chloride, a detergent (Innotox®: polysorbate 20; Alluzience®: polysorbate 80), an amino acid (Innotox®: methionine; Alluzience®: histidine) and an additional excipient (Innotox®: sodium phosphate as a buffer; Alluzience®: sucrose).

[007] Despite these advances in the preparation of liquid botulinum toxin formulations, there is still a need for new options to develop ready-to-use liquid formulations of botulinum toxin, which are stable during transport and storage.

OBJECT OF THE INVENTION

[008] It is an object of the present invention to provide a stable liquid formulation of botulinum toxin that is ready-to-use for therapeutic and cosmetic treatments.

SUMMARY

[009] The present disclosure is based on the surprising finding that the addition of a chelating agent (e.g., EDTA) or phosphate to a human serum albumin (HSA)-containing liquid formulation of botulinum toxin results in an improved formulation that is both heat and light stable.

[0010] Thus, in one example, the present disclosure provides a liquid formulation comprising:

(i) botulinum toxin,
(ii) a stabilizing protein, preferably human serum albumin (HSA), and
(iii) a chelating agent or phosphate.

[0010a] In one aspect, the present disclosure provides a liquid formulation, comprising:

(i) botulinum toxin,
(ii) a stabilizing protein, and
(iii) a chelating agent or phosphate.

[0011] Optionally, the liquid formulation of the present disclosure further comprises (iv) a salt of calcium, magnesium or zinc, or a mixture thereof, or (v) a tonicity agent (e.g., sodium chloride), or (vi) a buffering agent (e.g., a phosphate buffer or a histidine buffer or both), or two of components (iv)-(vi) (e.g., (iv) and (v), (iv) and (vi), or (v) and (vi)), or all three of components (iv)-(vi).

[0012] In another aspect, the present disclosure relates to a liquid formulation according to the present disclosure for use in therapy, in particular for use in the treatment of neuromuscular diseases, pain, sialorrhea, hyperhidrosis, urological disorders, and neurological disorders.

[0013] In a further example, the present disclosure relates to the cosmetic (aesthetic) use of the liquid formulation of the present disclosure for the treatment of a cosmetic condition, preferably a skin condition, in particular for the treatment of skin lines or folds or wrinkles.

[0013a] In a further aspect, the present disclosure relates to cosmetic use of the liquid formulation of the present disclosure for the treatment of a cosmetic condition.

[0014] In yet another example, the present disclosure relates to a method of treating a disease or condition, comprising administering an effective amount of the liquid formulation of the present disclosure to a person in need thereof.

[0014a] In yet another aspect, the present disclosure relates to use of the liquid formulation of the present disclosure in the manufacture of a medicament for the treatment of neuromuscular diseases, pain, sialorrhea, hyperhidrosis, urological disorders, or neurological disorders.

[0015] Preferred examples of the liquid botulinum toxin formulation, its use and methods of use according to the present disclosure are set forth in the appended claims.

[0016] The present disclosure may be understood more readily by reference to the following detailed description and the example included therein.

DETAILED DESCRIPTION OF THE INVENTION

[0017] The present invention is based on the unexpected finding that the presence of a chelating agent (e.g., EDTA) or phosphate in a human serum albumin (HSA)-containing liquid formulation of botulinum toxin results in an improved formulation that is not only heat but also light stable. In addition, it was unexpectedly found that the addition of a salt of calcium, magnesium, or zinc results in reduced injection pain.

[0018] The liquid formulation of the present invention advantageously provides an improved safety and dosing accuracy compared to lyophilized botulinum toxin preparations in powder form since the formulation does not need to be reconstituted prior to injection but is ready-to-use. Furthermore, the liquid formulation exhibits an

CLAIMS

1. A liquid formulation, comprising
   (i) botulinum toxin,
   (ii) a stabilizing protein, and
   (iii) a chelating agent or phosphate.

2. The liquid formulation of claim 1, wherein the stabilizing protein is selected from human serum albumin, ovalbumin, casein, and mixtures thereof, or wherein the stabilizing protein is human serum albumin.

3. The liquid formulation of claim 1 or 2, wherein the stabilizing protein is human serum albumin and the human serum albumin is present in the liquid formulation at a concentration of 0.001-1.00% w/v.

4. The liquid formulation of any one of claims 1 to 3, wherein the chelating agent is selected from the group consisting of aminopolycarboxylic acids having three to six carboxylic acid functional groups, citrate, porphyrins, N,N,N′,N′-tetrakis(2-pyridinylmethyl)-1,2-ethanediamine (TPEN), triethylenetetramine (TETA), and mixture thereof.

5. The liquid formulation of claim 4, wherein the chelating agent is an aminopolycarboxylic acid of general formula (I):

$$(HO_2CCH_2)_2N\text{-}R\text{-}N(CH_2CO_2H)_2 \qquad (I),$$

   wherein R comprises no carboxylic acid group or one or two carboxylic acid groups, the aminopolycarboxylic acid preferably being selected from the group consisting of ethylenediaminetetraacetic acid (EDTA), ethylene glycol-bis(β-aminoethylether)-*N,N,N′,N′*-tetraacetic acid (EGTA), 1,2-bis(*o*-aminophenoxy)ethane-*N*,*N*,*N′*,*N′*-tetraacetic acid (BAPTA), diethylenetriaminepentaacetic acid (DTPA), triethylenetetraminehexaacetate (TTHA), and mixture thereof.

6. The liquid formulation of any one of claims 1 to 5, wherein the chelating agent is present in the liquid formulation at a concentration of 0.01-100 mM.

7. The liquid formulation of any one of claims 1 to 6, wherein the botulinum toxin is botulinum neurotoxin free of complexing proteins, or wherein the botulinum toxin is of serotype A, or wherein the botulinum toxin is botulinum neurotoxin of serotype A free of complexing proteins, or wherein the botulinum toxin is of serotype A and is present at a concentration of 1-1000 U/ml, or wherein the botulinum toxin is botulinum neurotoxin of serotype A free of complexing proteins and is present at a concentration of 1-1000 U/ml.

8. The liquid formulation of any one of claims 1 to 7, comprising
   (i) botulinum toxin,
   (ii) human serum albumin, and
   (iii) EDTA.

9. The liquid formulation of any one of claims 1 to 8, wherein the liquid formulation further comprises:

   (iv) a salt of calcium, magnesium or zinc, or a mixture thereof,

   or wherein the liquid formulation further comprises:

   (iv) a salt of calcium, magnesium or zinc, or a mixture thereof, wherein the salt is present in the liquid formulation in an amount of 0.01-100 mM, wherein the salt is calcium chloride and is present in the liquid formulation in an amount of 0.01-100 mM.

10. The liquid formulation of any one of claims 1 to 9, wherein the liquid formulation further comprises:

    (v) a tonicity agent,

    or wherein the liquid formulation further comprises:

    (v) a tonicity agent, wherein the tonicity agent is present in the liquid formulation in an amount of 0.01-2.0% w/v, or wherein the tonicity agent is sodium

chloride, or wherein the tonicity agent is sodium chloride and is present in the liquid formulation in an amount of 0.01-2.0% w/v.

11. The liquid formulation of any one of claims 1 to 10, wherein the liquid formulation further comprises:

    (vi) a buffering agent,

    or wherein the liquid formulation further comprises:

    (vi) a buffering agent, wherein the buffering agent is present in the liquid formulation in an amount of 1-100 mM, or wherein the buffering agent is an amino acid, phosphate, or a mixture thereof, or wherein the buffering agent is histidine, or wherein the buffering agent is histidine, phosphate, or a mixture thereof, and the histidine and phosphate are present in the liquid formulation in an amount of 1-100 mM.

12. The liquid formulation of any one of claims 1 to 11, wherein the pH of the liquid formulation is in the range of 5.0-8.0.

13. A liquid formulation according to any one of claims 1 to 12 for use in therapy, particularly for use in the treatment of neuromuscular diseases, pain, sialorrhea, hyperhidrosis, urological disorders, and neurological disorders.

14. Cosmetic use of the liquid formulation of any one of claims 1 to 12 for the treatment of a cosmetic condition.

15. Use of the liquid formulation of any one of claims 1 to 12 in the manufacture of a medicament for the treatment of neuromuscular diseases, pain, sialorrhea, hyperhidrosis, urological disorders, or neurological disorders.