patients with placebo, 25% of patients with clazosentan 5 mg/h (OR, 0.918; 95% CI, 0.546-1.544; P=0.748), and 28% of patients with clazosentan 15 mg/h (OR, 1.337; 95% CI, 0.802-2.227; P=0.266). Pulmonary complications, anemia, and hypotension were more common in patients who received clazosentan than in those who received placebo. Clazosentan 15 mg/h significantly reduced post aneurysmal SAH vasospasm-related morbidity/all-cause mortality; however, neither dose improved outcome (extended Glasgow Outcome Scale). Clazosentan currently is not approved for use for SAH patients.

[000193] Current therapies to prevent or reduce the incidence of secondary complications after aSAH, such as DCI and angiographic vasosparm, are risky, only marginally efficacious, expensive and time-consuming. Thus, there is a large unmet medical need for safe, effective treatments to reduce the need for rescue therapy and improve functional outcome While conventional therapies have been focusing on treating cerebral vasospasms following SAH, accumulating evidence suggests that there are additional complications derived from SAH, which need to be targeted for treatment interventions in order to improve prognosis following SAH treatment. The described invention offers such an approach.

SUMMARY

[000194] According to one ~~aspect~~embodiment, the present disclosure ~~described invention~~ provides a method for treating at least one cerebral artery at risk of interruption due to subarachnoid hemorrhage (SAH) in a human subject, comprising: a) providing a flowable sustained release particulate composition comprising: (i) a microparticle formulation comprising a plurality of particles of uniform size distribution, and a therapeutic amount of at least one first therapeutic agent, wherein the first therapeutic agent is dispersed throughout each particle, adsorbed onto the particles, or in a core surrounded by a coating; (ii) and a pharmaceutical carrier; and b) administering the flowable sustained release particulate composition locally, via an injection apparatus, either intracisternally into the subarachnoid space in a cistern closest to the cerebral artery at risk for interruption; intraventricularly so that the pharmaceutical composition is carried by cerebrospinal flow; or intrathecally into the spinal subarachnoid space so that the pharmaceutical composition is carried by cerebrospinal flow; so as to contact the at least one artery of the subarachnoid space at risk of interruption due to the subarachnoid hemorrhage, without the first therapeutic agent entering systemic circulation in an amount to cause unwanted side effects, wherein interruption

release carrier. According to another embodiment, the pharmaceutically acceptable carrier is a long-term release carrier. According to another embodiment, the pharmaceutically acceptable carrier comprises aqueous channels. According to another embodiment, the pharmaceutically acceptable carrier is a biphasic release carrier. According to another embodiment, the pharmaceutically acceptable carrier is an extended release carrier. According to another embodiment, the concentration of the first therapeutic agent in plasma (PLASMA-C_{av}) is from 0.200 ng/ml/day to 30 mg/ml/day for at least 4 days after administration. According to another embodiment, the concentration of the first therapeutic agent in plasma (PLASMA-Cav) is less than 5 ng/ml/day for at least 14 days after administration. According to another embodiment, the concentration of the first therapeutic agent in cerebrospinal fluid (CSF) (CSF-Cav) is from 5 ng/ml/day to 30 mg/ml/day for at least 14 days after administration. According to another embodiment, the therapeutic amount of the first therapeutic agent is effective to decrease angiographic diameter of the cerebral artery at risk of interruption such that percent change in angiographic diameter of at least one cerebral artery is less than 50% compared to baseline. According to another embodiment, the therapeutic amount of the first therapeutic agent is effective to decrease occurrence of delayed cerebral ischemia (DCI) within 14 days of symptom onset of subarachnoid hemorrhage (SAH). According to another embodiment, the therapeutic amount of the first therapeutic agent is effective to decrease occurrence of delayed cerebral infarction on CT within 30 days of symptom onset of subarachnoid hemorrhage (SAH). According to another embodiment, the therapeutic amount of the first therapeutic agent is effective to decrease occurrence of delayed cerebral ischemia. According to another embodiment, occurrence of delayed cerebral ischemia is assessable as a decrease of at least 2 points on the modified glasgow coma score or an increase of at least 2 points on the abbreviated National Institutes of Health Stroke Scale lasting for at least 2 hours. According to another embodiment, the therapeutic amount of the first therapeutic agent is effective to reduce need for rescue therapy.

In one aspect, there is provided a flowable particulate composition for use in treating a delayed complication of a brain injury that deposits blood in a subarachnoid space of the brain, wherein the brain injury is mediated by decreased cerebral perfusion, comprising:

(i) a microparticle suspension comprising a plurality of particles of a uniform distribution of microparticle size, and a therapeutic amount of a therapeutic agent, wherein the therapeutic

agent is a calcium channel antagonist, an endothelin antagonist, a transient receptor potential (TRP) protein antagonist, or a combination thereof;

(ii) and a pharmaceutical carrier comprising an agent that affects viscosity of the suspension;

the flowable particulate pharmaceutical composition being characterized by:

(a) dispersal of the therapeutic agent throughout each particle;

(b) a drug load of 40%-100% (wt/wt) of the therapeutic agent;

the following release characteristics of the flowable particulate composition:

(1) release about 50%-100% of the therapeutic agent within 6 days to 14 days;

(2) upon release, the concentration of the therapeutic agent in plasma (PLASMA-C_{av}) is less than about 30-40 ng/mL;

(3) upon release, the concentration of the therapeutic agent in cerebrospinal fluid (CSF) (CSF-C_{av}) is at least about 5 ng/mL to about 5000 ng/mL;

(4) gradual release of the therapeutic agent from the composition over an extended period of time;

(5) as a dispersion, its fluidity around at least one cerebral artery in the subarachinoid space; and

(6) a local therapeutic effect that is effective to reduce signs or symptoms of the delayed complication without entering systemic circulation in an amount to cause unwanted side effects.

In another aspect, there is provided the use of a flowable particulate composition in the manufacture of a medicament for treating a delayed complication of a brain injury that deposits blood in a subarachinoid space of the brain, wherein the brain injury is mediated by decreased perfusion comprising:

(i) a microparticle suspension for local delivery into a site of administration via an injection apparatus comprising a plurality of particles of uniform distribution of microparticle size, and a therapeutic amount of a therapeutic agent, wherein the therapeutic agent is a calcium channel antagonist, an endothelin antagonist, a transient receptor potential (TRP) protein antagonist, or a combination thereof;

(ii) and a pharmaceutical carrier comprising an agent that affects viscosity of the suspension;

the pharmaceutical composition being characterized by:

(a) dispersal of the therapeutic agent throughout each microparticle;

(b) a drug load of 40%-100% (wt/wt) of the therapeutic agent

the following release characteristics of the flowable particulate composition:

(1) release about 50%-100% of the therapeutic agent within 6 days to 14 days;

(2) upon release, the concentration of the therapeutic agent in plasma (PLASMA-C_{av}) is less than about 30-40 ng/mL;

(3) upon release, the concentration of the therapeutic agent in cerebrospinal fluid (CSF) (CSF-C_{av}) is at least about 5 ng/mL to about 5000 ng/mL;

(4) gradual release of the therapeutic agent from the composition over an extended period of time;

(5) as a dispersion, its fluidity around at least one cerebral artery in the subarachinoid space; and

(6) a local therapeutic effect that is effective to reduce signs or symptoms of the delayed complication without entering systemic circulation in an amount to cause unwanted side effects.

BRIEF DESCRIPTION OF THE DRAWINGS

[000196] **Figure 1** shows an illustrative lateral view of the human brain (Stedman's Medical Dictionary, 27th Edition, plate 7 at A7 (2000)).

CLAIMS

What is claimed is:

1. A method for treating at least one cerebral artery at risk of interruption due to subarachnoid hemorrhage (SAH) in a human subject, comprising:

a) providing a flowable particulate composition comprising:

(i) a microparticle formulation comprising a plurality of particles of uniform size distribution, and a therapeutic amount of a therapeutic agent;

(ii) and a pharmaceutical carrier;

the flowable particulate pharmaceutical composition being characterized by:

dispersal of the therapeutic agent throughout each particle; adsorption of the therapeutic agent onto each particle, or presence of the therapeutic agent in a core of each particle surrounded by a coating;

sustained release of the therapeutic agent from the composition;

as a dispersion, its fluidity around the at least one cerebral artery at risk for the delayed complication associated with the brain injury following local delivery via injection;

the following release characteristics:

(1) about 50%-100% of the first therapeutic agent is released within 6 days to 14 days;

(2) upon release, the concentration of the first therapeutic agent in plasma (PLASMA-C_{av}) is less than about 30-40 ng/mL; and

(3) upon release, the concentration of the first therapeutic agent in cerebrospinal fluid (CSF) (CSF-C_{av}) is at least about 5 ng/mL to about 5000 ng/mL; and

a local therapeutic effect that is effective to reduce signs or symptoms of the delayed complication without entering systemic circulation in an amount to cause unwanted side effects,

and

b) administering the flowable particulate composition locally, via an injection apparatus, either

intracisternally into the subarachnoid space in a cistern closest to the cerebral artery at risk for interruption;

intraventricularly; or

intrathecally;

so as to contact the at least one artery of the subarachnoid space at risk of interruption due to the subarachnoid hemorrhage,

wherein interruption of the cerebral artery is associated with at least one delayed complication

2. The method according to claim 1, wherein the delayed complication associated with the interruption of the cerebral artery is at least one of an angiographic vasospasm, a plurality of microthromboemboli, a cortical spreading ischemia, or a delayed cerebral ischemia (DCI).

3. The method according to claim 1, wherein the cerebral artery is an anterior cerebral artery, a middle cerebral artery, an internal carotid artery, a basilar cerebral artery, a vertebral cerebral artery, or a combination thereof.

4. The method according to claim 1, wherein each microparticle is of a particle size from about 40 μm to about 100 μm.

5. The method according to claim 4, wherein the mean size distribution is about 70 μm.

6. The method according to claim 1, wherein each microparticle is loaded with at least 65% (wt/wt) of the at least one first therapeutic agent, wherein the therapeutic agent is a calcium channel antagonist, an endothelin antagonist, a transient receptor potential (TRP) protein antagonist, or a combination thereof.

7. The method according to claim 6, 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.

8. The method according to claim 7, 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.

9. The method according to claim 8, wherein the dihydropyridine is nimodipine.

10. The method according to claim 1, wherein the pharmaceutical carrier comprises 0 % to 5 % by weight hyaluronic acid or a derivative thereof, wherein the hyaluronic acid has an average molecular weight of about 500 kDa.

11. The method according to claim 1, wherein the injection apparatus is a needle, a cannula, a catheter, or a combination thereof.

12. The method according to claim 1, wherein viscosity of the flowable particulate pharmaceutical composition at 20 °C, when administered intracisternally, is from about 100 cP to about 1,000 cp.

13. The method according to claim 1, wherein viscosity of the flowable particulate pharmaceutical composition at 20 °C, when administered intraventricularly, is from about 0.5 cP to about 50 cp.

14. The method according to claim 1, wherein viscosity of the flowable particulate pharmaceutical composition at 20 °C, when administered intrathecally into the spinal subarachnoid space, is from about 0.5 cP to about 50 cp.

15. The method according to claim 1, wherein maximum tolerated dose of the therapeutic agent when administered intracisternally is from 40 mg to about 1,000 mg.

16. The method according to claim 1, wherein maximum tolerated dose of the therapeutic agent when administered intraventricularly is from 40 mg to about 1,000 mg.

17. The method according to claim 1, wherein maximum tolerated dose of the therapeutic agent when administered intrathecally is from 40 mg to about 1,000 mg.

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

19. The method according to claim 1, wherein the cerebral cistern is a carotid cistern, a chiasmatic cistern, a Sylvian cistern, an interhemispheric cistern, an ambient cistern, a crural cistern, an interpeduncular cistern, a prepontine cistern, a lateral medullary cistern, a cisterna magna, or a combination thereof.

20 The method according to claim 1, wherein the particulate formulation comprises a femtoparticle, a picoparticle, a microparticle, or a nanoparticle.

21. The method according to claim 1, wherein each particle of the microparticulate formulation is a microparticle.

22. The method according to claim 21, wherein each microparticle comprises a matrix.

23. The method according to claim 22, wherein the matrix comprises a biodegradable polymer.

24. The method according to claim 23, wherein the biodegradable polymer is a poly(lactide-co-glycolide) (PLGA) polymer, wherein the lactide to glycolide ratio is 65:35 or 50:50.

25 The method according to claim 1, wherein the pharmaceutically acceptable carrier comprises a matrix.

26. The method according to claim 1, wherein the pharmaceutically acceptable carrier comprises nanoparticles.

27. The method according to claim 26, wherein the therapeutic agent is dispersed throughout the nanoparticles, adsorbed into the nanoparticles, in a core of the nanoparticles surrounded by a coating, or a combination thereof.

28. The method according to claim 1, wherein the pharmaceutically acceptable carrier is a slow release carrier.

29. The method according to claim 1, wherein the pharmaceutically acceptable carrier is a localized release carrier.

30. The method according to claim 1, wherein the pharmaceutically acceptable carrier is a depot release carrier.

31. The method according to claim 1, wherein the pharmaceutically acceptable carrier is a delayed release carrier.

32. The method according to claim 1, wherein the pharmaceutically acceptable carrier is a long-term release carrier.

33. The method according to claim 1, wherein the pharmaceutically acceptable carrier comprises aqueous channels.

34. The method according to claim 1, wherein the pharmaceutically acceptable carrier is a biphasic release carrier.

35. The method according to claim 1, wherein the pharmaceutically acceptable carrier is an extended release carrier.

36. The method according to claim 1, wherein the concentration of the therapeutic agent in plasma (PLASMA-C_{av}) is from 0.200 ng/ml/day to 30 mg/ml/day for at least 4 days after administration.

37. The method according to claim 1, wherein the concentration of the therapeutic agent in plasma (PLASMA-Cav) is less than 5 ng/ml/day for at least 14 days after administration.

38. The method according to claim 1, wherein the concentration of the therapeutic agent in cerebrospinal fluid (CSF) (CSF-Cav) is from 5 ng/ml/day to 30 mg/ml/day for at least 14 days after administration.

39. The method according to claim 1, wherein the therapeutic amount of the therapeutic agent is effective to decrease angiographic diameter of the cerebral artery at risk of interruption such that percent change in angiographic diameter of at least one cerebral artery is less than 50% compared to baseline.

40. The method according to claim 1, wherein the therapeutic amount of the therapeutic agent is effective to decrease occurrence of delayed cerebral ischemia (DCI) within 14 days of symptom onset of subarachnoid hemorrhage (SAH).

41. The method according to claim 1, wherein the therapeutic amount of the therapeutic agent is effective to decrease occurrence of delayed cerebral infarction on CT within 30 days of symptom onset of subarachnoid hemorrhage (SAH).

42. The method according to claim 1, wherein the therapeutic amount of the therapeutic agent is effective to decrease occurrence of delayed cerebral ischemia.

43. The method according to claim 42, wherein occurrence of delayed cerebral ischemia is assessable as a decrease of at least 2 points on the modified glasgow coma score or an increase of at least 2 points on the abbreviated National Institutes of Health Stroke Scale lasting for at least 2 hours.

44. The method according to claim 1, wherein the therapeutic amount of the therapeutic agent is effective to reduce need for rescue therapy.

45. Use of a flowable particulate composition in the manufacture of a medicament for treating at least one cerebral artery at risk of interruption due to subarachnoid hemorrhage (SAH) in a human subject, wherein interruption of the cerebral artery is associated with at least one delayed complication, the flowable particulate composition comprising:

(i) a microparticle formulation for local delivery into a site of administration via an injection apparatus comprising a plurality of particles of uniform size distribution, and a therapeutic amount of a therapeutic agent;

(ii) and a pharmaceutical carrier;

the pharmaceutical composition being characterized by:

dispersal of the therapeutic agent throughout each microparticle; adsorption of the therapeutic agent onto the particles, or presence of the therapeutic agent in a core surrounded by a coating;

sustained release of the therapeutic gent from the composition;

as a dispersion, its fluidity around the at least one cerebral artery at risk for the delayed complication associated with the brain injury following local delivery via injection;

the following release characteristics of the flowable sustained release particulate composition:

(1) about 50%-100% of the first therapeutic agent is released within 6 days to 14 days;

(2) upon release, the concentration of the first therapeutic agent in plasma (PLASMA-C_{av}) is less than about 30-40 ng/mL; and

(3) upon release, the concentration of the first therapeutic agent in cerebrospinal fluid (CSF) (CSF-C_{av}) is at least about 5 ng/mL to about 5000 ng/mL.

and

a local therapeutic effect that is effective to reduce signs or symptoms of the delayed complication without entering systemic circulation in an amount to cause unwanted side effects.

46. The use according to claim 45, wherein the delayed complication associated with the interruption of the cerebral artery is at least one of an angiographic vasospasm, a

plurality of microthromboemboli, a cortical spreading ischemia, or a delayed cerebral ischemia (DCI).

47. The use according to claim 45, wherein the cerebral artery is an anterior cerebral artery, a middle cerebral artery, an internal carotid artery, a basilar cerebral artery, a vertebral cerebral artery, or a combination thereof.

48. The use according to claim 45, wherein each microparticle is of a particle size from about 40 μm to about 100 μm.

49. The use according to claim 48, wherein the mean size distribution is about 70 μm.

50. The use according to claim 45, wherein each microparticle is loaded with at least 65% (wt/wt) of the therapeutic agent, wherein the therapeutic agent is a calcium channel antagonist, an endothelin antagonist, a transient receptor potential (TRP) protein antagonist, or a combination thereof.

51. The use according to claim 50, 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.

52. The use according to claim 51, 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.

53. The use according to claim 52, wherein the dihydropyridine is nimodipine.

54. The use according to claim 45, wherein the pharmaceutical carrier comprises 0 % to 5 % by weight hyaluronic acid or a derivative thereof, wherein the hyaluronic acid has an average molecular weight of about 500 kDa.

55. The use according to claim 45, wherein the injection apparatus is a needle, a cannula, a catheter, or a combination thereof.

56. The use according to claim 45, wherein viscosity of the flowable pharmaceutical composition at 20 °C, when administered intracisternally, is from about 100 cP to about 1,000 cp.

57. The use according to claim 45, wherein viscosity of the flowable pharmaceutical composition at 20 °C, when administered intraventricularly, is from about 0.5 cP to about 50 cp.

58. The use according to claim 45, wherein viscosity of the flowable pharmaceutical composition at 20 °C, when administered intrathecally into a spinal subarachnoid space, is from about 0.5 cP to about 50 cp.

59. The use according to claim 45, wherein maximum tolerated dose of the therapeutic agent when administered intracisternally is from 40 mg to about 1,000 mg.

60. The use according to claim 45, wherein maximum tolerated dose of the therapeutic agent when administered intraventricularly is from 40 mg to about 1,000 mg.

61. The use according to claim 45, wherein maximum tolerated dose of the therapeutic agent when administered intrathecally is from 40 mg to about 1,000 mg.

62. The use according to claim 45, wherein the site of administration is a lateral ventricle, a third ventricle, a fourth ventricle, or a combination thereof.

63. The use according to claim 45, wherein the site of administration is cerebral cistern selected from the group consisting of a carotid cistern, a chiasmatic cistern, a Sylvian cistern, an interhemispheric cistern, an ambient cistern, a crural cistern, an interpeduncular cistern, a prepontine cistern, a lateral medullary cistern, a cisterna magna, or a combination thereof.

64 The use according to claim 45, wherein the particulate formulation comprises a femtoparticle, a picoparticle, a microparticle, or a nanoparticle.

65. The use according to claim 45, wherein each particle of the microparticulate formulation is a microparticle.

66. The use according to claim 65, wherein each microparticle comprises a matrix.

67. The use according to claim 66, wherein the matrix comprises a biodegradable polymer.

68. The use according to claim 67, wherein the biodegradable polymer is a poly(lactide-co-glycolide) (PLGA) polymer, wherein the lactide to glycolide ratio is 65:35 or 50:50.

69 The use according to claim 45, wherein the pharmaceutically acceptable carrier comprises a matrix.

70. The use according to claim 45, wherein the pharmaceutically acceptable carrier comprises nanoparticles.

71. The use according to claim 70, wherein the therapeutic agent is dispersed throughout the nanoparticles, adsorbed into the nanoparticles, in a core of the nanoparticles surrounded by a coating, or a combination thereof.

72. The use according to claim 45, wherein the pharmaceutically acceptable carrier is a slow release carrier.

73. The use according to claim 45, wherein the pharmaceutically acceptable carrier is a localized release carrier.

74. The use according to claim 45, wherein the pharmaceutically acceptable carrier is a depot release carrier.

75. The use according to claim 45, wherein the pharmaceutically acceptable carrier is a delayed release carrier.

76. The use according to claim 45, wherein the pharmaceutically acceptable carrier is a long-term release carrier.

77. The use according to claim 45, wherein the pharmaceutically acceptable carrier comprises aqueous channels.

78. The use according to claim 45, wherein the pharmaceutically acceptable carrier is a biphasic release carrier.

79. The use according to claim 45, wherein the pharmaceutically acceptable carrier is an extended release carrier.

80. The use according to claim 45, wherein the concentration of the therapeutic agent in plasma (PLASMA-C_{av}) is from 0.200 ng/ml/day to 30 mg/ml/day for at least 4 days after administration.

81. The use according to claim 45, wherein the concentration of the therapeutic agent in plasma (PLASMA-Cav) is less than 5 ng/ml/day for at least 14 days after administration.

82. The use according to claim 45, wherein the concentration of the therapeutic agent in cerebrospinal fluid (CSF) (CSF-Cav) is from 5 ng/ml/day to 30 mg/ml/day for at least 14 days after administration.

83. The use according to claim 45, wherein the therapeutic amount of the therapeutic agent is effective to decrease angiographic diameter of the cerebral artery at risk of interruption such that percent change in angiographic diameter of at least one cerebral artery is less than 50% compared to baseline.

84. The use according to claim 45, wherein the therapeutic amount of the therapeutic agent is effective to decrease occurrence of delayed cerebral ischemia (DCI) within 14 days of symptom onset of subarachnoid hemorrhage (SAH).

85. The use according to claim 45, wherein the therapeutic amount of the therapeutic agent is effective to decrease occurrence of delayed cerebral infarction on CT within 30 days of symptom onset of subarachnoid hemorrhage (SAH).

86. The use according to claim 45, wherein the therapeutic amount of the therapeutic agent is effective to decrease occurrence of delayed cerebral ischemia.

87. The use according to claim 86, wherein occurrence of delayed cerebral ischemia is assessable as a decrease of at least 2 points on the modified glasgow coma score or an increase of at least 2 points on the abbreviated National Institutes of Health Stroke Scale lasting for at least 2 hours.

88. The use according to claim 45, wherein the therapeutic amount of the therapeutic agent is effective to reduce need for rescue therapy.

CLAIMS

What is claimed is:

1. A flowable particulate composition for use in treating a delayed complication of a brain injury that deposits blood in a subarachnoid space of the brain, wherein the brain injury is mediated by decreased cerebral perfusion, comprising:

(i) a microparticle suspension comprising a plurality of particles of a uniform distribution of microparticle size, and a therapeutic amount of a therapeutic agent, wherein the therapeutic agent is a calcium channel antagonist, an endothelin antagonist, a transient receptor potential (TRP) protein antagonist, or a combination thereof;

(ii) and a pharmaceutical carrier comprising an agent that affects viscosity of the suspension;

the flowable particulate pharmaceutical composition being characterized by:

(a) dispersal of the therapeutic agent throughout each particle;

(b) a drug load of 40%-100% (wt/wt) of the therapeutic agent;

the following release characteristics of the flowable particulate composition:

(1) release about 50%-100% of the therapeutic agent within 6 days to 14 days;

(2) upon release, the concentration of the therapeutic agent in plasma (PLASMA-C_{av}) is less than about 30-40 ng/mL;

(3) upon release, the concentration of the therapeutic agent in cerebrospinal fluid (CSF) (CSF-C_{av}) is at least about 5 ng/mL to about 5000 ng/mL;

(4) gradual release of the therapeutic agent from the composition over an extended period of time;

(5) as a dispersion, its fluidity around at least one cerebral artery in the subarachinoid space; and

(6) a local therapeutic effect that is effective to reduce signs or symptoms of the delayed complication without entering systemic circulation in an amount to cause unwanted side effects.

2. The composition according to claim 1, wherein the delayed complication associated with the interruption of the cerebral artery is at least one of an angiographic vasospasm, a plurality of microthromboemboli, a cortical spreading ischemia, or a delayed cerebral ischemia (DCI).

3. The composition according to claim 1, wherein the cerebral artery is an anterior cerebral artery, a middle cerebral artery, an internal carotid artery, a basilar cerebral artery, a vertebral cerebral artery, or a combination thereof.

4. The composition according to claim 1, wherein each microparticle is of a particle size from about 40 μm to about 100 μm.

5. The composition according to claim 1, wherein each microparticle is loaded with at least 65% (wt/wt) of the therapeutic agent.

6. The composition according to claim 5, 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.

7. The composition according to claim 6, 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.

8. The composition according to claim 7, wherein the dihydropyridine is nimodipine.

9. The composition according to claim 1, wherein the agent that affects the viscosity of the suspension comprises between 0 % to 5 % by weight hyaluronic acid or a derivative thereof, wherein the hyaluronic acid has an average molecular weight of about 500 kDa.

10. The composition according to claim 1, wherein the viscosity of the suspension at 20 °C, when administered intracisternally, is from about 100 cP to about 1,000 cp.

11. The composition according to claim 1, wherein the viscosity of the suspension at 20 °C, when administered (i) intraventricularly or (ii) intrathecally, is from about 0.5 cP to about 50 cp.

12. The composition according to claim 1, wherein maximum tolerated dose of the therapeutic agent when administered (i) intracisternally or (ii) intraventricularly or (iii) intrathecally is from 40 mg to about 1,000 mg.

13. The composition according to claim 1, wherein the flowable particulate composition is administered intraventricularly in a lateral ventricle, a third ventricle, a fourth ventricle, or a combination thereof.

14. The composition according to claim 1, wherein the cerebral cistern is a carotid cistern, a chiasmatic cistern, a Sylvian cistern, an interhemispheric cistern, an ambient cistern, a crural cistern, an interpeduncular cistern, a prepontine cistern, a lateral medullary cistern, a cisterna magna, or a combination thereof.

15. The composition according to claim 1, wherein the particulate formulation comprises a femtoparticle, a picoparticle, a microparticle, or a nanoparticle.

16. The composition according to claim 1, wherein each particle of the microparticulate formulation is a microparticle.

17. The composition according to claim 16, wherein each microparticle comprises a matrix.

18. The composition according to claim 17, wherein the matrix comprises a biodegradable polymer.

19. The composition according to claim 18, wherein the biodegradable polymer is a poly(lactide-co-glycolide) (PLGA) polymer, wherein the lactide to glycolide ratio is 65:35 or 50:50.

20. The composition according to claim 1, wherein the pharmaceutical carrier comprises (i) a matrix or (ii) nanoparticles.

21. The composition according to claim 20, wherein the therapeutic agent is dispersed throughout the nanoparticles, adsorbed into the nanoparticles, in a core of the nanoparticles surrounded by a coating, or a combination thereof.

22. The composition according to claim 1, wherein the pharmaceutical carrier is (1) a slow release carrier, (2) a localized release carrier, (3) a depot release carrier, (4) a delayed release carrier, (5) a long-term release carrier, (6) biphasic release carrier or (7) an extended release carrier.

23. The composition according to claim 1, wherein the pharmaceutical carrier comprises aqueous channels.

24. The composition according to claim 1, wherein concentration of the therapeutic agent in plasma (PLASMA-C_{av}) is from 0.200 ng/ml/day to 30 mg/ml/day for at least 4 days after administration or is less than 5 ng/ml/day for at least 14 days after administration.

25. The composition according to claim 1, wherein concentration of the therapeutic agent in cerebrospinal fluid (CSF) (CSF-Cav) is from 5 ng/ml/day to 30 mg/ml/day for at least 14 days after administration.

26. The composition according to claim 1, wherein the therapeutic amount of the therapeutic agent is effective to decrease angiographic diameter of the cerebral artery at risk of interruption such that percent change in angiographic diameter of at least one cerebral artery is less than 50% compared to baseline.

27. The composition according to claim 1, wherein the therapeutic amount of the therapeutic agent is (i) effective to decrease occurrence of delayed cerebral ischemia (DCI) within 14 days of symptom onset of subarachnoid hemorrhage (SAH), (ii) is effective to decrease occurrence of delayed cerebral infarction on CT within 30 days of symptom onset of subarachnoid hemorrhage (SAH) or (iii) is effective to decrease occurrence of delayed cerebral ischemia.

28. The composition according to claim 27, wherein the occurrence of delayed cerebral ischemia is assessable as a decrease of at least 2 points on the modified glasgow

coma score or an increase of at least 2 points on the abbreviated National Institutes of Health Stroke Scale lasting for at least 2 hours.

29. The composition according to claim 1, wherein the therapeutic amount of the therapeutic agent is effective to reduce need for rescue therapy.

30. Use of a flowable particulate composition in the manufacture of a medicament for treating a delayed complication of a brain injury that deposits blood in a subarachinoid space of the brain, wherein the brain injury is mediated by decreased perfusion comprising:

(i) a microparticle suspension for local delivery into a site of administration via an injection apparatus comprising a plurality of particles of uniform distribution of microparticle size, and a therapeutic amount of a therapeutic agent, wherein the therapeutic agent is a calcium channel antagonist, an endothelin antagonist, a transient receptor potential (TRP) protein antagonist, or a combination thereof;

(ii) and a pharmaceutical carrier comprising an agent that affects viscosity of the suspension;

the pharmaceutical composition being characterized by:

(a) dispersal of the therapeutic agent throughout each microparticle;
(b) a drug load of 40%-100% (wt/wt) of the therapeutic agent

the following release characteristics of the flowable particulate composition:

(1) release about 50%-100% of the therapeutic agent within 6 days to 14 days;

(2) upon release, the concentration of the therapeutic agent in plasma (PLASMA-C_{av}) is less than about 30-40 ng/mL;

(3) upon release, the concentration of the therapeutic agent in cerebrospinal fluid (CSF) (CSF-C_{av}) is at least about 5 ng/mL to about 5000 ng/mL;

(4) gradual release of the therapeutic agent from the composition over an extended period of time;

(5) as a dispersion, its fluidity around at least one cerebral artery in the subarachinoid space; and

(6) a local therapeutic effect that is effective to reduce signs or symptoms of the delayed complication without entering systemic circulation in an amount to cause unwanted side effects.

31. The use according to claim 30, wherein the delayed complication associated with the interruption of the cerebral artery is at least one of an angiographic vasospasm, a plurality of microthromboemboli, a cortical spreading ischemia, or a delayed cerebral ischemia (DCI).

32. The use according to claim 30, wherein the cerebral artery is an anterior cerebral artery, a middle cerebral artery, an internal carotid artery, a basilar cerebral artery, a vertebral cerebral artery, or a combination thereof.

33. The use according to claim 30, wherein each microparticle is of a particle size from about 40 μm to about 100 μm.

34. The use according to claim 30, wherein each microparticle is loaded with at least 65% (wt/wt) of the therapeutic agent.

35. The use according to claim 30, 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.

36. The use according to claim 35, 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.

37. The use according to claim 36, wherein the dihydropyridine is nimodipine.

38. The use according to claim 30, wherein the agent that affects the viscosity of the suspension comprises between 0 % to 5 % by weight hyaluronic acid or a derivative thereof, wherein the hyaluronic acid has an average molecular weight of about 500 kDa..

39. The use according to claim 30, wherein the injection apparatus is a needle, a cannula, a catheter, or a combination thereof.

40. The use according to claim 30, wherein the viscosity of the suspension at 20 °C, when administered intracisternally, is from about 100 cP to about 1,000 cp.

41. The use according to claim 30, wherein viscosity of the flowable pharmaceutical composition at 20 °C, when administered (i) intraventricularly or (ii) intrathecally, is from about 0.5 cP to about 50 cp.

42. The use according to claim 30, wherein maximum tolerated dose of the therapeutic agent when administered (i) intracisternally or (ii) intraventricularly or (iii) intrathecally is from 40 mg to about 1,000 mg.

43. The use according to claim 30, wherein the flowable particulate composition is administered intraventricularly in a lateral ventricle, a third ventricle, a fourth ventricle, or a combination thereof.

44. The use according to claim 30, wherein the site of administration is a cerebral cistern selected from the group consisting of a carotid cistern, a chiasmatic cistern, a Sylvian cistern, an interhemispheric cistern, an ambient cistern, a crural cistern, an interpeduncular cistern, a prepontine cistern, a lateral medullary cistern, a cisterna magna, or a combination thereof.

45. The use according to claim 30, wherein each particle of the microparticulate formulation is a microparticle.

46. The use according to claim 45, wherein each microparticle comprises a matrix.

47. The use according to claim 46, wherein the matrix comprises a biodegradable polymer.

48. The use according to claim 47, wherein the biodegradable polymer is a poly(lactide-co-glycolide) (PLGA) polymer, wherein the lactide to glycolide ratio is 65:35 or 50:50.

49. The use according to claim 30, wherein the pharmaceutical carrier comprises (i) a matrix or (ii) nanoparticles.

50. The use according to claim 49, wherein the therapeutic agent is dispersed throughout the nanoparticles, adsorbed into the nanoparticles, in a core of the nanoparticles surrounded by a coating, or a combination thereof.

51. The use according to claim 30, wherein the pharmaceutical carrier (1) a slow release carrier, (2) a localized release carrier, (3) a depot release carrier, (4) a delayed release carrier, (5) a long-term release carrier, (6) biphasic release carrier or (7) an extended release carrier.

52. The use according to claim 30, wherein the pharmaceutical carrier comprises aqueous channels.

53. The use according to claim 30, wherein concentration of the therapeutic agent in plasma (PLASMA-C_{av}) is from 0.200 ng/ml/day to 30 mg/ml/day for at least 4 days after administration or is less than 5 ng/ml/day for at least 14 days after administration.

54. The use according to claim 30, wherein concentration of the therapeutic agent in cerebrospinal fluid (CSF) (CSF-Cav) is from 5 ng/ml/day to 30 mg/ml/day for at least 14 days after administration.

55. The use according to claim 30, wherein the therapeutic amount of the therapeutic agent is effective to decrease angiographic diameter of the cerebral artery at risk of interruption such that percent change in angiographic diameter of at least one cerebral artery is less than 50% compared to baseline.

56. The use according to claim 30, wherein the therapeutic amount of the therapeutic agent is (i) effective to decrease occurrence of delayed cerebral ischemia (DCI) within 14 days of symptom onset of subarachnoid hemorrhage (SAH), (ii) is effective to decrease occurrence of delayed cerebral infarction on CT within 30 days of symptom onset of

subarachnoid hemorrhage (SAH) or (iii) is effective to decrease occurrence of delayed cerebral ischemia.

57. The use according to claim 56, wherein the occurrence of delayed cerebral ischemia is assessable as a decrease of at least 2 points on the modified glasgow coma score or an increase of at least 2 points on the abbreviated National Institutes of Health Stroke Scale lasting for at least 2 hours.

58. The use according to claim 30, wherein the therapeutic amount of the therapeutic agent is effective to reduce need for rescue therapy.