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 in a human subject that deposits blood in a subarachnoid space of the brain, wherein the brain injury is a result of an underlying condition selected from the group consisting of aneurysm, sudden traumatic head injury, subarachnoid hemorrhage or a combination thereof, includes interruption of at least one cerebral artery, and is mediated by

decreased cerebral perfusion, and the delayed complication is a delayed cortical ischemia (DCI) due to formation of microthromboemboli, cortical spreading ischemia, angiographic vasospasm or a combination thereof, the composition comprising:

(i) a microparticle suspension comprising a plurality of particles of a uniform distribution of microparticle size, a biodegradable polymer matrix comprising poly (D,L-lactide-co-glycolide, 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 a hyaluronic acid of average molecular weight of from about 5 kDa to about 20,000 kDa~~an agent that affects viscosity of the suspension~~;

~~the flowable particulate pharmaceutical composition being characterized by~~wherein:

(a) ~~dispersal of~~ the therapeutic agent is dispersed throughout each particle; and each microparticle is loaded with at least 40% by weight

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

(b) viscosity of the microparticle suspension at 20 °C, when formulated for administration intracisternally, is from about 100 centipoise (cP) to about 1,000 cP; and when formulated for administration (i) intraventricularly, or (ii) intrathecally, is from about 0.5 cP to about 50 cP; and

(c) the site-specific, sustained release, targeted delivery achieves avoidance of hypotension, hypoxia and other factors that adversely affect cerebral blood flow. ~~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 in a human subject that deposits blood in a subarachinoid space of the brain, wherein the brain injury is a result of an underlying condition selected from the group consisting of aneurysm, sudden traumatic head injury, subarachnoid hemorrhage or a combination thereof, includes interruption of at least one cerebral artery, and is mediated by decreased perfusion, and the delayed complication is a delayed cortical ischemia (DCI) due to formation of microthromboemboli, cortical spreading ischemia, angiographic vasospasm or a combination thereof, the composition 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, a biodegradable polymer matrix comprising poly (D,L-lactide-co-glycolide), 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 a hyaluronic acid of average molecular weight of from about 5 kDa to about 20,000 kDa;~~an agent that affects viscosity of the suspension; the pharmaceutical composition being characterized by:~~

~~(a)~~ ~~dispersal of~~ the therapeutic agent is dispersed throughout each microparticle; and each microparticle is loaded with at least 40% by weight of the therapeutic agent;

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

(b) viscosity of the microparticle suspension at 20 °C, when formulated for dministration intracisternally, is from about 100 centipoise (cP) to about 1,000 cP; and when formulated for administration (i) intraventricularly, or (ii) intrathecally, is from about 0.5 cP to about 50 cP; and

(c) the site-specific, sustained release, targeted delivery is effective to achieve avoidance of hypotension, hypoxia and other factors that adversely affect cerebral blood flow. ~~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 ($PLASMA\text{-}C_{av}$) is less than about 30-40 ng/mL;~~

~~(3) upon release, the concentration of the therapeutic agent in cerebrospinal fluid (CSF) ($CSF\text{-}C_{av}$) 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 subarachnoid 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 flowable particulate composition for use in treating a delayed complication of a brain injury in a human subject that deposits blood in a subarachnoid space of the brain, wherein the brain injury is a result of an underlying condition selected from the group consisting of aneurysm, sudden traumatic head injury, subarachnoid hemorrhage or a combination thereof, includes interruption of at least one cerebral artery, and is mediated by decreased cerebral perfusion, and the delayed complication is a delayed cortical ischemia (DCI) due to formation of microthromboemboli, cortical spreading ischemia, angiographic vasospasm or a combination thereof, the composition comprising:

(i) a microparticle suspension comprising a plurality of particles of a uniform distribution of microparticle size, a biodegradable polymer matrix comprising poly (D,L-lactide-co-glycolide, 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;~~ a hyaluronic acid of average molecular weight of from about 5 kDa to about 20,000 kDa;

wherein~~the flowable particulate pharmaceutical composition being characterized by~~:

(a) ~~dispersal of~~ the therapeutic agent is dispersed throughout each particle; and each microparticle is loaded with at least 40% by weight

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

(b) viscosity of the microparticle suspension at 20 °C,

when formulated for administration intracisternally, is from about 100 centipoise (cP) to about 1,000 cP; and

when formulated for administration (i) intraventricularly, or (ii) intrathecally, is from about 0.5 cP to about 50 cP; and

(c) the site-specific, sustained release, targeted delivery is effective to achieve avoidance of hypotension, hypoxia and other factors that adversely affect cerebral blood flow. ~~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~~2. The composition for use in treating a delayed complication of a brain injury in a human subject that deposits blood in a subarachnoid space of the brain 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.

43. The composition for use in treating a delayed complication of a brain injury in a human subject that deposits blood in a subarachnoid space of the brain 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~~4. The composition for use in treating a delayed complication of a brain injury in a human subject that deposits blood in a subarachnoid space of the brain according to claim ~~5~~1, 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~~5. The composition for use in treating a delayed complication of a brain injury in a human subject that deposits blood in a subarachnoid space of the brain according to claim ~~6~~4, 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~~6. The composition for use in treating a delayed complication of a brain injury in a human subject that deposits blood in a subarachnoid space of the brain according to claim ~~7~~5, wherein the dihydropyridine is nimodipine.

~~9~~7. The composition for use in treating a delayed complication of a brain injury in a human subject that deposits blood in a subarachnoid space of the brain 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~~8. The composition for use in treating a delayed complication of a brain injury in a human subject that deposits blood in a subarachnoid space of the brain according to claim ~~1~~6, wherein maximum tolerated dose of the nimodipine~~therapeutic agent when administered (i) intracisternally or (ii) intraventricularly or (iii) intrathecally~~ is from 40 mg to about 1,000 mg.

~~13~~9. The composition for use in treating a delayed complication of a brain injury in a human subject that deposits blood in a subarachnoid space of the brain according to claim 1, wherein the flowable particulate composition is ~~administered~~ formulated for administration intraventricularly in a lateral ventricle, a third ventricle, a fourth ventricle, or a combination thereof.

~~14~~10. The composition for use in treating a delayed complication of a brain injury in a human subject that deposits blood in a subarachnoid space of the brain 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~~11. The composition for use in treating a delayed complication of a brain injury in a human subject that deposits blood in a subarachnoid space of the brain according to claim ~~18~~1, ~~wherein the biodegradable polymer is a poly(lactide-co-glycolide) (PLGA) polymer,~~ wherein the lactide to glycolide ratio of the poly(lactide-co-glycolide) polymer is 85:15, 75:25, 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~~12. The composition for use in treating a delayed complication of a brain injury in a human subject that deposits blood in a subarachnoid space of the brain 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~~13. The composition for use in treating a delayed complication of a brain injury that deposits blood in a subarachnoid space of the brain according to claim 1, wherein the pharmaceutical carrier comprises aqueous channels.

~~24~~14. The composition for use in treating a delayed complication of a brain injury in a human subject that deposits blood in a subarachnoid space of the brain according to claim ~~1~~6, wherein

(a) concentration of the ~~therapeutic agent~~ nimodipine 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; or

(b) upon release, the concentration of the nimodipine in plasma (PLASMA-Cav) is less than about 30-40 ng/mL; or

(c) upon release, the concentration of the nimodipine in plasma (PLASMA-Cav) is less than a concentration in plasma known to cause a mean arterial pressure of less than 60 mm Hg for 15 minutes to develop after and to occur within 14 days of administration.

~~25~~15. The composition for use in treating a delayed complication of a brain injury in a human subject that deposits blood in a subarachnoid space of the brain according to claim ~~1~~6, wherein

(a) concentration of the ~~therapeutic agent~~ nimodipine in cerebrospinal fluid (CSF) (CSF-Cav) is from 5 ng/ml/day to 30 mg/ml/day for at least 14 days after administration; or

(b) upon release, the concentration of the nimodipine in cerebrospinal fluid (CSF) (CSF-Cav) is at least about 5 ng/mL to about 5000 ng/mL; or

(c) area under the plot of CSF concentration against time after administration (AUCCSF) at 14 days is from at least about 1,000 ng/ml day to at least about 15,000 ng/ml.

~~26~~16. The composition for use in treating a delayed complication of a brain injury in a human subject that deposits blood in a subarachnoid space of the brain 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~~17. The composition for use in treating a delayed complication of a brain injury in a human subject that deposits blood in a subarachnoid space of the brain 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~~18. The composition for use in treating a delayed complication of a brain injury in a human subject that deposits blood in a subarachnoid space of the brain according to claim 1, wherein the therapeutic amount of the therapeutic agent is effective to reduce need for rescue therapy.

~~30~~19. Use of a flowable particulate composition in the manufacture of a medicament for treating a delayed complication of a brain injury in a human subject that deposits blood in a subarachinoid space of the brain, wherein the brain injury is a result of an underlying condition selected from the group consisting of aneurysm, sudden traumatic head injury, subarachnoid hemorrhage or a combination thereof, includes interruption of at least one cerebral artery, and is mediated by decreased perfusion, and the delayed complication is a delayed cortical ischemia (DCI) due to formation of microthromboemboli, cortical spreading ischemia, angiographic vasospasm or a combination thereof, the composition 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, a biodegradable polymer matrix comprising poly (D,L-lactide-co-glycolide), 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~~ a hyaluronic acid of average molecular weight of from about 5 kDa to about 20,000 kDa;

wherein~~the pharmaceutical composition being characterized by~~:

~~(a) dispersal of~~ (a) the therapeutic agent is dispersed throughout each microparticle; and each microparticle is loaded with at least 40% by weight

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

~~———~~(b) viscosity of the microparticle suspension at 20 °C,

when formulated for administration intracisternally, is from about 100 centipoise (cP) to about 1,000 cP; and

when formulated for administration (i) intraventricularly, or (ii) intrathecally, is from about 0.5 cP to about 50 cP; and

(c) the site-specific, sustained release, targeted delivery is effective to achieve avoidance of hypotension, hypoxia and other factors that adversely affect cerebral blood flow. ~~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~~20. The use according to claim ~~30~~19, 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~~21. The use according to claim ~~30~~19, 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~~22. The use according to claim ~~30~~19, 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~~23. The use according to claim ~~35~~22, 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~~24. The use according to claim ~~36~~23, wherein the dihydropyridine is nimodipine.

~~38~~25. The use according to claim ~~30~~19, ~~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~~26. The use according to claim ~~30~~19, 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~~27. The use according to claim ~~30~~19, wherein maximum tolerated dose of the therapeutic agent when ~~administered~~ formulated for administration (i) intracisternally or (ii) intraventricularly or (iii) intrathecally is from 40 mg to about 1,000 mg.

~~43~~28. The use according to claim ~~30~~19, wherein the flowable particulate composition is ~~administered~~ formulated for administration intraventricularly in a lateral ventricle, a third ventricle, a fourth ventricle, or a combination thereof.

~~44~~29. The use according to claim ~~30~~19, 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.~~

4830. The use according to claim 4729, ~~wherein the biodegradable polymer is a poly(lactide-co-glycolide) (PLGA) polymer,~~ wherein the lactide to glycolide ratio of the poly(lactide-co-glycolide) polymer is 85:15, 75:25, 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.~~

5131. The use according to claim 3019, 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.

5232. The use according to claim 3019, wherein the pharmaceutical carrier comprises aqueous channels.

5333. The use according to claim 3024, wherein

(a) concentration of the ~~therapeutic agent~~nimodipine 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; or

(b) upon release, the concentration of the nimodipine in plasma (PLASMA-Cav) is less than about 30-40 ng/mL; or

(c) upon release, the concentration of the nimodipine in plasma (PLASMA-Cav) is less than a concentration in plasma known to cause a mean arterial pressure of less than 60 mm Hg for 15 minutes to develop after and to occur within 14 days of administration.

5434. The use according to claim 3024, wherein

(a) concentration of the ~~therapeutic agent~~nimodipine in cerebrospinal fluid (CSF) (CSF-Cav) is from 5 ng/ml/day to 30 mg/ml/day for at least 14 days after administration; or

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

(c) area under the plot of CSF concentration against time after administration (AUCCSF) at 14 days is from at least about 1,000 ng/ml day to at least about 15,000 ng/ml day.

~~55~~35. The use according to claim ~~30~~19, 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~~36. The use according to claim ~~30~~19, 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~~37. The use according to claim ~~30~~19, wherein the therapeutic amount of the therapeutic agent is effective to reduce need for rescue therapy.

38. The composition for use in treating a delayed complication of a brain injury in a human subject that deposits blood in a subarachnoid space of the brain according to claim 1, wherein the mean particle diameter is about 70 μm.

39. The composition for use in treating a delayed complication of a brain injury in a human subject that deposits blood in a subarachnoid space of the brain according to claim 6, wherein each microparticle is loaded with an initial drug load of at least 65% (wt/wt) nimodipine and 35% polymer.

40. The use according to claim 19, wherein the mean particle diameter is about 70 μm.

41. The use according to claim 24, wherein each microparticle is loaded with an initial drug load of at least 65% (wt/wt) nimodipine and 35% polymer.