products from community pharmacies, and has found that of nearly 900 tested medicines, 22% have failed to be within the limits of ±10% for the active ingredient (which is the limit commonly required for US Pharmacopoeia formulations) (Australian National Coordinating Committee on Therapeutic Goods, 2008). Serious adverse effects that have been reported in association with compounded topical anesthetics include arrythmia, seizures, coma, methemoglobinemia and hypoxemia. The US FDA has cautioned against factors such as using too much agent, covering too much body surface area and applying to irritated or broken skin (Fry et al; Kennedy et al.; Wolf et al.).

[0010] LAT has needed to be compounded by pharmacies due to issues with the stability of the product. For example, it has been necessary to store LAT at low temperatures (for example 0-4 °C) and LAT is photosensitive. However, there can be difficulties for compounding pharmacies to appropriately dissolve a gelling agent (if the composition is to be formulated as a gel), and difficulties in ensuring appropriate concentrations of the active agents, not to mention difficulties in providing sterile compositions. There may also be difficulties for pharmacists if compounding instructions are not sufficiently clear. To the inventors' knowledge, there are no compositions comprising lignocaine, adrenaline and tetracaine which have been authorized by a regulatory body.

[0011] In various aspects, there is therefore a need to be able to prepare a pharmaceutical composition that is able to topically treat wounds for both blood loss and pain. In another embodiment, there is a need to be able to prepare a pharmaceutical composition that can be produced industrially, that is storage stable, and which can be prepared in a sterile manner.

BRIEF SUMMARY

[0011a] In one aspect of the present disclosure, there is provided a method of preparing a topical pharmaceutical composition, the method comprising stirring an aqueous liquid comprising at least one local anesthetic agent and a vasoconstrictive agent, wherein the stirring is performed substantially without forming a vortex and under an inert gas; wherein the topical pharmaceutical composition has a viscosity of from 0.01 cPs to 2,500 cPs at 20 °C, or a viscosity of from 2,500 cPs to 15,000 cPs at 20 °C.

[0011b] In another aspect of the present disclosure, there is provided a method of preparing a topical pharmaceutical composition, the method comprising:

(i) Preparing a first liquid by dry blending at least one local anesthetic agent and a gelation agent, and then adding the dry blend to a stirred aqueous liquid, wherein the liquid is

stirred substantially without forming a vortex and under an inert gas;

(ii) Preparing a second liquid by adding an oxygen scavenger and a vasoconstrictive agent to a stirred aqueous liquid, wherein the liquid is stirred substantially without forming a vortex and under an inert gas; and

(iii) Combining and stirring the first and second liquids together, wherein the stirring is performed substantially without forming a vortex and under an inert gas;

wherein the topical pharmaceutical composition has a viscosity of from 0.01 cPs to 2,500 cPs at 20 °C, or a viscosity of from 2,500 cPs to 15,000 cPs at 20 °C.

[0011c] In yet another aspect of the present disclosure, there is provided a topical pharmaceutical composition comprising at least one local anesthetic agent and a vasoconstrictive agent in an aqueous liquid, wherein the liquid comprises less than 1 ppm oxygen; wherein the topical pharmaceutical composition has a viscosity of from 0.01 cPs to 2,500 cPs at 20 °C, or a viscosity of from 2,500 cPs to 15,000 cPs at 20 °C.

[0011d] In a further aspect of the present disclosure, there is provided a use of a pharmaceutical composition as disclosed herein in the manufacture of a medicament for reducing blood loss and pain at a topical area of a subject.

[0011e] In another aspect of the present disclosure, there is provided a pharmaceutical composition as disclosed herein, for use in therapy.

SUMMARY ~~OF INVENTION~~

[0012] In one aspect, the present invention is directed to a method of preparing a topical pharmaceutical composition, which may at least partially overcome at least one of the abovementioned disadvantages or provide the consumer with a useful or commercial choice. With the foregoing in view, the present invention in one form, resides broadly in a method of preparing a topical pharmaceutical composition, wherein the topical pharmaceutical composition comprises at least one local anesthetic agent, and a vasoconstrictive agent.

[0013] In a first aspect, the present invention provides a method of preparing a topical pharmaceutical composition, the method comprising stirring an aqueous liquid comprising at least one local anesthetic agent and a vasoconstrictive agent, wherein the stirring is performed substantially without forming a vortex and under an inert gas.

[0014] When the vasoconstrictive agent is adrenaline, the stability of adrenaline can pose

CLAIMS

1. A method of preparing a topical pharmaceutical composition, the method comprising stirring an aqueous liquid comprising at least one local anesthetic agent and a vasoconstrictive agent, wherein the stirring is performed substantially without forming a vortex and under an inert gas; wherein the topical pharmaceutical composition has a viscosity of from 0.01 cPs to 2,500 cPs at 20 °C, or a viscosity of from 2,500 cPs to 15,000 cPs at 20 °C.

2. The method according to claim 1, wherein the method comprises combining a first liquid comprising the at least one local anesthetic agent and a second liquid comprising the vasoconstrictive agent to thereby provide the aqueous liquid comprising the at least one local anesthetic agent and the vasoconstrictive agent.

3. The method of claim 2, wherein the method further comprises preparing the second liquid by adding an oxygen scavenger to a stirred liquid, and then adding the vasoconstrictive agent to the stirred liquid, wherein the liquid is stirred substantially without forming a vortex and under an inert gas.

4. The method of claim 3, wherein the oxygen scavenger is metabisulfite.

5. The method of any one of claims 1 to 4, wherein the vasoconstrictive agent is selected from the group consisting of: adrenaline, metaraminol, phenylephrine and norepinephrine.

6. The method of claim 5, wherein the vasoconstrictive agent is adrenaline.

7. The method of claim 1, wherein the liquid further comprises a gelation agent, and the topical pharmaceutical composition is in the form of a gel.

8. The method according to any one of claims 2 to 6, wherein the first liquid further comprises a gelation agent.

9. The method of ~~any one of claims 2 to 6 and 8~~claim 7 or claim 8, wherein the method further comprises preparing the first liquid by dry blending the at least one local anesthetic agent and the gelation agent, and then adding the dry blend to a stirred liquid, wherein the liquid is stirred substantially without forming a vortex and under an inert gas.

10. The method of any one of claims 7~~2~~ to 9, wherein the gelation agent is selected from the group consisting of: a starch, cellulose, a cellulose ester, a poloxamer, a carbomer, an acrylate, an acrylate copolymer, cetostearyl alcohol, gelatin, an alginate, a pectin, acacia gum, locust bean

gum, karaya gum, tragacanth gum, xanthan gum, guar gum and carrageenan.

11. The method of claim 10, wherein the gelation agent is hydroxypropylmethyl cellulose.

12. The method of any one of claims 1 to 11, wherein the at least one local anesthetic agent is selected from the group consisting of: acetamidoeugenol, alfadolone acetate, alfaxalone, amucaine, amolanone, amylocaine, articaine, benoxinate, benzocaine, betoxycaine, biphenamine, bupivacaine, burethamine, butacaine, butaben, butanilicaine, buthalital, butoxycaine, carticaine, 2-chloroprocaine, cocaethylene, cocaine, cyclomethycaine, dibucaine, dimethisoquin, dimethocaine, diperadon, dyclonine, ecgonidine, ecgonine, ethyl aminobenzoate, ethyl chloride, etidocaine, etoxadrol, β-eucaine, euprocin, fenalcomine, fomocaine, hexobarbital, hexylcaine, hydroxydione, hydroxyprocaine, hydroxytetracaine, isobutylp-aminobenzoate, kentamine, leucinocaine mesylate, levoxadrol, lignocaine, mepivacaine, meprylcaine, metabutoxycaine, methohexital, methyl chloride, midazolam, myrtecaine, naepaine, octacaine, orthocaine, oxethazaine, parethoxycaine, phenacaine, phencyclidine, phenol, piperocaine, piridocaine, polidocanol, pramoxine, prilocaine, procaine, propanidid, propanocaine, proparacaine, propipocaine, propofol, propoxycaine, pseudococaine, pyrrocaine, risocaine, ropivacaine, salicyl alcohol, tetracaine, thialbarbital, thimylal, thiobutabarbital, thiopental, tolycaine, trimecaine and zolamine and combinations thereof.

13. The method of any one of claims 1 to 12, wherein the at least one local anesthetic agent is two anesthetic agents.

14. The method of claim 13, wherein the at least one local anesthetic agent is lignocaine and tetracaine.

15. A method of preparing a topical pharmaceutical composition, the method comprising:

    (i) Preparing a first liquid by dry blending at least one local anesthetic agent and a gelation agent, and then adding the dry blend to a stirred aqueous liquid, wherein the liquid is stirred substantially without forming a vortex and under an inert gas;

    (ii) Preparing a second liquid by adding an oxygen scavenger and a vasoconstrictive agent to a stirred aqueous liquid, wherein the liquid is stirred substantially without forming a vortex and under an inert gas; and

    (iii) Combining and stirring the first and second liquids together, wherein the stirring is performed substantially without forming a vortex and under an inert gas;

wherein the topical pharmaceutical composition has a viscosity of from 0.01 cPs to 2,500 cPs at 20 °C, or a viscosity of from 2,500 cPs to 15,000 cPs at 20 °C.

16. The method of claim 15, wherein in step (i) the first liquid is heated to greater than 85 °C and then cooled to from 25 to 35 °C before standing for at least 10 hours.

17. The method of claim 15 or claim 16, wherein in step (iii) the first and second liquids are cooled to less than about 30 °C before being combined.

18. The method of any one of claims 15 to 17, wherein the at least one anesthetic agent is lignocaine and tetracaine; wherein the at least one vasoconstrictive agent is adrenaline; and wherein the gelation agent is hydroxypropylmethyl cellulose.

~~19. The topical pharmaceutical composition prepared by the method of any one of claims 1 to 18.~~

~~20.~~19. A topical pharmaceutical composition comprising at least one local anesthetic agent and a vasoconstrictive agent in an aqueous liquid, wherein the liquid comprises less than 1 ppm oxygen; wherein the topical pharmaceutical composition has a viscosity of from 0.01 cPs to 2,500 cPs at 20 °C, or a viscosity of from 2,500 cPs to 15,000 cPs at 20 °C.

~~21.~~20. The topical pharmaceutical composition of claim 19~~20~~, wherein: the at least one local anesthetic agent is lignocaine and tetracaine; the vasoconstrictive agent is adrenaline; the liquid further comprises a gelation agent, and the topical pharmaceutical composition is in the form of a gel.

~~22.~~21. Use of a pharmaceutical composition of claim 19 or claim 20 in the manufacture of a medicament for ~~A method of~~ reducing blood loss and pain at a topical area of a subject~~, comprising administering the pharmaceutical composition of any one of claims 19 to 21 to the subject~~.

~~23.~~22. The ~~method~~ use of claim 21~~22~~, wherein the pharmaceutical composition is to be applied to broken skin of the subject.

23. A pharmaceutical composition of claim 19 or claim 20, for use in therapy.