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.

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 comprising a therapeutic amount of a voltage-gated calcium channel blocker, wherein the microparticulate formulation comprises a plurality of microparticles; and

(ii) a pharmaceutically acceptable carrier comprising between 0 % to 5 % hyaluronic acid;

wherein:

(1) The microparticulate formulation of the pharmaceutical composition is flowable;
(2) The microparticles are of uniform size distribution;
(3) Each microparticle comprises a matrix;
(4) The voltage-gated calcium channel blocker is dispersed throughout each microparticle;
(5) The voltage-gated calcium channel blocker is released from the composition by gradual release over an extended period of time;
(6) Delivery of the pharmaceutical composition is locally into a site of delivery;
(7) Cerebrospinal fluid (CSF) concentration of the voltage gated calcium channel blocker remains in therapeutic range while plasma concentration is below therapeutic range during therapy, thereby circumventing unwanted side effects associated with systemic delivery; and
(8) The therapeutic amount of the voltage gated calcium channel blocker is effective to reduce signs or symptoms of the at least one delayed complication of the brain injury;

and

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

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.

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

4. The system according to claim 3, wherein the 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 further comprises a plurality of microparticles impregnated with the voltage-gated calcium channel blocker.

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

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

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

18. The system according to claim 17, wherein the slow release compound is a polymer.

19. The system according to claim 18, wherein the voltage-gated calcium channel blocker is disposed on or in the slow-release polymer.

20. The system according to claim 17, wherein the microparticulate formulation of a voltage-gated calcium channel blocker comprises poly (D, L-lactide-co-glycolide).

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

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

23. 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.

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

25. The system according to claim 24, wherein the dihydropyridine calcium channel blocker is nimodipine.

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

27. The system according to claim 26, wherein the gel compound is a biodegradable hydrogel.

28. The method according to claim 1, wherein the pharmaceutically acceptable carrier comprises less than 2.3 % hyaluronic acid.

29. The method according to claim 1, wherein the pharmaceutically acceptable carrier comprises less than 5 % hyaluronic acid.

30. Use of a flowable microparticulate sustained release pharmaceutical composition comprising a voltage-gated calcium channel blocker, wherein the microparticulate formulation comprises a plurality of microparticles of uniform size distribution and wherein each microparticle comprises a matrix, and a pharmaceutically acceptable carrier comprising between 0 % to 5 % hyaluronic acid 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 comprises one or more of a delayed cerebral ischemia (DCI), a plurality of microthromboemboli, a cortical spreading ischemia (CSI), and or an angiographic vasospasm,

wherein

(i) The microparticulate formulation of the pharmaceutical composition is flowable;

(ii) The voltage-gated calcium channel blocker is dispersed throughout each microparticle;

(iii) The voltage-gated calcium channel blocker is released from the composition by gradual release over an extended period of time;

(iv) Delivery of the pharmaceutical composition is locally into a site of delivery;

(v) Cerebrospinal fluid (CSF) concentration of the voltage gated calcium channel blocker remains in therapeutic range while plasma concentration is below therapeutic range during therapy, thereby circumventing unwanted side effects associated with systemic delivery; and

(vi) The therapeutic amount of the voltage gated calcium channel blocker is effective to reduce signs or symptoms of the at least one delayed complication of the brain injury comprising a subarachnoid hemorrhage.

31. The use according to claim 30, wherein the brain injury is a result of an aneurysm, sudden traumatic head injury, subarachnoid hemorrhage (SAH), or a combination thereof.

32. The use according to claim 31, wherein the brain injury is a result of subarachnoid hemorrhage.

33. The use according to claim 30, 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.

34. The use according to claim 30, wherein the microparticulate formulation further comprises a plurality of microparticles impregnated with the voltage-gated calcium channel blocker.

35. The use according to claim 30, wherein the microparticle formulation comprises a liquid suspension of microparticles.

36. The use according to claim 30, wherein the microparticulate formulation of the voltage-gated calcium channel blocker comprises a slow-release compound.

37. The use according to claim 36, wherein the slow release compound is a polymer.

38. The use according to claim 36, wherein the voltage-gated calcium channel blocker is disposed on or in the slow-release polymer.

39. The use according to claim 30, wherein the microparticulate sustained release composition comprises the voltage-gated calcium channel blocker comprising poly (D, L-lactide-co-glycolide).

40. The use according to claim 38, wherein the microparticulate formulation of the voltage-gated calcium channel blocker comprises a poly(orthoester).

41. The use according to claim 38, wherein the microparticulate sustained release composition of the voltage-gated calcium channel blocker comprises a polyanhydride.

42. The use according to claim 30, 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.

43. The use according to claim 30, wherein the voltage-gated calcium channel blocker is a dihydropyridine calcium channel blocker.

44. The use according to claim 43, wherein the dihydropyridine calcium channel blocker is nimodipine.

45. The use according to claim 30, wherein the pharmaceutically acceptable carrier comprises a gel compound.

46. The use according to claim 45, wherein the gel compound is a biodegradable hydrogel.

47. The use according to claim 30, wherein the pharmaceutically acceptable carrier comprises less than 2.3 % hyaluronic acid.

48. The use according to claim 30, wherein the pharmaceutically acceptable carrier comprises less than 5 % hyaluronic acid.