CLAIMS:

1. An ophthalmic formulation comprising:

(a) an aqueous suspension of micronized Compound A from 0.1 to 5.0 % (w/v),

(b) a surfactant,

(c) boric acid from about 0.05 to about 2.0 % (w/v), and.

(d) a buffering agent that maintains the pH from about 6.0 to about 7.0.

2. The formulation of clam 1, wherein the suspension of Compound A comprises fine particles of less than about 25 microns.

3. The formulation of claim 2, wherein the fine particles are less than about 10 microns.

4. The formulation of claim 2, wherein the fine particles are between about 3 to about 7 microns.

5. The formulation of claim 1, wherein Compound A is present in the ophthalmic formulation between about 0.5 to about 5.0 % (w/v).

6. The formulation claim 5, wherein Compound A is present in the ophthalmic formulation between about 1.0 to about 4.0 % (w/v).

7. The formulation of claim 5, wherein Compound A is present in the ophthalmic formulation between about 2.0 to about 3.5 % (w/v).

8. The formulation of claim 1, wherein Compound A is present in the ophthalmic formulation at about 3.0 % (w/v).

9. The formulation of claim 1, wherein the surfactant is selected from polysorbate 80, polysorbate 60, polysorbate 40, polysorbate 20, polyoxyl 40 stearate, poloxamers, tyloxapol and POE 35 castor oil.

10. The formulation of claim 1, wherein the surfactant is present in the ophthalmic formulation between about 0.01 to about 0.5 %, w/v.

11. The formulation of claim 10, wherein the surfactant is present from about 0.01 to about 0.1 % (w/v).

12. The formulation of claim 1, wherein the surfactant is present from about 0.01 to about 0.005% (w/v).

13. The formulation of claim 1, wherein the surfactant is polysorbate 80.

14. The formulation of claim 1, wherein the boric acid is present from about 0.5 to about 1.0% (w/v).

15. The formulation of claim 1, wherein the boric acid is present at about 0.8% (w/v).

16. The formulation of claim 1, wherein the formulation further includes a preservative between about 0.005 and about 0.05% (w/v).

17. The formulation according to claim 16, wherein the preservative is benzalkonium chloride.

18. The formulation according to claim 17, wherein the benzalkonium chloride is present in the ophthalmic formulation between about 0.005 and about 0.02 % (w/v).

19. The formulation according to claim 17, wherein the benzalkonium chloride present in the ophthalmic formulation is about 0.01 % (w/v).

20. The formulation according to claim 1, wherein the buffering agent is a pharmaceutically acceptable phosphate buffer.

21. The formulation according to claim 20, wherein the phosphate buffer is present at about 10 mM.

22. The formulation according to claims 20, wherein the phosphate buffer is monobasic sodium phosphate present at between about 0.1 to 0.12%.

23. The formulation according to claim 1, further including a suspending agent selected from sodium carboxymethylcellulose (NaCMC), hydroxyethylcellulose, hypromellose, polyvinyl alcohol, povidone, carbomers, hyaluronic acid and its salts, chondroitin sulfate and its salts, natural gums, and other pharmaceutically acceptable polymers.

24. The formulation according to claim 23, wherein the suspending agent is selected from sodium carboxymethylcellulose (NaCMC) or hypromellose.

25. The formulation according to claim 1, wherein the pH is about 6.5±0.1.

26. The formulation according to claim 1, further comprising edetate disodium.

27. The formulation according to claim 26, wherein the edetate disodium is present between 0.01 – 0.08% (w/v).

28. The formulation according to claim 26, wherein the edetate disodium is present at about 0.03 % w/v.

29. The formulation according to claim 1, comprising:

Ingredient	**%, w/v**
Compound A, micronized	0.4 – 5.0
A suspending agent	0.5-1.5
Boric acid	0.05 – 2.0
A preservative	0.01-0.05
A surfactant	0.01-0.1
A phosphate buffering agent	0.05-0.5
NaCl	TBD (qs to 270-330 mOsm)
NaOH/HCl (pH adjustment)	pH 6.0 – 7.0 ±0.1

30. The formulation according to claim 1, comprising:

Ingredient	**%, w/v**
Compound A, micronized	0.5-3.0
Sodium CMC, low viscosity	0.7
Boric Acid	0.8
Benzalkonium Chloride	0.005-0.15
Polysorbate 80	0.05
Phosphate Buffer	0.12
edetate disodium	0.015-0.06
NaCl	0.4
NaOH/HCl (pH adjustment)	pH 6.5±0.1
Purified Water	q.s. 100.00.

31. The formulation according to claim 1, comprising:

Ingredient	**%, w/v**
Compound A, micronized	0.5-3.0
Sodium CMC, low viscosity	0.70
Boric Acid	0.8
Benzalkonium Chloride	0.01
Polysorbate 80	0.05
Phosphate Buffer	0.12
edetate disodium	0.015
NaOH/HCl (pH adjustment)	pH 6.5±0.1
Purified Water	q.s. 100.00.

32. The formulation according to claim 1, comprising:

Ingredient	**%, w/v**
Compound A, micronized	0.5-3.0
Sodium CMC, low viscosity	0.70
Boric Acid	0.8
Benzalkonium Chloride	0.005
Polysorbate 80	0.05
Phosphate Buffer	0.12
edetate disodium	0.03

NaCl	0.4	
NaOH/HCl (pH adjustment)	pH	6.5±0.1
Purified Water	q.s.	100.00.

33. The formulation according to claim 1, comprising:

Ingredient	**%, w/v**	
Compound A, micronized	0.5-3.0	
Sodium CMC, low viscosity	0.70	
Boric Acid	0.8	
Benzalkonium Chloride	0.01	
Polysorbate 80	0.05	
Phosphate Buffer	0.12	
edetate disodium	0.03	
NaCl	0.4	
NaOH/HCl (pH adjustment)	pH	6.5±0.1
Purified Water	q.s.	100.00.

34. The formulation according to claim 1, comprising:

Ingredient	**%, w/v**	
Compound A, micronized	0.5-3.0	
Sodium CMC, low viscosity	0.70	
Boric Acid	0.8	
Benzalkonium Chloride	0.015	
Polysorbate 80	0.05	
Phosphate Buffer	0.12	
edetate disodium	0.03	
NaCl	0.4	
NaOH/HCl (pH adjustment)	pH	6.5±0.1
Purified Water	q.s.	100.00.

35. The formulation according to claim 1, comprising:

Ingredient	**%, w/v**
Compound A, micronized	0.5-3.0
Sodium CMC, low viscosity	0.70

Boric Acid	0.8	
Benzalkonium Chloride	0.01	
Polysorbate 80	0.05	
Phosphate Buffer	0.12	
edetate disodium	0.06	
NaCl	0.4	
NaOH/HCl (pH adjustment)	pH	6.5±0.1
Purified Water	q.s.	100.00.

36. The formulation of claim 1, further including a second therapeutic ophthalmic agent.

37. The formulation of claim 35, wherein the second ophthalmic agent is selected from the group comprising prostaglandin analogs, β-blockers, carbonic anhydrase inhibitors, rho-kinase inhibitors, α_2 adrenergic agonists, miotics, neuroprotectants, adenosine A_3 antagonists, adenosine A_{2A} agonists, ion channel modulators and combinations thereof.

38. The formulation of claim 36, wherein the second ophthalmic agent is a prostaglandin analog.

39. The formulation of claim 38, wherein the prostaglandin analog is latanoprost.

40. The formulation of claim 39, wherein the latanoprost is present between about 1-200 μg/ml.

41. The formulation of claim 40, wherein the latanoprost is present in about 50 μg/ml.

42. A method of reducing intraocular pressure comprising the step of: topically applying an effective amount of an ophthalmic formulation according to claim 1 to an affected eye of a subject.

43. The method according to claim 42, wherein the ophthalmic formulation is administered to the affected eye of the subject in about 30 to about 50 μl drops.

44. The method according to claim 42, wherein the ophthalmic formulation is administered in about 1 to about 2 drops once or twice daily.

45. The method according to claim 42, wherein the subject has normal-tension glaucoma, OHT, or POAG.

46. A method of treating retinal ganglion cell damage comprising the step of: applying an effective amount of an ophthalmic formulation according to claim 1 to an affected eye of a subject.

47. The method of claim 46, wherein the ophthalmic formulation is administered to the affected eye of the subject in about 30 to about 50 µl drops.

48. The method of claim 46, wherein the ophthalmic formulation is administered in 1 to 2 drops once or twice daily.

49. A method of preventing retinal ganglion cell damage comprising the step of: applying an effective amount of an ophthalmic formulation as according to claim 1 to an eye of a subject.

50. The method as claimed in claim 49 wherein the ophthalmic formulation is administered to the affected eye of the subject in about 30 to about 50 µl drops.

51. The method as claimed in claim 50 wherein the ophthalmic formulation is administered in 1 to 2 drops once or twice daily.

52. The method of claim 42, further comprising administering a second ophthalmic agent.

53. The method of claim 52, wherein the second ophthalmic agent is selected from the group comprising prostaglandin analogs, β-blockers, carbonic anhydrase inhibitors, rho-kinase inhibitors, α_2 agonists, miotics, neuroprotectants, A_3 antagonists, A_2A agonists, ion channel modulators and combinations thereof.

54. The method of claim 53, wherein the second ophthalmic agent is a prostaglandin analog.

55. The method of claim 54, wherein the prostaglandin analog is latanoprost.

56. A kit or packaged formulation comprising a topically applicable ophthalmic formulation of claim 1.

57. A process for preparing an ophthalmic formulation according to claim 1, comprising the steps of:

(a) micronizing Compound A into particle sizes of less than about 50 microns;

(b) suspending the particles of Compound A in an aqueous suspension with a surfactant and a buffering agent;

(c) curing the product from step (b) at about 40° Celsius for between about 24 to about 96 hours; and

(e) adding boric acid from about 0.05 to about 2.0 % (w/v).

58. The process of claim 57, wherein steps (a)-(c) are performed with a volume of less than about 20% of the final volume of the ophthalmic formulation.

59. The process of claim 57, further comprising filtering the cured product of step (c) as a concentrated slurry.

60. The process of claim 57, wherein the milled Compound A is sterilized by gamma irradiation up to a maximum of 40 kGray (kGy).

61. The process of claim 57, wherein the curing step takes place at about 40° Celsius for between about 48 to about 96 hours.

62. The process of claim 57, further comprising adjusting the pH of the aqueous suspension to between about 6.0 and about 7.0 or in a further embodiment to a pH of about 6.5 ± 0.1.

63. The process of claim 57, wherein the process is performed under aseptic conditions.

64. The process of claim 57, further comprising adding a second ophthalmic agent.

65. The process of claim 64, wherein the second ophthalmic agent is selected from the group comprising prostaglandin analogs, β-blockers, carbonic anhydrase inhibitors, rho-kinase inhibitors, α_2 agonists, miotics, neuroprotectants, A_3 antagonists, A_2A agonists, ion channel modulators and combinations thereof.

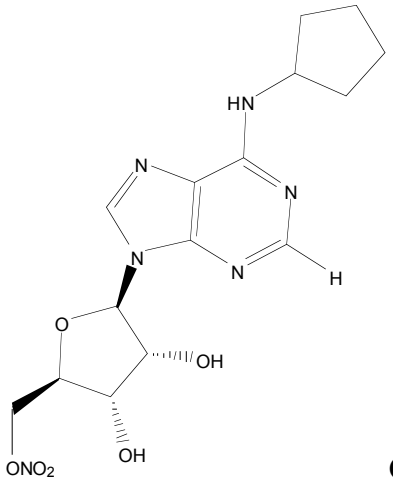
66. The process of claim 65, wherein the second ophthalmic agent is a prostaglandin analog.

67. The process of claim 66, wherein the prostaglandin analog is latanoprost.

CLAIMS

1. An ophthalmic formulation comprising:

(a) an aqueous suspension of micronized Compound A from 0.1 to 5.0 % (w/v),



Compound A

(b) a surfactant,

(c) boric acid from about 0.05 to about 2.0 % (w/v), and

(d) a buffering agent that maintains the pH from about 6.0 to about 7.0.

2. An ophthalmic formulation according to Claim 1, in which the suspension of Compound A comprises fine particles of less than about 25 microns.

3. An ophthalmic formulation according to Claim 2, in which the fine particles are less than about 10 microns.

4. An ophthalmic formulation according to Claim 2 or 3, in which the fine particles are between about 3 to about 7 microns.

5. An ophthalmic formulation according to any preceding claim, in which Compound A is present in the ophthalmic formulation between about 0.5 to about 5.0 % (w/v).

6. An ophthalmic formulation according to any preceding claim, in which Compound A is present in the ophthalmic formulation between about 1.0 to about 4.0 % (w/v).

7. An ophthalmic formulation according to any preceding claim, in which Compound A is present in the ophthalmic formulation between about 2.0 to about 3.5 % (w/v).

8. An ophthalmic formulation according to any preceding claim, in which Compound A is present in the ophthalmic formulation at about 3.0 % (w/v).

9. An ophthalmic formulation according to any preceding claim, in which the surfactant is selected from polysorbate 80, polysorbate 60, polysorbate 40, polysorbate 20, polyoxyl 40 stearate, poloxamers, tyloxapol and POE 35 castor oil.

10. An ophthalmic formulation according to any preceding claim, in which the surfactant is present in the ophthalmic formulation between about 0.01 to about 0.5 %, w/v.

11. An ophthalmic formulation according to any preceding claim, in which the surfactant is present from about 0.01 to about 0.1 % (w/v).

12. An ophthalmic formulation according to any preceding claim, in which the surfactant is present from about 0.01 to about 0.005% (w/v).

13. An ophthalmic formulation according to any preceding claim, in which the surfactant is polysorbate 80.

14. An ophthalmic formulation according to any preceding claim, in which the boric acid is present from about 0.5 to about 1.0% (w/v).

15. An ophthalmic formulation according to any preceding claim, in which the boric acid is present at about 0.8% (w/v).

16. An ophthalmic formulation according to any preceding claim, in which the formulation further includes a preservative between about 0.005 and about 0.05% (w/v).

17. An ophthalmic formulation according to Claim 16, in which the preservative is benzalkonium chloride.

18. An ophthalmic formulation according to Claim 17, in which the benzalkonium chloride is present in the ophthalmic formulation between about 0.005 and about 0.02 % (w/v).

19. An ophthalmic formulation according to Claim 17, in which the benzalkonium chloride present in the ophthalmic formulation is about 0.01 % (w/v).

20. An ophthalmic formulation according to any preceding claim, in which the buffering agent is a pharmaceutically acceptable phosphate buffer.

21. An ophthalmic formulation according to Claim 20, in which the phosphate buffer is present at about 10 mM.

22. An ophthalmic formulation according to Claim 20 or 21, in which the phosphate buffer is monobasic sodium phosphate present at between about 0.1 to 0.12%.

23. An ophthalmic formulation according to any preceding claim, further including a suspending agent selected from sodium carboxymethylcellulose (NaCMC), hydroxyethylcellulose, hypromellose, polyvinyl alcohol, povidone, carbomers, hyaluronic acid and its salts, chondroitin sulfate and its salts, natural gums, and other pharmaceutically acceptable polymers.

24. An ophthalmic formulation according to Claim 23, in which the suspending agent is selected from sodium carboxymethylcellulose (NaCMC) or hypromellose.

25. An ophthalmic formulation according to any preceding claim, in which the pH is about 6.5±0.1.

26. An ophthalmic formulation according to any preceding claim, further comprising edetate disodium.

27. An ophthalmic formulation according to Claim 26, in which the edetate disodium is present between 0.01 – 0.08% (w/v).

28. An ophthalmic formulation according to Claim 26, in which the edetate disodium is present at about 0.03 % w/v.

29. An ophthalmic formulation according to Claim 1 comprising:

Ingredient	**%, w/v**
Compound A, micronized	0.4 – 5.0
A suspending agent	0.5-1.5
Boric acid	0.05 – 2.0
A preservative	0.01-0.05
A surfactant	0.01-0.1
A phosphate buffering agent	0.05-0.5

NaCl	TBD (qs to 270-330 mOsm)
NaOH/HCl (pH adjustment)	pH 6.0 – 7.0 ±0.1

30. An ophthalmic formulation according to Claim 1 comprising:

Ingredient	**%, w/v**
Compound A, micronized	0.5-3.0
Sodium CMC, low viscosity	0.7
Boric Acid	0.8
Benzalkonium Chloride	0.005-0.15
Polysorbate 80	0.05
Phosphate Buffer	0.12
edetate disodium	0.015-0.06
NaCl	0.4
NaOH/HCl (pH adjustment)	pH 6.5±0.1
Purified Water	q.s. 100.00.

31. An ophthalmic formulation according to Claim 1 comprising:

Ingredient	**%, w/v**
Compound A, micronized	0.5-3.0
Sodium CMC, low viscosity	0.70
Boric Acid	0.8
Benzalkonium Chloride	0.01
Polysorbate 80	0.05
Phosphate Buffer	0.12
edetate disodium	0.015
NaOH/HCl (pH adjustment)	pH 6.5±0.1
Purified Water	q.s. 100.00.

32. An ophthalmic formulation according to Claim 1 comprising:

Ingredient	%, w/v
Compound A, micronized	0.5-3.0
Sodium CMC, low viscosity	0.70
Boric Acid	0.8
Benzalkonium Chloride	0.005
Polysorbate 80	0.05
Phosphate Buffer	0.12
edetate disodium	0.03
NaCl	0.4
NaOH/HCl (pH adjustment)	pH 6.5±0.1
Purified Water	q.s. 100.00.

33. An ophthalmic formulation according to Claim 1 comprising:

Ingredient	**%, w/v**
Compound A, micronized	0.5-3.0
Sodium CMC, low viscosity	0.70
Boric Acid	0.8
Benzalkonium Chloride	0.01
Polysorbate 80	0.05
Phosphate Buffer	0.12
edetate disodium	0.03
NaCl	0.4
NaOH/HCl (pH adjustment)	pH 6.5±0.1
Purified Water	q.s. 100.00.

34. An ophthalmic formulation according to Claim 1 comprising:

Ingredient	**%, w/v**
Compound A, micronized	0.5-3.0

Sodium CMC, low viscosity	0.70
Boric Acid	0.8
Benzalkonium Chloride	0.015
Polysorbate 80	0.05
Phosphate Buffer	0.12
edetate disodium	0.03
NaCl	0.4
NaOH/HCl (pH adjustment)	pH 6.5±0.1
Purified Water	q.s. 100.00.

35. An ophthalmic formulation according to Claim 1 comprising:

Ingredient	**%, w/v**
Compound A, micronized	0.5-3.0
Sodium CMC, low viscosity	0.70
Boric Acid	0.8
Benzalkonium Chloride	0.01
Polysorbate 80	0.05
Phosphate Buffer	0.12
edetate disodium	0.06
NaCl	0.4
NaOH/HCl (pH adjustment)	pH 6.5±0.1
Purified Water	q.s. 100.00.

36. An ophthalmic formulation according to any preceding claim, further including a second therapeutic ophthalmic agent.

37. An ophthalmic formulation according to Claim 35, in which the second ophthalmic agent is selected from the group comprising prostaglandin analogs, β-blockers, carbonic anhydrase inhibitors, rho-kinase inhibitors, α2 adrenergic agonists, miotics, neuroprotectants,

adenosine A3 antagonists, adenosine A2A agonists, ion channel modulators and combinations thereof.

38. An ophthalmic formulation according to Claim 36, in which the second ophthalmic agent is a prostaglandin analog.

39. An ophthalmic formulation according to Claim 38, in which the prostaglandin analog is latanoprost.

40. An ophthalmic formulation according to Claim 39, in which the latanoprost is present between about 1-200 μg/ml.

41. An ophthalmic formulation according to Claim 40, in which the latanoprost is present in about 50 μg/ml.

42. An ophthalmic formulation according to any preceding claim for use in a method of reducing intraocular pressure, in which the method comprises a step of topically applying an effective amount of the ophthalmic formulation to an affected eye of a subject.

43. An ophthalmic formulation according to Claim 42 for a use as specified therein, in which the formulation is administered to the affected eye of the subject in about 30 to about 50 μl drops.

44. An ophthalmic formulation according to Claim 42 or 43 for a use as specified therein, in which the formulation is administered in about 1 to about 2 drops once or twice daily.

45. An ophthalmic formulation according to any of Claims 42 to 44 for a use as specified therein, in which the subject has normal-tension glaucoma, OHT, or POAG.

46. An ophthalmic formulation according to any of Claims 1 to 41 for use in a method of treating retinal ganglion cell damage, in which the method comprises a step of applying an effective amount of the ophthalmic formulation to an affected eye of a subject.

47. An ophthalmic formulation according to Claim 46 for a use as specified therein, in which the ophthalmic formulation is administered to the affected eye of the subject in about 30 to about 50 μl drops.

48. An ophthalmic formulation according to any of Claim 46 or 47 for a use as specified therein, in which the ophthalmic formulation is administered in 1 to 2 drops once or twice daily.

49. An ophthalmic formulation according to any of Claims 1 to 41 for use in a method of preventing retinal ganglion cell damage, in which the method comprises the step of applying an effective amount of the ophthalmic formulation to an eye of a subject.

50. An ophthalmic formulation according to Claim 49 for a use as specified therein, in which the ophthalmic formulation is administered to the affected eye of the subject in about 30 to about 50 µl drops.

51. An ophthalmic formulation according to Claim 50, for a use as specified therein in which the ophthalmic formulation is administered in 1 to 2 drops once or twice daily.

52. An ophthalmic formulation according to any of Claims 41 to 51 for a use as specified therein, in which the method further comprises administering a second ophthalmic agent.

53. An ophthalmic formulation according to Claim 52 for a use as specified therein, in which the second ophthalmic agent is selected from the group comprising prostaglandin analogs, β-blockers, carbonic anhydrase inhibitors, rho-kinase inhibitors, α2 agonists, miotics, neuroprotectants, A3 antagonists, A2A agonists, ion channel modulators and combinations thereof.

54. An ophthalmic formulation according to Claim 53 for a use as specified therein, in which the second ophthalmic agent is a prostaglandin analog.

55. An ophthalmic formulation according to Claim 54 for a use as specified therein, in which the prostaglandin analog is latanoprost.

56. A kit or packaged formulation comprising a topically applicable ophthalmic formulation according to any of Claims 1 to 41.

57. A process for preparing an ophthalmic formulation according to any of Claims 1 to 41, comprising the steps of

(a) micronizing Compound A into particle sizes of less than about 50 microns;

(b) suspending the particles of Compound A in an aqueous suspension with a surfactant and a buffering agent;

(c) curing the product from step (b) at about 40° Celsius for between about 24 to about 96 hours; and

(e) adding boric acid from about 0.05 to about 2.0 % (w/v).

58. A process according to Claim 57, in which steps (a)-(c) are performed with a volume of less than about 20% of the final volume of the ophthalmic formulation.

59. A process according to Claim 56 or 57, further comprising filtering the cured product of step (c) as a concentrated slurry.

60. A process according to any of Claims 56 to 59, in which the milled Compound A is sterilized by gamma irradiation up to a maximum of 40 kGray (kGy).

61. A process according to any of Claims 56 to 60, in which the curing step takes place at about 40° Celsius for between about 48 to about 96 hours.

62. A process according to any of Claims 56 to 61, further comprising adjusting the pH of the aqueous suspension to between about 6.0 and about 7.0 or in a further embodiment to a pH of about 6.5 ± 0.1.

63. A process according to any of Claims 56 to 62, in which the process is performed under aseptic conditions.

64. A process according to any of Claims 56 to 63, further comprising adding a second ophthalmic agent.

65. A process according to Claim 64, in which the second ophthalmic agent is selected from the group comprising prostaglandin analogs, β-blockers, carbonic anhydrase inhibitors, rho-kinase inhibitors, α2 agonists, miotics, neuroprotectants, A3 antagonists, A2A agonists, ion channel modulators and combinations thereof.

66. A process according to Claim 65, in which the second ophthalmic agent is a prostaglandin analog.

67. A process according to Claim 66, in which the prostaglandin analog is latanoprost.