMT has a possible therapeutic role in the treatment of depression, obsessive-compulsive disorder, and substance abuse disorders (S. A. Barker, 2018, *supra*). Viewed from a fifth aspect, therefore, the disclosure provides a formulation of the first aspect for use in therapy.

Viewed from a sixth aspect, the disclosure provides a formulation of the first aspect for use in a method of treating a psychiatric or neurological disorder in a patient. Often, the psychiatric or neurological disorder is selected from the group consisting of (i) an obsessive compulsive disorder, (ii) a depressive disorder, (iii) an anxiety disorder, (iv) substance abuse, and (v) an avolition disorder. Often, the disorder is selected from the group consisting of major depressive disorder, treatment resistant major depressive disorder, post-partum depression, an obsessive compulsive disorder and an eating disorder such as a compulsive eating disorder.

Viewed from a seventh 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. The psychiatric or neurological disorder may be any of those described in relation to the sixth aspect. For example, the disorder may be selected from the group consisting of major depressive disorder, treatment resistant major depressive disorder, post-partum depression, an obsessive compulsive disorder and an eating disorder such as a compulsive eating disorder.

In order to treat the disorder, the formulation comprises an effective amount of the DMT compound, i.e. an amount that is sufficient to reduce or halt the rate of progression of the disorder, or to ameliorate or cure the disorder and thus produce the desired therapeutic or inhibitory effect.

The formulation is optionally suitable for injection, thus its administration in therapy typically comprises injection of the formulation.

CLAIMS

1. A pharmaceutical formulation suitable for injection, comprising:

a salt of a dimethyltryptamine compound optionally substituted with deuterium and optionally substituted at position 4 or 5 with acetoxy or methoxy or position 4 with monohydrogen phosphate, and a Brønsted acid having a pKa at 25 ° C in water of from 3± 5% to 5± 5%;

a buffer which is separate to the salt; and

water,

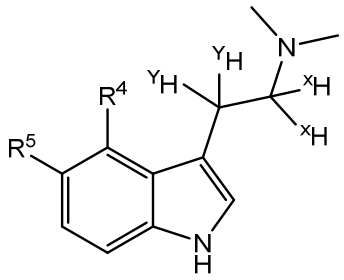
wherein the formulation has a pH of 3.75 ± 5% to 6.5 ± 5% and an osmolality of 250 mOsm/Kg ± 5% to 350 mOsm/Kg ± 5%.

2. The formulation of claim 1, wherein the pH is from 3.75 ± 5% to 5.75 ± 5%.

3. The formulation of claim 1, wherein the pH is from 3.75 ± 5% to 4.25 ± 5%.

4. The formulation of claim 1, wherein the formulation has an osmolality of 275 ± 5% to 325 mOsm/Kg ± 5%.

5. The formulation of claim 1, wherein the salt of the dimethyltryptamine compound comprises a compound of Formula I:



Formula I

wherein:

R^4 and R^5 are both H and each ^{x}H and each ^{Y}H is independently selected from H and D, or

one of R^4 and R^5 is H and the other is acetoxy or methoxy, each ^{Y}H is H and each ^{x}H is independently selected from H and D, or

the salt comprises a compound of Formula I wherein R^4 is monohydrogen phosphate, R^5 is H and each ^{Y}H and each ^{x}H is H.

6. The formulation of claim 5, wherein

(i) R^4 and R^5 are both H; or

(ii) R^4 is acetoxy and R^5 is H; or

(iii) R^4 is H and R^5 is methoxy.

7. The formulation of claim 1, wherein the optionally substituted dimethyltryptamine compound is dimethyltryptamine.

8. The formulation of claim 1, wherein the salt is of an optionally substituted dimethyltryptamine compound and an acid selected from the group consisting of fumaric acid, tartaric acid, citric acid, acetic acid, lactic acid and gluconic acid.

9. The formulation of claim 1, wherein the salt is of an optionally substituted dimethyltryptamine compound and wherein the acid is fumaric acid.

10. The formulation of claim 1, wherein the salt of the dimethyltryptamine compound has a purity of greater than or equal to 99% when measured by HPLC.

11. The formulation of claim 1, wherein the concentration of the optionally substituted dimethyltryptamine is 2.5 mg/mL ± 5%.

12. The formulation of claim 1, wherein the buffer comprises sodium acetate and acetic acid, or potassium acetate and acetic acid.

13. The formulation of claim 1, further comprising a tonicity agent.

14. The formulation of claim 13, wherein the tonicity agent is sodium chloride at a concentration of 120 mM ± 5% to 140 mM ± 5%.

15. The formulation of claim 1, wherein the formulation consists essentially of the salt, the buffer, water, and optionally a tonicity agent.

16. The formulation of claim 1, wherein the formulation has an oxygen content of less than 2ppm.

17. The pharmaceutical formulation suitable for injection of claim 1, comprising:
a salt of dimethyltryptamine optionally substituted with deuterium;
a buffer which is separate to the salt; and
water,
wherein the formulation has a pH of 3.75 ± 5% to 6.5 ± 5% and an osmolality of 250 mOsm/Kg ± 5% to 350 mOsm/Kg ± 5%.

18. The pharmaceutical formulation suitable for injection of claim 1, comprising:
a salt of dimethyltryptamine compound with deuterium;
a buffer which is separate to the salt; and
water,
wherein the formulation has a pH of 3.75 ± 5% to 6.5 ± 5% and an osmolality of 250 mOsm/Kg ± 5% to 350 mOsm/Kg ± 5%.

19. The formulation of claim 1, wherein the pH is from 4.0 ± 5% to 6.5 ± 5%.

20. The formulation of claim 5, wherein the pH is from 4.0 ± 5% to 6.5 ± 5%.