CLAIMS

What is claimed is:

1. Use of a microparticulate pharmaceutical composition for the manufacture of a medicament for reducing severity or incidence of a delayed complication associated with a brain injury in a mammal including interruption of at least one cerebral artery that deposits blood in the subarachnoid space, wherein the delayed complication is selected from the group consisting of a microthromboembolism, a cortical spreading ischemia, or a delayed cerebral ischemia (DCI) caused by formation of microthromboemboli or a cortical spreading ischemia (CSI), the composition comprising:

(a) a microparticulate formulation of a therapeutic amount of a voltage-gated calcium channel blocker, which microparticulate formulation comprises a suspension of microparticles of uniform size distribution formed from a polymer matrix impregnated with the voltage-gated calcium channel blocker; and

(b) a pharmaceutically acceptable carrier;

wherein

(i) the pharmaceutical composition is flowable;

(ii) the pharmaceutical composition is formulated for parenteral injection into a subarachnoid space of the brain;

(iii) the pharmaceutical composition has a release profile such that one half of the voltage-gated channel blocker is released from the composition from 1 day to 30 days *in vivo* after delivery;

(iv) the therapeutic amount of the voltage gated calcium channel blocker is effective to maintain cerebrospinal fluid (CSF) concentration of the voltage gated calcium channel blocker in therapeutic range to treat the delayed complication, while plasma concentration is below therapeutic range, thereby circumventing unwanted side effects associated with systemic delivery; and

(v) the therapeutic amount that contacts and flows around the cerebral artery in the subarachnoid space is effective in reducing signs or symptoms of the delayed complication associated with the brain injury.

2. The use according to claim 1, wherein the brain injury that deposits blood in the subarachnoid space is a result of an aneurysm, sudden traumatic head injury, subarachnoid hemorrhage (SAH), or a combination thereof.

3. The use according to claim 2, wherein the brain injury that deposits blood in the subarachnoid space is a result of subarachnoid hemorrhage.

4. The use according to claim 1, wherein the delayed complication associated with the brain injury that deposits blood in the subarachnoid space further comprises an intracerebral hematoma, an intraventricular hemorrhage, a fever, a behavioral deficit, a neurological deficit, a cerebral infarction, and neuronal cell death.

5. The use according to claim 1, wherein the voltage-gated calcium channel blocker is disposed in the polymer matrix.

6. The use according to claim 1, wherein the polymer matrix is selected from the group consisting of:

(i) a poly (D, L-lactide-co-glycolide),

(ii) a poly(orthoester), and

(iii) a polyanhydride.

7. The use 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.

8. The use according to claim 7, wherein the L-type voltage-gated calcium channel blocker is a dihydropyridine L-type calcium channel blocker.

9. The use according to claim 8, wherein the L-type calcium channel blocker is nimodipine.

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

11. The use according to claim 10, wherein the gel compound is a biodegradable hydrogel.

12. The use according to claim 1, wherein the pharmaceutically acceptable carrier comprises hyaluronic acid.

13. The use according to claim 1, wherein the pharmaceutically acceptable carrier comprises 2.3% to 5 % hyaluronic acid.

14. The use according to claim 9, wherein the microparticulate formulation comprises 65% nimodipine and 35% polymer.

15. The use according to claim 1, wherein mean size of the microparticles is about 52 μm.

16. The use according to claim 1, wherein the brain injury results in decreased cerebral perfusion.

17. The use according to claim 1, wherein the therapeutic amount is effective to increase the internal diameter of the cerebral artery affected by the brain injury that deposits blood in the subarachnoid space, as compared to a control.

18. The use according to claim 4, wherein the composition is effective to improve the behavioral deficit such that the improved behavioral deficit comprises an increase in appetite.

19. The use according to claim 4, wherein the composition is effective to improve the neurological deficit such that the improved neurological deficit comprises an improvement of ataxia or paresis.

20. The use according to claim 1, wherein size of the microparticles is between about 25 μm to about 100 μm.

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 inhibitor, wherein the microparticulate formulation comprises a plurality of microparticles; and

(ii) a pharmaceutically acceptable carrier comprising between 0 % and 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 inhibitor is dispersed throughout each microparticle;

(5) The voltage-gated calcium channel inhibitor 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 inhibitor 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 inhibitor is effective to reduce signs or symptoms of the at least one delayed complication of the brain injury, wherein the at least one delayed complication is delayed cerebral ischemia (DCI) comprising a plurality of microthromboemboli, a cortical spreading ischemia (CSI), an angiographic vasospasm, or a combination thereof;

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 means for administration is an injection apparatus and the site of administration is a cerebral ventricle.

3. The system according to claim 2, wherein the injection apparatus is a needle, a cannula, a catheter, or a combination thereof.

4. 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.

5. 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.

6. 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.

7. The system according to claim 6, wherein the brain injury is a result of subarachnoid hemorrhage.

8. 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.

9. The system according to claim 8, wherein the behavioral deficit is improved such that the improved behavioral deficit comprises an increase in appetite.

10. 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.

11. 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.

12. 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.

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

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

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

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

17. The system according to claim 16, wherein the slow release compound is a polymer.

18. The system according to claim 17, wherein the voltage-gated calcium channel blocker is disposed on or in the slow-release polymer.

19. The system according to claim 16, wherein the microparticulate formulation of a voltage-gated calcium channel inhibitor comprises poly (D, L-lactide-co-glycolide).

20. The system according to claim 19, wherein the microparticulate formulation of a voltage-gated calcium channel inhibitor comprises poly(orthoester).

21. The system according to claim 19, wherein the microparticulate formulation of a voltage-gated calcium channel inhibitor comprises polyanhydride.

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

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

24. The system according to claim 23, wherein the dihydropyridine calcium channel blocker is nimodipine.

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

26. The system according to claim 25, wherein the gel compound is a biodegradable hydrogel.

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

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

29. Use of a flowable microparticulate sustained release pharmaceutical composition comprising a voltage-gated calcium channel inhibitor, 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 % and 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 is delayed cerebral ischemia (DCI) comprising a plurality of microthromboemboli, a cortical spreading ischemia (CSI), an angiographic vasospasm, or a combination thereof,

wherein

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

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

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

30. The use according to claim 29, wherein the brain injury is a result of an aneurysm, sudden traumatic head injury, subarachnoid hemorrhage (SAH), or a combination thereof.

31. The use according to claim 30, wherein the brain injury is a result of subarachnoid hemorrhage.

32. The use according to claim 29, 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.

33. The use according to claim 29, wherein the microparticulate formulation further comprises a plurality of microparticles impregnated with the voltage-gated calcium channel inhibitor.

34. The use according to claim 29, wherein the microparticle formulation comprises a liquid suspension of microparticles.

35. The use according to claim 29, wherein the microparticulate formulation of the voltage-gated calcium channel inhibitor comprises a slow-release compound.

36. The use according to claim 35, wherein the slow release compound is a polymer.

37. The use according to claim 35, wherein the voltage-gated calcium channel inhibitor is disposed on or in the slow-release polymer.

38. The use according to claim 29, wherein the microparticulate sustained release composition comprises the voltage-gated calcium channel inhibitor comprising poly (D, L-lactide-co-glycolide).

39. The use according to claim 37, wherein the microparticulate formulation of the voltage-gated calcium channel inhibitor comprises a poly(orthoester).

40. The use according to claim 37, wherein the microparticulate sustained release composition of the voltage-gated calcium channel inhibitor comprises a polyanhydride.

41. The use according to claim 29, wherein the voltage-gated calcium channel inhibitor is selected from the group consisting of an L-type voltage-gated calcium channel inhibitor, an N-type voltage-gated calcium channel inhibitor, a P/Q-type voltage-gated calcium channel inhibitor, or a combination thereof.

42. The use according to claim 29, wherein the voltage-gated calcium channel inhibitor is a dihydropyridine calcium channel inhibitor.

43. The use according to claim 42, wherein the dihydropyridine calcium channel inhibitor is nimodipine.

44. The use according to claim 29, wherein the pharmaceutically acceptable carrier comprises a gel compound.

45. The use according to claim 44, wherein the gel compound is a biodegradable hydrogel.

46. The use according to claim 29, wherein the pharmaceutically acceptable carrier comprises less than 2.3 % hyaluronic acid.

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