outpatients. Therefore, oral drugs for cancer treatment have a future and will play a more important role than they have done in the past.

Arsenic compounds have been used as pharmaceutical agents to treat a large variety of diseases including cancer. Inorganic arsenic compounds are highly toxic. With the rapid evolvement of medicine in the 20th century, the use of medicinal arsenic waned rapidly. Interest in arsenic compounds revived when it was shown that daily intravenous administration of arsenic trioxide (As_2O_3) alone caused complete responses in a large majority of patients with newly diagnosed and relapsed acute promyelocytic leukaemia. A drawback of arsenic trioxide is that it is administered intravenously daily in 1-4 hr infusion for up to 6 weeks.

When arsenic trioxide is taken orally, it binds to the chloride ions in the stomach and produces arsenic chloride ($AsCl_3$). Arsenic chloride is toxic and shows serious adverse side effects. Due to the inherent toxicity of arsenic compounds when taken orally, interest in arsenic compounds for therapy has remained low. However, it is recognised that oral formulations are easy to administer to patients, and promote better patient compliance.

Thus, there is a need for improved pharmaceutical compositions comprising arsenic compounds suitable for oral administration, for use in the treatment of diseases and conditions, such as cancer and cancer pain.

SUMMARY

The present inventor has developed an enteric coated solid pharmaceutical composition comprising sodium meta-arsenite ($O=As\text{-}O^- Na^+$) or potassium meta-arsenite ($O=As\text{-}O^- K^+$), which is suitable for oral administration, and which passes through the stomach and commences dissolution in the small intestines (where acidity is between pH 6.5-7.5).

In one aspect, the present disclosure refers to a pharmaceutical composition, which is in the form of an enteric coated tablet or an enteric coated capsule, suitable for oral administration comprising:

(a) a solid core comprising sodium meta arsenite or potassium meta arsenite, and the following pharmaceutically acceptable excipients:

(i) a filler or diluent in a range of from 5 to 95% w/w of the solid core, wherein the filler or diluent is selected from dibasic calcium phosphate anhydrous, partially pregelatinised starch, silicified microcrystalline cellulose, microcrystalline cellulose, calcium sulphate dihydrate, lactose, calcium hydrogen phosphate, calcium carbonate, sodium carbonate, calcium phosphate, sodium phosphate, or a mixture thereof;

(ii) a disintegrant in a range of from 10 to 90% w/w of the solid core, wherein the disintegrant is selected from L-hydroxypropyl cellulose, partially pregelatinised starch, crospovidone, potato starch, corn starch, sodium starch glycolate, and alginic acid;

(iii) a glidant in a range of from 0.1 to 5% w/w of the solid core, wherein the glidant is selected from colloidal silicon dioxide and talc;

(iv) a lubricant in a range of from 0.1 to 5% w/w of the solid core, wherein the lubricant is selected from sodium stearyl fumarate, magnesium stearate, stearic acid, talc, and silica; and

(v) optionally a binder in a range of from 0 to 30% w/w of the solid core; wherein the binder is selected from silicified microcrystalline cellulose, microcrystalline cellulose, partially pregelatinised starch, L-hydroxypropyl cellulose (low substituted hydroxypropylcellulose), hydroxypropyl cellulose, copovidone (polyvinylpyrrolidone), pregelatinised maize starch, hydroxypropylmethylcellulose, starch, acacia, corn starch, and gelatin; and

(b) an enteric coating comprising an enteric polymer, wherein the enteric polymer is selected from copolymers of acrylic acids and their esters or methacrylic acids or their esters, cellulose acetate phthalate polymers, hydroxypropyl methylcellulose phthalate polymers, hydroxypropyl methylcellulose acetate succinate, polyvinyl acetate phthalate, cellulose acetate trimellitate, and combinations thereof;

wherein the pharmaceutically acceptable excipients are selected such that oxidation of meta arsenite to meta arsenate is minimised,

wherein the weight percentage of the enteric coating is from 6% w/w to 20% w/w with respect to the total weight of the pharmaceutical composition, and

wherein the enteric coating provides a weight gain of about 9.5% w/w of the solid core, a weight gain of about 10% w/w of the solid core, a weight gain of about 10.5% w/w of the solid core, a weight gain of about 11% w/w of the solid core, a weight gain of about 11.5% w/w of the solid core, a weight gain of about 12% w/w of the solid core, a weight gain of about 12.5% w/w of the solid core, a weight gain of about 13% w/w of the solid core, a weight gain of about 13.5% w/w of the solid core, or a weight gain of about 14% w/w of the solid core, and

wherein the coating thickness is from 6.5% to 15% of the thickness of the pharmaceutical composition.

In another aspect, the present disclosure refers to a pharmaceutical composition as disclosed herein for use in the treatment of a disease or condition, wherein the disease or condition is selected from solid malignancy, bone metastatis, metastatic neoplastic disease, primary or metastatic lung tumour, urogenital cancers, leukemia, pain, blood cancers, metastatic cancers, cancer pain, chronic pain, inflammation, autoimmune disorders, immunological disorders, diabetic retinopathy, diabetic vasculopathy, diabetic neuralgia, symptoms associated with insulitis, and ulcerative colitis.

In yet another aspect, the present disclosure refers to a method of manufacturing the pharmaceutical composition as disclosed herein, the method comprising the following steps:

(a) blending an active pharmaceutical ingredient (API) selected from sodium meta-arsenite and potassium meta-arsenite with the following pharmaceutically acceptable excipients to form a powder blend:

(i) a filler or diluent in a range of from 5 to 95% w/w of the solid core, wherein the filler or diluent is selected from dibasic calcium phosphate anhydrous, partially pregelatinised starch, silicified microcrystalline cellulose, microcrystalline cellulose, calcium sulphate dihydrate, lactose, calcium hydrogen phosphate, calcium carbonate, sodium carbonate, calcium phosphate, sodium phosphate, or a mixture thereof,

(ii) a disintegrant in a range of from 10 to 90% w/w of the solid core, wherein the disintegrant is selected from L-hydroxypropyl cellulose, partially pregelatinised starch, crospovidone, potato starch, corn starch, sodium starch glycolate, and alginic acid,

(iii) a glidant in a range of from 0.1 to 5% w/w of the solid core, wherein the glidant is selected from colloidal silicon dioxide and talc,

(iv) a lubricant in a range of from 0.1 to 5% w/w of the solid core, and wherein the lubricant is selected from sodium stearyl fumarate, magnesium stearate, stearic acid, talc, and silica, and

(v) optionally a binder in a range of from 0 to 30% w/w of the solid core; wherein the binder is selected from silicified microcrystalline cellulose, microcrystalline cellulose, partially pregelatinised starch, L-hydroxypropyl cellulose (low substituted hydroxypropylcellulose), hydroxypropyl cellulose, copovidone (polyvinylpyrrolidone), pregelatinised maize starch, hydroxypropylmethylcellulose, starch, acacia, corn starch, and gelatin;

(b) compressing the powder blend formed in step (a) to form a solid core;

and

(c) coating the solid core with an enteric coating comprising an enteric polymer, wherein the enteric polymer is selected from copolymers of acrylic acids and their esters or methacrylic acids or their esters, cellulose acetate phthalate polymers, hydroxypropyl methylcellulose phthalate polymers, hydroxypropyl methylcellulose acetate succinate, polyvinyl acetate phthalate, cellulose acetate trimellitate, and combinations thereof;

wherein the pharmaceutically acceptable excipients are selected such that oxidation of meta-arsenite to meta-arsenate is minimised,

wherein the weight percentage of the enteric coating is from 6% w/w to 20% w/w with respect to the total weight of the pharmaceutical composition,

wherein the enteric coating provides a weight gain of about 9.5% w/w of the solid core, a weight gain of about 10% w/w of the solid core, a weight gain of about 10.5% w/w of the solid core, a weight gain of about 11% w/w of the solid core, a weight gain of about 11.5% w/w of the solid core, a weight gain of about 12% w/w of the solid core, a weight gain of about 12.5% w/w of the solid core, a weight gain of about 13% w/w of the solid core, a weight gain of about 13.5% w/w of the solid core, or a weight gain of about 14% w/w of the solid core, and

wherein the coating thickness is from 6.5% to 15% of the thickness of the pharmaceutical composition.

In yet another aspect, the present disclosure refers to a use of a pharmaceutical composition as disclosed herein in the manufacture of an oral medicament for the treatment of a disease or condition, wherein the disease or condition is selected from solid malignancy, bone metastatis, metastatic neoplastic disease, primary or metastatic lung tumour, urogenital cancers, leukemia, pain, blood cancers, metastatic cancers, cancer pain, chronic pain,

CLAIMS:

1. A pharmaceutical composition, which is in the form of an enteric coated tablet or an enteric coated capsule, suitable for oral administration comprising:

(a) a solid core comprising sodium meta-arsenite or potassium meta-arsenite, and the following pharmaceutically acceptable excipients:

(i) a filler or diluent in a range of from 5 to 95% w/w of the solid core, wherein the filler or diluent is selected from dibasic calcium phosphate anhydrous, partially pregelatinised starch, silicified microcrystalline cellulose, microcrystalline cellulose, calcium sulphate dihydrate, lactose, calcium hydrogen phosphate, calcium carbonate, sodium carbonate, calcium phosphate, sodium phosphate, or a mixture thereof;

(ii) a disintegrant in a range of from 10 to 90% w/w of the solid core, wherein the disintegrant is selected from L-hydroxypropyl cellulose, partially pregelatinised starch, crospovidone, potato starch, corn starch, sodium starch glycolate, and alginic acid;

(iii) a glidant in a range of from 0.1 to 5% w/w of the solid core, wherein the glidant is selected from colloidal silicon dioxide and talc;

(iv) a lubricant in a range of from 0.1 to 5% w/w of the solid core, wherein the lubricant is selected from sodium stearyl fumarate, magnesium stearate, stearic acid, talc, and silica; and

(v) optionally a binder in a range of from 0 to 30% w/w of the solid core; wherein the binder is selected from silicified microcrystalline cellulose, microcrystalline cellulose, partially pregelatinised starch, L-hydroxypropyl cellulose (low substituted hydroxypropylcellulose), hydroxypropyl cellulose, copovidone (polyvinylpyrrolidone), pregelatinised maize starch, hydroxypropylmethylcellulose, starch, acacia, corn starch, and gelatin;

and

(b) an enteric coating comprising an enteric polymer, wherein the enteric polymer is selected from copolymers of acrylic acids and their esters or methacrylic acids or their esters, cellulose acetate phthalate polymers, hydroxypropyl methylcellulose phthalate polymers, hydroxypropyl methylcellulose acetate succinate, polyvinyl acetate phthalate, cellulose acetate trimellitate, and combinations thereof;

wherein the pharmaceutically acceptable excipients are selected such that oxidation of meta-arsenite to meta-arsenate is minimised,

wherein the weight percentage of the enteric coating is from 6% w/w to 20% w/w with respect to the total weight of the pharmaceutical composition,

wherein the enteric coating provides a weight gain of about 9.5% w/w of the solid core, a weight gain of about 10% w/w of the solid core, a weight gain of about 10.5% w/w of the solid core, a weight gain of about 11% w/w of the solid core, a weight gain of about 11.5% w/w of the solid core, a weight gain of about 12% w/w of the solid core, a weight gain of about 12.5% w/w of the solid core, a weight gain of about 13% w/w of the solid core, a weight gain of about 13.5% w/w of the solid core, or a weight gain of about 14% w/w of the solid core, and

wherein the coating thickness is from 6.5% to 15% of the thickness of the pharmaceutical composition.

2. The pharmaceutical composition according to claim 1, wherein the amount of sodium meta-arsenite or potassium meta-arsenite in the solid core is 0.1 to 5.0% w/w of the solid core.

3. The pharmaceutical composition according to claim 1 or 2, wherein the solid core comprises sodium meta-arsenite.

4. The pharmaceutical composition according to any one of claims 1 to 3, wherein the filler or diluent is present in the solid core of the pharmaceutical composition in an amount of from 10 to 90% w/w of the solid core.

5. The pharmaceutical composition according to any one of claims 1 to 4, wherein the filler or diluent is selected from dibasic calcium phosphate anhydrous, partially pregelatinised starch, silicified microcrystalline cellulose, microcrystalline cellulose, lactose, calcium hydrogen phosphate, calcium carbonate, sodium carbonate, calcium phosphate, sodium phosphate, or a mixture thereof.

6. The pharmaceutical composition according to claim 5, wherein the filler or diluent is dibasic calcium phosphate anhydrous, partially pregelatinised starch, or a mixture thereof.

7. The pharmaceutical composition according to any one of claims 1 to 6, wherein the disintegrant is present in the solid core of the pharmaceutical composition in an amount of from 10 to 50% w/w of the solid core.

8. The pharmaceutical composition according to any one of claims 1 to 7, wherein the disintegrant is selected from L-hydroxypropyl cellulose, partially pregelatinised starch, potato starch, corn starch, sodium starch glycolate, and alginic acid.

9. The pharmaceutical composition according to claim 8, wherein the disintegrant is L-hydroxypropyl cellulose, partially pregelatinised starch, sodium starch glycolate, or a mixture of two or more thereof.

10. The pharmaceutical composition according to any one of claims 1 to 9, wherein the glidant is present in the solid core of the pharmaceutical composition in an amount of from 0.3 to 4.0% w/w of the solid core.

11. The pharmaceutical composition according to any one of claims 1 to 10, wherein the glidant is colloidal silicon dioxide.

12. The pharmaceutical composition according to any one of claims 1 to 10, wherein the glidant is talc.

13. The pharmaceutical composition according to any one of claims 1 to 12, wherein the lubricant is present in the solid core of the pharmaceutical composition in an amount of from 0.3 to 4.0% w/w of the solid core.

14. The pharmaceutical composition according to any one of claims 1 to 13, wherein the lubricant is selected from sodium stearyl fumarate, magnesium stearate, stearic acid, and silica.

15. The pharmaceutical composition according to claim 14, wherein the lubricant is sodium stearyl fumarate.

16. The pharmaceutical composition according to any one of claims 1 to 15, further comprising a binder in an amount of from 1 to 30% w/w of the solid core, wherein the binder is selected from silicified microcrystalline cellulose, microcrystalline cellulose, partially pregelatinised starch, L-hydroxypropyl cellulose (low substituted hydroxypropylcellulose), hydroxypropyl cellulose, pregelatinised maize starch, hydroxypropylmethylcellulose, starch, acacia, corn starch, and gelatin.

17. The pharmaceutical composition according to claim 16, wherein the binder is L-hydroxypropyl cellulose (low substituted hydroxypropylcellulose), a mixture of L-hydroxypropyl cellulose (low substituted hydroxypropylcellulose) and hydroxypropyl cellulose, or partially pregelatinised starch.

18. The pharmaceutical composition according to any one of claims 1 to 17, wherein the enteric coating provides a weight gain of about 10% w/w of the solid core, a weight gain of about 10.5% w/w of the solid core, a weight gain of about 11% w/w of the solid core, a weight gain of about 11.5% w/w of the solid core, a weight gain of about 12% w/w of the solid core, a weight gain of about 12.5% w/w of the solid core, a weight gain of about 13% w/w of the solid core, a weight gain of about 13.5% w/w of the solid core, or a weight gain of about 14% w/w of the solid core.

19. The pharmaceutical composition according to any one of claims 1 to 18, wherein the enteric coating polymer is selected from copolymers of acrylic acids and their esters or methacrylic acids or their esters, cellulose acetate phthalate polymers, hydroxypropyl methylcellulose phthalate polymers, hydroxypropyl methylcellulose acetate succinate, cellulose acetate trimellitate, and combinations thereof.

20. The pharmaceutical composition according to claim 19, wherein the enteric coating polymer is a copolymer of methacrylic acid and ethyl acrylate (1:1).

21. The pharmaceutical composition according to any one of claims 1 to 20, wherein the solid core comprises sodium meta-arsenite, dibasic calcium phosphate anhydrous, L-hydroxypropyl cellulose, hydroxypropyl cellulose, colloidal silicon dioxide, and sodium stearyl fumarate.

22. The pharmaceutical composition according to any one of claims 1 to 20, wherein the solid core comprises sodium meta-arsenite, dibasic calcium phosphate anhydrous powder, partially pregelatinised starch, dibasic calcium phosphate anhydrous, sodium starch glycolate, colloidal silicon dioxide, and sodium stearyl fumarate.

23. The pharmaceutical composition according to any one of claims 1 to 20, wherein the solid core comprises sodium meta-arsenite, dibasic calcium phosphate anhydrous powder, dibasic calcium phosphate anhydrous, L-hydroxypropyl cellulose, sodium starch glycolate, colloidal silicon dioxide, and sodium stearyl fumarate.

24. The pharmaceutical composition according to any one of claims 1 to 20, wherein the solid core comprises sodium meta-arsenite, dibasic calcium phosphate anhydrous, partially pregelatinised starch, sodium starch glycolate, colloidal silicon dioxide, and sodium stearyl fumarate.

25. The pharmaceutical composition according to any one of claims 1 to 20, wherein the solid core comprises sodium meta-arsenite, dibasic calcium phosphate anhydrous,

silicified microcrystalline cellulose, sodium starch glycolate, colloidal silicon dioxide, and sodium stearyl fumarate.

26. The pharmaceutical composition according to any one of claims 1 to 20, wherein the pharmaceutical composition is an enteric coated tablet comprising 1.67% w/w sodium meta-arsenite of the solid core, and having a solid core diameter of about 6.5 mm, a solid core mass of 150 mg, and an enteric coating which has added about 12% w/w of the solid core.

27. A pharmaceutical composition according to any one of claims 1 to 26 for use in the treatment of a disease or condition, wherein the disease or condition is selected from solid malignancy, bone metastatis, metastatic neoplastic disease, primary or metastatic lung tumour, urogenital cancers, leukemia, pain, blood cancers, metastatic cancers, cancer pain, chronic pain, inflammation, autoimmune disorders, immunological disorders, diabetic retinopathy, diabetic vasculopathy, diabetic neuralgia, symptoms associated with insulitis, and ulcerative colitis.

28. A method of manufacturing the pharmaceutical composition according to any one of claims 1 to 26, the method comprising the following steps:

(a) blending an active pharmaceutical ingredient (API) selected from sodium meta-arsenite and potassium meta-arsenite with the following pharmaceutically acceptable excipients to form a powder blend:

(i) a filler or diluent in a range of from 5 to 95% w/w of the solid core, wherein the filler or diluent is selected from dibasic calcium phosphate anhydrous, partially pregelatinised starch, silicified microcrystalline cellulose, microcrystalline cellulose, calcium sulphate dihydrate, lactose, calcium hydrogen phosphate, calcium carbonate, sodium carbonate, calcium phosphate, sodium phosphate, or a mixture thereof,

(ii) a disintegrant in a range of from 10 to 90% w/w of the solid core, wherein the disintegrant is selected from L-hydroxypropyl cellulose, partially pregelatinised starch, crospovidone, potato starch, corn starch, sodium starch glycolate, and alginic acid,

(iii) a glidant in a range of from 0.1 to 5% w/w of the solid core, wherein the glidant is selected from colloidal silicon dioxide and talc,

(iv) a lubricant in a range of from 0.1 to 5% w/w of the solid core, and wherein the lubricant is selected from sodium stearyl fumarate, magnesium stearate, stearic acid, talc, and silica, and

(v) optionally a binder in a range of from 0 to 30% w/w of the solid core; wherein the binder is selected from silicified microcrystalline cellulose, microcrystalline cellulose, partially pregelatinised starch, L-hydroxypropyl cellulose (low substituted hydroxypropylcellulose), hydroxypropyl cellulose, copovidone (polyvinylpyrrolidone), pregelatinised maize starch, hydroxypropylmethylcellulose, starch, acacia, corn starch, and gelatin;

(b) compressing the powder blend formed in step (a) to form a solid core;

and

(c) coating the solid core with an enteric coating comprising an enteric polymer, wherein the enteric polymer is selected from copolymers of acrylic acids and their esters or methacrylic acids or their esters, cellulose acetate phthalate polymers, hydroxypropyl methylcellulose phthalate polymers, hydroxypropyl methylcellulose acetate succinate, polyvinyl acetate phthalate, cellulose acetate trimellitate, and combinations thereof;

wherein the pharmaceutically acceptable excipients are selected such that oxidation of meta-arsenite to meta-arsenate is minimised,

wherein the weight percentage of the enteric coating is from 6% w/w to 20% w/w with respect to the total weight of the pharmaceutical composition,

wherein the enteric coating provides a weight gain of about 9.5% w/w of the solid core, a weight gain of about 10% w/w of the solid core, a weight gain of about 10.5% w/w of the solid core, a weight gain of about 11% w/w of the solid core, a weight gain of about 11.5% w/w of the solid core, a weight gain of about 12% w/w of the solid core, a weight gain of about 12.5% w/w of the solid core, a weight gain of about 13% w/w of the solid core, a weight gain of about 13.5% w/w of the solid core, or a weight gain of about 14% w/w of the solid core, and

wherein the coating thickness is from 6.5% to 15% of the thickness of the pharmaceutical composition.

29. A method according to claim 28, wherein step (a) comprises two steps:

(i) blending the API with a portion of the filler to form an API premix; and

(ii) blending the glidant, the disintegrant, the lubricant, and optionally the binder with the API premix.

30. A method according to claim 28, wherein step (a) comprises three steps:

(i) blending the API with a portion of the filler to form an API premix;

(ii) blending the glidant, the disintegrant, and optionally the binder with the API premix; and then

(iii) adding the lubricant (which has optionally been mixed with a portion of the mixture from step (ii)), and then blending.

31. A method according to any one of claims 28 to 30, wherein step (a) and/or step (b) do not involve the addition of water or solvent.

32. Use of a pharmaceutical composition according to any one of claims 1 to 26 in the manufacture of an oral medicament for the treatment of a disease or condition, wherein the disease or condition is selected from solid malignancy, bone metastatis, metastatic neoplastic disease, primary or metastatic lung tumour, urogenital cancers, leukemia, pain, blood cancers, metastatic cancers, cancer pain, chronic pain, inflammation, autoimmune disorders, immunological disorders, diabetic retinopathy, diabetic vasculopathy, diabetic neuralgia, symptoms associated with insulitis, and ulcerative colitis.