CLAIMS

What is claimed is:

1. A method for treating a delayed complication associated with a brain injury in a mammal in need thereof, wherein the brain injury includes interruption of at least one cerebral artery, the method comprising:

(a) providing a pharmaceutical composition comprising

(i) a microparticulate formulation of a voltage-gated calcium channel blocker; and optionally

(ii) a pharmaceutically acceptable carrier; and

(b) administering a therapeutic amount of the pharmaceutical composition by a means for administration of the therapeutic amount of the pharmaceutical composition at a site of administration,

wherein the therapeutic amount is effective in reducing signs or symptoms of the at least one delayed complication associated with the brain injury, and

wherein the at least one delayed complication is at least one of delayed cerebral ischemia (DCI), a plurality of microthromboemboli a cortical spreading ischemia (CSI), and an angiographic vasospasm.

2. The method according to claim 1 wherein in step (b), the means for administration is a surgical injection apparatus and the site of administration is in close proximity to at least one cerebral artery affected by the brain injury.

3. The method according to claim 1, wherein in step (b), the means for administration is a surgical injection apparatus and the site of administration is a cerebral ventricle.

4. The method according to claim 2, wherein the surgical injection apparatus is a needle, a cannula, a catheter, or a combination thereof.

5. The method according to claim 3, wherein the microparticulate formulation is carried by cerebrospinal fluid to contact the cerebral artery affected by the brain injury.

6. The method according to claim 1, wherein the therapeutic amount is effective to increase the internal diameter of the cerebral artery affected by the brain injury,as compared to a control.

7. The method according to claim 1, wherein the brain injury is a result of an aneurysm, sudden traumatic head injury, subarachnoid hemorrhage (SAH), or a combination thereof.

8. The method according to claim 7, wherein the brain injury is a result of subarachnoid hemorrhage.

9. The method according to claim 1, wherein the at least one delayed complication associated with the brain injury further comprises at least one of an intracerebral hematoma, an intraventricular hemorrhage, a fever, a behavioral deficit, a neurological deficit, a cerebral infarction, and neuronal cell death.

10. The method according to claim 9, wherein the behavioral deficit is improved such that the improved behavioral deficit comprises an increase in appetite.

11. The method according to claim 9, wherein the neurological deficit is improved such that the improved neurological deficit comprises an improvement of ataxia or paresis.

12. The method according to claim 1, wherein the pharmaceutical composition exerts a predominantly localized pharmacologic effect in treating the at least one delayed complication associated with brain injury.

13. The method according to claim 1, wherein the pharmaceutical composition exerts a diffuse pharmacologic effect throughout the brain in treating the at least one delayed complication associated with brain injury.

14. The method according to claim 1, wherein the microparticulate formulation comprises a plurality of microparticles, wherein the microparticles are of uniform size distribution, and wherein each microparticle comprises a matrix.

15. The method according to claim 1, wherein the microparticulate formulation further comprises a plurality of microparticles impregnated with the voltage-gated calcium channel blocker.

16. The method according to claim 1, wherein the microparticle formulation comprises a liquid suspension of microparticles.

17. The method according to claim 1, wherein the cerebral ventricle is a lateral ventricle, a third ventricle, a fourth ventricle, or a combination thereof.

18. The method according to claim 1, wherein the microparticulate formulation of the voltage-gated calcium channel blocker comprises a slow-release compound.

19. The method according to claim 18, wherein the slow release compound is a polymer.

20. The method according to claim 19, wherein the voltage-gated calcium channel blocker is disposed on or in the slow-release polymer.

21. The method according to claim 20, wherein the microparticulate formulation of the voltage-gated calcium channel blocker comprises poly (D, L-lactide-co-glycolide).

22. The method according to claim 20, wherein the microparticulate formulation of a voltage-gated calcium channel blocker comprises poly(orthoester).

23. The method according to claim 20, wherein the microparticulate formulation of the voltage-gated calcium channel blocker comprises polyanhydride.

24. The method according to claim 1, wherein the voltage-gated calcium channel blocker is selected from the group consisting of an L-type voltage-gated calcium channel blocker, an N-type voltage-gated calcium channel blocker, a P/Q-type voltage-gated calcium channel blocker, or a combination thereof.

25. The method according to claim 1, wherein the voltage-gated calcium channel blocker is a dihydropyridine calcium channel blocker.

26. The method according to claim 25, wherein the dihydropyridine calcium channel blocker is nimodipine.

27. The method according to claim 1, wherein the pharmaceutically acceptable carrier comprises a gel compound.

28. The method according to claim 27, wherein the gel compound is a biodegradable hydrogel.

29. The method according to claim 1, wherein the pharmaceutical composition does not comprise the pharmaceutically acceptable carrier.

30. The method according to claim 1, wherein the pharmaceutically acceptable carrier does not comprise hyaluronic acid.

31. The method according to claim 1, wherein the pharmaceutically acceptable carrier comprises hyaluronic acid.

32. The method according to claim 31, wherein the pharmaceutically acceptable carrier ranges between 0 % to 5 % hyaluronic acid.

33. The method according to claim 33, wherein the pharmaceutically acceptable carrier comprises less than 2.3 % hyaluronic acid.

34. The method according to claim 33, wherein the pharmaceutically acceptable carrier comprises less than 5 % hyaluronic acid.

35. A semisolid multiparticulate delivery system for treating a delayed complication associated with a brain injury in a mammal in need thereof, wherein the brain injury includes interruption of at least one cerebral artery, the system comprising:

(a) a pharmaceutical composition comprising

(i) a microparticulate formulation of a voltage-gated calcium channel blocker; and optionally

(ii) a pharmaceutically acceptable carrier; and

(b) a means for administering a therapeutic amount of the pharmaceutical composition at a site for administration

wherein the therapeutic amount is effective in reducing signs or symptoms of the at least one delayed complication associated with the brain injury.

36. The system according to claim 35, wherein the at least one delayed complication is at least one of delayed cerebral ischemia (DCI), a plurality of microthromboemboli a cortical spreading ischemia (CSI), and an angiographic vasospasm. The system according to claim 31, wherein the means for administration is a surgical injection apparatus and the site of administration is in close proximity to at least one cerebral artery affected by the brain injury.

37. The system according to claim 35, wherein the means for administration is a surgical injection apparatus and the site of administration is a cerebral ventricle.

38. The system according to claim 37, wherein the surgical injection apparatus is a needle, a cannula, a catheter, or a combination thereof.

39. The system according to claim 35, wherein the microparticulate formulation is capable of being carried by cerebrospinal fluid to contact the cerebral artery affected by the brain injury.

40. The system according to claim 35, wherein the therapeutic amount is effective to increase the internal diameter of the cerebral artery affected by the brain injury,as compared to a control.

41. The system according to claim 35, wherein the brain injury is a result of an aneurysm, sudden traumatic head injury, subarachnoid hemorrhage (SAH), or a combination thereof.

42. The system according to claim 41, wherein the brain injury is a result of subarachnoid hemorrhage.

43. The system according to claim 35, wherein the at least one delayed complication associated with the brain injury further comprises at least one of an intracerebral hematoma, an intraventricular hemorrhage, a fever, a behavioral deficit, a neurological deficit, a cerebral infarction, and neuronal cell death.

44. The system according to claim 43, wherein the behavioral deficit is improved such that the improved behavioral deficit comprises an increase in appetite.

45. The system according to claim 43, wherein the neurological deficit is improved such that the improved neurological deficit comprises an improvement of ataxia or paresis.

46. The system according to claim 35, wherein the pharmaceutical composition exerts a predominantly localized pharmacologic effect in treating the at least one delayed complication associated with brain injury.

47. The system according to claim 35, wherein the pharmaceutical composition exerts a diffuse pharmacologic effect throughout the brain in treating the at least one delayed complication associated with brain injury.

48. The system according to claim 35, wherein the microparticulate formulation comprises a plurality of microparticles, wherein the microparticles are of uniform size distribution, and wherein each microparticle comprises a matrix.

49. The system according to claim 35, wherein the microparticulate formulation further comprises a plurality of microparticles impregnated with the voltage-gated calcium channel blocker.

50. The system according to claim 35, wherein the microparticle formulation comprises a liquid suspension of microparticles.

51. The system according to claim 35, wherein the cerebral ventricle is a lateral ventricle, a third ventricle, a fourth ventricle, or a combination thereof.

52. The system according to claim 35, wherein the microparticulate formulation of the voltage-gated calcium channel blocker comprises a slow-release compound.

53. The system according to claim 52, wherein the slow release compound is a polymer.

54. The system according to claim 53, wherein the voltage-gated calcium channel blocker is disposed on or in the slow-release polymer.

55. The system according to claim 52, wherein the microparticulate formulation of a voltage-gated calcium channel blocker comprises poly (D, L-lactide-co-glycolide).

56. The system according to claim 55, wherein the microparticulate formulation of a voltage-gated calcium channel blocker comprises poly(orthoester).

57. The system according to claim 55, wherein the microparticulate formulation of a voltage-gated calcium channel blocker comprises polyanhydride.

58. The system according to claim 35, wherein the voltage-gated calcium channel blocker is selected from the group consisting of an L-type voltage-gated calcium channel blocker, an N-type voltage-gated calcium channel blocker, a P/Q-type voltage-gated calcium channel blocker, or a combination thereof.

59. The system according to claim 35, wherein the voltage-gated calcium channel blocker is a dihydropyridine calcium channel blocker.

60. The system according to claim 59, wherein the dihydropyridine calcium channel blocker is nimodipine.

61. The system according to claim 35, wherein the pharmaceutically acceptable carrier comprises a gel compound.

62. The system according to claim 61, wherein the gel compound is a biodegradable hydrogel.

63. The system according to claim 35, wherein the pharmaceutical composition does not comprise the pharmaceutically acceptable carrier.

64. The system according to claim 35, wherein the pharmaceutically acceptable carrier does not comprise hyaluronic acid.

65. The system according to claim 35, wherein the pharmaceutically acceptable carrier is hyaluronic acid.

66. The system according to claim 64, wherein the pharmaceutically acceptable carrier ranges between 0 % to 5 % hyaluronic acid.

67. The method according to claim 66, wherein the pharmaceutically acceptable carrier comprises less than 2.3 % hyaluronic acid.

68. The method according to claim 66, wherein the pharmaceutically acceptable carrier comprises less than 5 % hyaluronic acid.

CLAIMS

What is claimed is:

1. A semisolid multiparticulate delivery system for treating a delayed complication associated with a brain injury in a mammal in need thereof, wherein the brain injury includes interruption of at least one cerebral artery, the system comprising:

   (a) a pharmaceutical composition comprising

      (i) a microparticulate formulation of a voltage-gated calcium channel blocker; and optionally

      (ii) a pharmaceutically acceptable carrier; and

   (b) a means for administering a therapeutic amount of the pharmaceutical composition at a site for administration wherein the therapeutic amount is effective in reducing signs or symptoms of the at least one delayed complication associated with the brain injury.

2. The system according to claim 1, wherein the at least one delayed complication is at least one of delayed cerebral ischemia (DCI), a plurality of microthromboemboli a cortical spreading ischemia (CSI), and an angiographic vasospasm. The system according to claim 31, wherein the means for administration is a surgical injection apparatus and the site of administration is in close proximity to at least one cerebral artery affected by the brain injury.

3. The system according to claim 1, wherein the means for administration is a surgical injection apparatus and the site of administration is a cerebral ventricle.

4. The system according to claim 3, wherein the surgical injection apparatus is a needle, a cannula, a catheter, or a combination thereof.

5. The system according to claim 1, wherein the microparticulate formulation is capable of being carried by cerebrospinal fluid to contact the cerebral artery affected by the brain injury.

6. The system according to claim 1, wherein the therapeutic amount is effective to increase the internal diameter of the cerebral artery affected by the brain injury,as compared to a control.

7. The system according to claim 1, wherein the brain injury is a result of an aneurysm, sudden traumatic head injury, subarachnoid hemorrhage (SAH), or a combination thereof.

8. The system according to claim 7, wherein the brain injury is a result of subarachnoid hemorrhage.

9. The system according to claim 1, wherein the at least one delayed complication associated with the brain injury further comprises at least one of an intracerebral hematoma, an intraventricular hemorrhage, a fever, a behavioral deficit, a neurological deficit, a cerebral infarction, and neuronal cell death.

10. The system according to claim 9, wherein the behavioral deficit is improved such that the improved behavioral deficit comprises an increase in appetite.

11. The system according to claim 1, wherein the neurological deficit is improved such that the improved neurological deficit comprises an improvement of ataxia or paresis.

12. The system according to claim 1, wherein the pharmaceutical composition exerts a predominantly localized pharmacologic effect in treating the at least one delayed complication associated with brain injury.

13. The system according to claim 1, wherein the pharmaceutical composition exerts a diffuse pharmacologic effect throughout the brain in treating the at least one delayed complication associated with brain injury.

14. The system according to claim 1, wherein the microparticulate formulation comprises a plurality of microparticles, wherein the microparticles are of uniform size distribution, and wherein each microparticle comprises a matrix.

15. The system according to claim 1, wherein the microparticulate formulation further comprises a plurality of microparticles impregnated with the voltage-gated calcium channel blocker.

16. The system according to claim 1, wherein the microparticle formulation comprises a liquid suspension of microparticles.

17. The system according to claim 1, wherein the cerebral ventricle is a lateral ventricle, a third ventricle, a fourth ventricle, or a combination thereof.

18. The system according to claim 1, wherein the microparticulate formulation of the voltage-gated calcium channel blocker comprises a slow-release compound.

19. The system according to claim 18, wherein the slow release compound is a polymer.

20. The system according to claim 19, wherein the voltage-gated calcium channel blocker is disposed on or in the slow-release polymer.

21. The system according to claim 18, wherein the microparticulate formulation of a voltage-gated calcium channel blocker comprises poly (D, L-lactide-co-glycolide).

22. The system according to claim 21, wherein the microparticulate formulation of a voltage-gated calcium channel blocker comprises poly(orthoester).

23. The system according to claim 21, wherein the microparticulate formulation of a voltage-gated calcium channel blocker comprises polyanhydride.

24. The system according to claim 1, wherein the voltage-gated calcium channel blocker is selected from the group consisting of an L-type voltage-gated calcium channel blocker, an N-type voltage-gated calcium channel blocker, a P/Q-type voltage-gated calcium channel blocker, or a combination thereof.

25. The system according to claim 1, wherein the voltage-gated calcium channel blocker is a dihydropyridine calcium channel blocker.

26. The system according to claim 25, wherein the dihydropyridine calcium channel blocker is nimodipine.

27. The system according to claim 1, wherein the pharmaceutically acceptable carrier comprises a gel compound.

28. The system according to claim 27, wherein the gel compound is a biodegradable hydrogel.

29. The system according to claim 1, wherein the pharmaceutical composition does not comprise the pharmaceutically acceptable carrier.

30. The system according to claim 1, wherein the pharmaceutically acceptable carrier does not comprise hyaluronic acid.

31. The system according to claim 1, wherein the pharmaceutically acceptable carrier is hyaluronic acid

32. The system according to claim 30, wherein the pharmaceutically acceptable carrier ranges between 0 % to 5 % hyaluronic acid.

33. The method according to claim 32, wherein the pharmaceutically acceptable carrier comprises less than 2.3 % hyaluronic acid.

34. The method according to claim 32, wherein the pharmaceutically acceptable carrier comprises less than 5 % hyaluronic acid.

35. Use of a flowable microparticulate sustained release pharmaceutical composition comprising a voltage-gated calcium channel blocker and a pharmaceutically acceptable carrier for the manufacture of a medicament for therapeutic treatment of a delayed complication associated with a brain injury in a mammal in need thereof, wherein the brain injury includes interruption of at least one cerebral artery in subarachnoid space, wherein the at least one delayed complication is at least one of delayed cerebral ischemia (DCI), a plurality of microthromboemboli a cortical spreading ischemia (CSI), and an angiographic vasospasm.

36. The use according to claim 35, wherein the brain injury is a result of an aneurysm, sudden traumatic head injury, subarachnoid hemorrhage (SAH), or a combination thereof.

37. The use according to claim 36, wherein the brain injury is a result of subarachnoid hemorrhage.

38. The use according to claim 35, wherein the at least one delayed complication associated with the brain injury further comprises at least one of an intracerebral hematoma, an intraventricular

hemorrhage, a fever, a behavioral deficit, a neurological deficit, a cerebral infarction, and neuronal cell death.

39. The use according to claim 35, wherein the pharmaceutical composition exerts a localized pharmacologic effect.

40. The use according to claim 35, wherein the pharmaceutical composition exerts a diffuse pharmacologic effect throughout the brain.

41. The use according to claim 35, wherein the microparticulate sustained release composition comprises a plurality of microparticles, wherein the microparticles are of uniform size distribution, and wherein each microparticle comprises a matrix.

42. The use according to claim 35, wherein the microparticulate formulation further comprises a plurality of microparticles impregnated with the voltage-gated calcium channel blocker.

43. The use according to claim 35, wherein the microparticle formulation comprises a liquid suspension of microparticles.

44. The use according to claim 35, wherein the microparticulate formulation of the voltage-gated calcium channel blocker comprises a slow-release compound.

45. The use according to claim 44, wherein the slow release compound is a polymer.

46. The use according to claim 44, wherein the voltage-gated calcium channel blocker is disposed on or in the slow-release polymer.

47. The use according to claim 35, wherein the microparticulate sustained release composition comprises the voltage-gated calcium channel blocker comprising poly (D, L-lactide-co-glycolide).

48. The use according to claim 46, wherein the microparticulate formulation of the voltage-gated calcium channel blocker comprises a poly(orthoester).

49. The use according to claim 46, wherein the microparticulate sustained release composition of the voltage-gated calcium channel blocker comprises a polyanhydride.

50. The use according to claim 35, wherein the voltage-gated calcium channel blocker is selected from the group consisting of an L-type voltage-gated calcium channel blocker, an N-type voltage-gated calcium channel blocker, a P/Q-type voltage-gated calcium channel blocker, or a combination thereof.

51. The use according to claim 35, wherein the voltage-gated calcium channel blocker is a dihydropyridine calcium channel blocker.

52. The use according to claim 51, wherein the dihydropyridine calcium channel blocker is nimodipine.

53. The use according to claim 35, wherein the pharmaceutically acceptable carrier comprises a gel compound.

54. The use according to claim 53, wherein the gel compound is a biodegradable hydrogel.

55. The use according to claim 35, wherein the pharmaceutically acceptable carrier does not comprise hyaluronic acid.

56. The use according to claim 35, wherein the pharmaceutically acceptable carrier comprises hyaluronic acid.

57. The use according to claim 56, wherein the pharmaceutically acceptable carrier ranges between 0 % to 5 % hyaluronic acid.

58. The use according to claim 57, wherein the pharmaceutically acceptable carrier comprises less than 2.3 % hyaluronic acid.

59. The use according to claim 57, wherein the pharmaceutically acceptable carrier comprises less than 5 % hyaluronic acid.

60. The use according to claim 49 wherein the voltage gated calcium channel blocker is in a core of the microparticles surrounded by a coating, dispersed throughout the particles, adsorbed into the particles, or a combination thereof.