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

(ii) a pharmaceutically acceptable carrier comprising between 0 % ~~to~~ 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 ~~blocker~~ is dispersed throughout each microparticle;

(5) The voltage-gated calcium channel inhibitor ~~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~~ 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 ~~blocker~~ 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 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.~~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.

~~4.~~3. The system according to claim ~~3~~2, wherein the injection apparatus is a needle, a cannula, a catheter, or a combination thereof.

~~5.~~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.

~~6.~~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.

~~7.~~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.

~~8.~~7. The system according to claim ~~7~~6, wherein the brain injury is a result of subarachnoid hemorrhage.

~~9.~~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.

~~10.~~9. The system according to claim ~~9~~8, wherein the behavioral deficit is improved such that the improved behavioral deficit comprises an increase in appetite.

~~11.~~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.

~~12.~~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.

~~13.~~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.

~~14.~~13. The system according to claim 1, wherein the microparticulate formulation further comprises a plurality of microparticles impregnated with the voltage-gated calcium channel ~~blocker~~ inhibitor.

~~15.~~14. The system according to claim 1, wherein the microparticle formulation comprises a liquid suspension of microparticles.

~~16.~~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.

~~17.~~16. The system according to claim 1, wherein the microparticulate formulation of the voltage-gated calcium channel blocker comprises a slow-release compound.

~~18.~~17. The system according to claim ~~17~~16, wherein the slow release compound is a polymer.

~~19.~~18. The system according to claim ~~18~~17, wherein the voltage-gated calcium channel blocker is disposed on or in the slow-release polymer.

~~20.~~19. The system according to claim ~~17~~16, wherein the microparticulate formulation of a voltage-gated calcium channel inhibitor ~~blocker~~ comprises poly (D, L-lactide-co-glycolide).

~~21.~~20. The system according to claim ~~20~~19, wherein the microparticulate formulation of a voltage-gated calcium channel inhibitor ~~blocker~~ comprises poly(orthoester).

~~22.~~21. The system according to claim ~~20~~19, wherein the microparticulate formulation of a voltage-gated calcium channel inhibitor ~~blocker~~ comprises polyanhydride.

~~23.~~22. The system according to claim 1, wherein the voltage-gated calcium channel inhibitor ~~blocker~~ is selected from the group consisting of an L-type voltage-gated calcium channel inhibitor~~blocker~~, an N-type voltage-gated calcium channel inhibitor~~blocker~~, a P/Q-type voltage-gated calcium channel inhibitor~~blocker~~, or a combination thereof.

~~24.~~23. The system according to claim 1, wherein the voltage-gated calcium channel inhibitor ~~blocker~~ is a dihydropyridine calcium channel inhibitor~~blocker~~.

~~25.~~24. The system according to claim ~~24~~23, wherein the dihydropyridine calcium channel blocker is nimodipine.

~~26.~~25. The system according to claim 1, wherein the pharmaceutically acceptable carrier comprises a gel compound.

~~27.~~26. The system according to claim ~~26~~25, wherein the gel compound is a biodegradable hydrogel.

~~28.~~27. The ~~method~~ system according to claim 1, wherein the pharmaceutically acceptable carrier comprises less than 2.3 % hyaluronic acid.

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

30.29. Use of a flowable microparticulate sustained release pharmaceutical composition comprising a voltage-gated calcium channel inhibitor~~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~~ 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 ~~comprises one or more of a~~ is delayed cerebral ischemia (DCI)~~,~~ comprising a plurality of microthromboemboli, a cortical spreading ischemia (CSI), ~~and or~~ 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 ~~blocker~~ is dispersed throughout each microparticle;

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

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

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

~~33.~~32. The use according to claim ~~30~~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.

~~34.~~33. The use according to claim ~~30~~29, wherein the microparticulate formulation further comprises a plurality of microparticles impregnated with the voltage-gated calcium channel inhibitor~~blocker~~.

~~35.~~34. The use according to claim ~~30~~29, wherein the microparticle formulation comprises a liquid suspension of microparticles.

~~36.~~35. The use according to claim ~~30~~29, wherein the microparticulate formulation of the voltage-gated calcium channel ~~blocker~~ inhibitor comprises a slow-release compound.

~~37.~~36. The use according to claim ~~36~~35, wherein the slow release compound is a polymer.

~~38.~~37. The use according to claim ~~36~~35, wherein the voltage-gated calcium channel ~~blocker~~ inhibitor is disposed on or in the slow-release polymer.

~~39.~~38. The use according to claim ~~30~~29, wherein the microparticulate sustained release composition comprises the voltage-gated calcium channel ~~blocker~~ inhibitor comprising poly (D, L-lactide-co-glycolide).

~~40.~~39. The use according to claim ~~38~~37, wherein the microparticulate formulation of the voltage-gated calcium channel ~~blocker~~ inhibitor comprises a poly(orthoester).

~~41.~~40. The use according to claim ~~38~~37, wherein the microparticulate sustained release composition of the voltage-gated calcium channel ~~blocker~~ inhibitor comprises a polyanhydride.

~~42.~~41. The use according to claim ~~30~~29, wherein the voltage-gated calcium channel ~~blocker~~ inhibitor is selected from the group consisting of an L-type voltage-gated calcium channel ~~blocker~~ inhibitor, an N-type voltage-gated calcium channel ~~blocker~~ inhibitor, a P/Q-type voltage-gated calcium channel ~~blocker~~ inhibitor, or a combination thereof.

~~43.~~42. The use according to claim ~~30~~29, wherein the voltage-gated calcium channel ~~blocker~~ inhibitor is a dihydropyridine calcium channel ~~blocker~~ inhibitor.

~~44.~~43. The use according to claim ~~43~~42, wherein the dihydropyridine calcium channel ~~blocker~~ inhibitor is nimodipine.

~~45.~~44. The use according to claim ~~30~~29, wherein the pharmaceutically acceptable carrier comprises a gel compound.

~~46.~~45. The use according to claim ~~45~~44, wherein the gel compound is a biodegradable hydrogel.

~~47.~~46. The use according to claim ~~30~~29, wherein the pharmaceutically acceptable carrier comprises less than 2.3 % hyaluronic acid.

~~48.~~47. The use according to claim ~~30~~29, wherein the pharmaceutically acceptable carrier comprises less than 5 % hyaluronic acid.