CLAIMS

What is claimed is:

1. ~~A method of treating at least one cerebral artery in a subarachnoid space at risk of interruption due to a brain injury in a human subject, comprising:~~

~~a) providing~~ Use of a ~~flowable sustained release~~ microparticulate composition comprising

(~~i~~a) a microparticulate formulation comprising a therapeutic amount of at least one therapeutic agent, ~~wherein the microparticulate formulation comprises a plurality of microparticles of uniform size distribution, wherein the therapeutic agent is dispersed throught out each microparticle, and~~ wherein the therapeutic amount is effective to treat a delayed complication of the interruption of the cerebral artery, the microparticulate formulation being characterized by:

(i) a plurality of microparticles of uniform size distribution;

(ii) dispersal of the therapeutic amount of the therapeutic agent throughout each microparticle, in a core surrounded by a coating; adsorbed into the particles or a combination thereof;

(iii) sustained release of the therapeutic amount of the therapeutic agent from each microparticle;

(iv) as a dispersion, its flowability around a cerebral artery in a subarachnoid space of the brain at risk of interruption due to a brain injury,

(~~i~~b) and a pharmaceutical carrier;

in the manufacture of a medicament for treating at least one cerebral artery in a subarachnoid space at risk of interruption due to a brain injury in a human subject,

and

~~b) administering~~ wherein the composition is to be administered locally into a cerebral ventricle ~~so that the microparticulate formulation flows from the cerebrospinal fluid (CSF) in the cerebral ventricle into the cerebrospinal fluid (CSF) in the subarachnoid space before releasing the therapeutic agent in the subarachnoid space, wherein~~such that the therapeutic agent contacts and flows around the at least one cerebral artery in the subarachnoid space without entering systemic circulation in an amount to cause unwanted side effects.

2. The ~~method~~ use according to claim 1, wherein each microparticle comprises a matrix.

3. The ~~method~~ use according to claim 1, wherein the at least one therapeutic agent is a calcium channel antagonist, an endothelin antagonist, a transient receptor potential (TRP) protein antagonist, or a combination thereof.

4. The ~~method~~ use according to claim 1, wherein the delayed complication is selected from the group consisting of an angiographic vasospasm, formation of a plurality of microthromboemboli, a cortical spreading ischemia, a delayed cerebral ischemia (DCI), or a combination thereof.

5. The ~~method~~ use according to claim 1, wherein the at least one therapeutic agent is a calcium channel antagonist selected from the group consisting of an L-type voltage dependent calcium channel inhibitor, an R-type voltage dependent calcium channel inhibitor, an N-type voltage dependent calcium channel inhibitor, a P/Q-type voltage dependent calcium channel inhibitor, a T-type voltage dependent calcium channel inhibitor, or a combination thereof.

6. The ~~method~~ use according to claim 5, wherein the L-type voltage dependent calcium channel inhibitor is a dihydropyridine, selected from the group consisting of amlodipine, aranidipine, azelnidipine, bamidipine, benidipine, cinaldipine, efonidipine, felodipine, isradipine, lacidipine, lemildipine, lercanidipine, nicardipine, nifedipine, nilvadipine, nimodipine, nisoldipine, nitrendipine, manidipine, pranidipine, or a combination thereof.

7. The ~~method~~ use according to claim 6, wherein the dihydropyridine is nimodipine.

8. The ~~method~~ use according to claim 1, wherein the microparticulate formulation comprises a powder suspension of microparticles.

9. The ~~method~~ use according to claim 1, wherein the microparticulate formulation further comprises a slow-release compound.

10. The ~~method~~ use according to claim 9, wherein the ~~slow-release~~ slow-release compound is a biodegradable polymer.

11. The ~~method~~ use according to claim 10, wherein the biodegradable polymer is selected from the group consisting of polylactide-polyglycolide, poly(orthoester), and poly(anhydride).

12. The ~~method~~ use according to claim 1, wherein administering occurs via an injection apparatus.

13. The ~~method~~ use according to claim 12, wherein the injection apparatus is a needle, a cannula, a catheter, or a combination thereof.

14. The ~~method~~ use according to claim 1, wherein the flowable sustained release microparticulate composition is effective to release the therapeutic amount of the therapeutic agent prior to onset of the delayed complication.

15. The ~~method~~ use according to claim 1, wherein the sustained release of the therapeutic amount of the therapeutic agent occurs within a half-life ranging from 1 day to 30 days from delivery of the composition to the cerebral ventricle.

16. The ~~method~~ use according to claim 1, wherein the cerebral ventricle is at least 0.001 mm from the cerebral artery in the subarachnoid space.

17. The ~~method~~ use according to claim 16, wherein the cerebral ventricle is a lateral ventricle, a third ventricle, a fourth ventricle, or a combination thereof.

18. The ~~method~~ use according to claim 1, wherein the flowable sustained release microparticulate composition produces a localized pharmacological effect around the cerebral artery in the subarachnoid space.

19. The ~~method~~ use according to claim 1, wherein the therapeutic amount of the therapeutic agent is effective to increase internal diameter of the cerebral artery in the subarachnoid space.

~~20. The method according to claim 1, wherein the pharmaceutical carrier is a buffer solution.~~

~~21~~20. A ~~flowable sustained release~~ microparticulate composition comprising:

(i) a microparticulate formulation comprising at least one therapeutic agent, and

(ii) a pharmaceutically acceptable carrier,

wherein the microparticulate composition is formulated for delivery into a cerebral ventrical;

the microparticulate formulation being characterized by:

(iii) ~~comprises~~ a plurality of microparticle of uniform size distribution,

~~wherein the at least one therapeutic agent is dispersed throughout each microparticle, and wherein the composition is suitable for delivery into a cerebral ventricle and is capable of flow in the cerebrospinal fluid (CSF) from the centricle into the subarachnoid space~~

(iv) dispersal of the therapeutic amount of the therapeutic agent throughout each microparticle, in a core surrounded by a coating; adsorbed into the particles or a combination therof;

(v) sustained release of the therapeutic amount of the therapeutic agent from each microparticle;

(vi) as a dispersion, its flowability around a cerebral artery in a subarachnoid space of the brain at risk of interruption due to a brain injury.

~~22~~21. The composition according to claim ~~21~~20, wherein the therapeutic agent is a calcium channel antagonist, an endothelin antagonist, a transient receptor potential (TRP) protein antagonist, or a combination thereof.

~~23~~22. The composition according to claim ~~21~~20, wherein the microparticles comprise a matrix.

~~24~~23. The composition according to claim ~~21~~20, wherein the flowable sustained release microparticulate composition, upon delivery into the cerebral ventricle, is effective to flow from the cerebrospinal fluid (CSF) in the cerebral ventricle into the cerebrospinal fluid (CSF) in the subarachnoid space before sustained release of the therapeutic agent in the subarachnoid space.

~~25~~24. The composition according to claim ~~21~~20, wherein the therapeutic agent is a calcium channel antagonist selected from the group consisting of an L-type voltage dependent calcium channel inhibitor, an R-type voltage dependent calcium channel inhibitor, an N-type

voltage dependent calcium channel inhibitor, a P/Q-type voltage dependent calcium channel inhibitor, a T-type voltage dependent calcium channel inhibitor, or a combination thereof.

~~26~~25. The composition according to claim ~~25~~24, wherein the L-type voltage dependent calcium channel inhibitor is a dihydropyridine, selected from the group consisting of amlodipine, aranidipine, azelnidipine, bamidipine, benidipine, cinaldipine, efonidipine, felodipine, isradipine, lacidipine, lemildipine, lercanidipine, nicardipine, nifedipine, nilvadipine, nimodipine, nisoldipine, nitrendipine, manidipine, pranidipine, or a combination thereof.

~~27~~26. The composition according to claim ~~26~~25, wherein the dihydropyridine is nimodipine.

~~28~~27. The composition according to claim ~~21~~20, wherein the microparticulate formulation comprises a powder suspension of microparticles.

~~29~~28. The composition according to claim ~~28~~27, wherein the microparticulate formulation further comprises a slow-release compound.

~~30~~29. The composition according to claim ~~29~~28, wherein the ~~slow-release~~ slow-release compound is a biodegradable polymer.

~~31~~30. The composition according to claim ~~30~~29, wherein the biodegradable polymer is selected from the group consisting of polylactide-polyglycolide, poly(orthoester), and poly(anhydride).

~~32~~31. The composition according to claim ~~21~~20, wherein one-half of the ~~sustained release of the therapeutic amount of the~~ therapeutic agent is released from the microparticulate formulation within ~~capable of occurring within a half-life ranging from~~ 1 day to 30 days from delivery of the composition to the cerebral ventricle.

3332. The composition according to claim 2120, wherein the cerebral ventricle is at least 0.001 mm from the cerebral artery in the subarachnoid space.

3433. The composition according to claim 3332, wherein the cerebral ventricle is a lateral ventricle, a third ventricle, a fourth ventricle, or a combination thereof.

3534. The composition according to claim 2120, wherein the flowable sustained release microparticulate composition is effective to produce a predominantly localized effect around the cerebral artery in the subarachnoid space.

3635. The composition according to claim 2120, wherein the therapeutic amount of the therapeutic agent is effective to increase internal diameter of the cerebral artery in the subarachnoid space.

3736. The composition according to claim 2120, wherein the pharmaceutical carrier is a buffer solution.

3837. A sterile kit for treating at least one cerebral artery in a subarachnoid space at risk of interruption due to a brain injury comprising:

(i) a sterile injection apparatus;

(ii) a sterile first syringe comprising a barrel, and a plunger;

(iii) a sterile second syringe comprising a barrel and a plunger;

(iv) a sterile female luer cap;

(v) a sterile male luer cap;

(vi) a sterile female syringe connector;

(vii) a sterile microparticulate formulation for administration into a cerebral ventricle comprising a therapeutic amount of at least one therapeutic agent, wherein the therapeutic amount is effective to reduce a delayed complication of an interruption of a cerebral artery in a subarachnoid space,

~~wherein~~ the microparticulate formulation ~~comprises~~ being characterized by:

(i) a plurality of microparticles of uniform size distribution, ~~and wherein the at least one therapeutic agent is dispersed throughout each microparticle,~~

(ii) dispersal of the therapeutic amount of the therapeutic agent throughout each microparticle, in a core surrounded by a coating; adsorbed into the particles or a combination thereof;

(iii) sustained release of the therapeutic amount of the therapeutic agent from each microparticle;

(iv) as a dispersion, its flowability around a cerebral artery in a subarachnoid space of the brain at risk of interruption due to a brain injury,

and

(viii) a sterile pharmaceutically acceptable carrier.

~~39~~38. The kit according to claim ~~38~~37, wherein the injection apparatus is a needle, a cannula, a catheter, or a combination thereof.

~~40~~39. The kit according to claim ~~38~~37, wherein the microparticulate formulation comprises a powder suspension of microparticles.

~~41~~40. The kit according to claim ~~38~~37, wherein the microparticles are of a diameter ranging from about 30 μm to about 100 μm.

~~42~~41. The kit according to claim ~~38~~37, wherein the microparticulate formulation further comprises a slow-release compound.

~~43~~42. The kit according to claim ~~42~~41, wherein the slow release compound is a biodegradable polymer.

~~44~~43. The kit according to claim ~~43~~42, wherein the biodegradable polymer is selected from the group consisting of polylactide-polyglycolide, poly(orthoester), and poly(anhydride).

4544. The kit according to claim 3837, wherein the at least one therapeutic agent is a calcium channel antagonist, an endothelin antagonist, a transient receptor potential (TRP) protein antagonist, or a combination thereof.

4645. The kit according to claim 3837, wherein the calcium channel antagonist is selected from the group consisting of an L-type voltage dependent calcium channel inhibitor, an R-type voltage dependent calcium channel inhibitor, an N-type voltage dependent calcium channel inhibitor, a P/Q-type voltage dependent calcium channel inhibitor, a T-type voltage dependent calcium channel inhibitor, or a combination thereof.

4746. The kit according to claim 4645, wherein the L-type voltage dependent calcium channel inhibitor is a dihydropyridine, selected from the group consisting of amlodipine, aranidipine, azelnidipine, bamidipine, benidipine, cinaldipine, efonidipine, felodipine, isradipine, lacidipine, lemildipine, lercanidipine, nicardipine, nifedipine, nilvadipine, nimodipine, nisoldipine, nitrendipine, manidipine, pranidipine, or a combination thereof.

4847. The kit according to claim 4746, wherein the dihydropyridine is nimodipine.

~~49. The kit according to claim 38, wherein the pharmaceutical carrier is a buffer solution.~~

5048. The kit according to claim 3837, wherein the kit further comprises at least two sterile containers, wherein the sterile first container is suitable to hold the sterile microparticulate formulation and the sterile second container is suitable to hold the sterile pharmaceutical carrier.

5149. The kit according to claim 5048, wherein the container is a vial, a bottle, a tube, a bag, a packet, a pillow, an ampoule, or a combination thereof.

~~52~~50. The kit according to claim ~~38~~37, wherein the microparticulate formulation is prepacked in the first syringe.

~~53~~51. The kit according to claim ~~38~~37, wherein the pharmaceutical carrier is prepacked in the second syringe.

~~54~~52. A method of preparing a sterile flowable sustained release microparticulate composition comprising, in order:

(a) providing a sterile microparticulate formulation comprising a therapeutic amount of at least one therapeutic agent, wherein the therapeutic amount is effective to reduce a delayed complication of an interruption of a cerebral artery in a subarachnoid space,

~~wherein~~ the microparticle formulation ~~comprises~~ being characterized by:

(i) a plurality of microparticles of uniform size distribution, ~~and wherein the at least one therapeutic agent is dispersed throughout each microparticle;~~

(ii) dispersal of the therapeutic amount of the therapeutic agent throughout each microparticle, in a core surrounded by a coating; adsorbed in the particles or a combination thereof;

(b) drawing the sterile microparticulate formulation of step (a) into a sterile first syringe comprising a first syringe barrel, a first syringe plunger and a female luer cap, and removing air trapped within the first syringe;

(c) providing a sterile pharmaceutically acceptable carrier;

(d) drawing the sterile pharmaceutical carrier of (c) into a sterile second syringe fitted with a male luer cap comprising a second syringe barrel and a second syringe plunger;

(e) replacing the male luer cap in step (c) with a sterile female syringe connector;

(f) connecting the sterile first syringe containing the sterile microparticulate formulation of step (b) with the sterile second syringe containing the sterile pharmaceutically acceptable carrier of step (c) via the female syringe connector of step (d);

(g) pushing the sterile first syringe plunger so that the sterile microparticulate formulation and the sterile pharmaceutical carrier mix in the sterile second syringe barrel;

(h) pushing the sterile second syringe plunger so that the sterile microparticulate formulation and the sterile pharmaceutical carrier mix in the sterile first syringe barrel; and

(i) repeating steps (g) and (i) at least 5-50 times to yield the sterile flowable sustained release microparticulate composition for delivery into a cerebral ventricle.

~~55~~53. The method according to claim ~~54~~52, wherein the microparticulate formulation comprises a powder suspension of microparticles.

~~56~~54. The method according to claim ~~54~~52, wherein each microparticle comprises a matrix.

~~57~~55. The method according to claim ~~54~~52, wherein the microparticulate formulation further comprises a slow-release compound.

~~58~~56. The method according to claim ~~57~~55, wherein the ~~slow release~~ slow-release compound is a biodegradable polymer.

~~59~~57. The method according to claim ~~58~~56, wherein the biodegradable polymer is selected from the group consisting of polylactide-polyglycolide, poly(orthoester), and poly(anhydride).

~~60~~58. The method according to claim ~~54~~52, wherein the therapeutic agent is a calcium channel antagonist, an endothelin antagonist, a transient receptor potential (TRP) protein antagonist, or a combination thereof.

~~61~~59. The method according to claim ~~54~~52, wherein the therapeutic agent is a calcium channel antagonist selected from the group consisting of an L-type voltage dependent calcium channel inhibitor, an R-type voltage dependent calcium channel inhibitor, an N-type voltage dependent calcium channel inhibitor, a P/Q-type voltage dependent calcium channel inhibitor, a T-type voltage dependent calcium channel inhibitor, or a combination thereof.

~~62~~60. The method according to claim ~~61~~59, wherein the L-type voltage dependent calcium channel inhibitor is a dihydropyridine, selected from the group consisting of amlodipine, aranidipine, azelnidipine, bamidipine, benidipine, cinaldipine, efonidipine, felodipine, isradipine, lacidipine, lemildipine, lercanidipine, nicardipine, nifedipine, nilvadipine, nimodipine, nisoldipine, nitrendipine, manidipine, pranidipine, or a combination thereof.

~~63~~61. The method according to claim ~~62~~60, wherein the dihydropyridine is nimodipine.

~~64~~62. The ~~kit~~ method according to claim ~~54~~52, wherein the pharmaceutical carrier is a buffer solution.

~~65~~63. The method according to claim ~~54~~52, wherein the injection apparatus is a needle, a cannula, a catheter, or a combination thereof.