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 an embodiment, 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;

(ii) and a pharmaceutical carrier comprising a hyaluronic acid of average molecular weight of from about 5 kDa to about 20,000 kDa;

wherein:

(a) the therapeutic agent is dispersed throughout each particle; and each microparticle is loaded with at least 40% by weightof 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.

In one 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 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 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;

(ii) and a pharmaceutical carrier comprising a hyaluronic acid of average molecular weight of from about 5 kDa to about 20,000 kDa; wherein

the therapeutic agent is dispersed throughout each microparticle; and each microparticle is loaded with at least 40% by weight 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) maximum tolerated dose of the therapeutic agent when formulated for administration (i) intracisternally or (ii) intraventricularly or (iii) intrathecally is from 200 mg to about 1,000 mg; and

(d) the site-specific, sustained release, targeted delivery is effective to achieve avoidance of hypotension, hypoxia and other factors that adversely affect cerebral blood flow.

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. 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 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 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;

(ii) and a pharmaceutical carrier comprising a hyaluronic acid of average molecular weight of from about 5 kDa to about 20,000 kDa;

wherein:

(a) the therapeutic agent is dispersed throughout each microparticle; and each microparticle is loaded with at least 40% by weight 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) maximum tolerated dose of the therapeutic agent when formulated for administration (i) intracisternally or (ii) intraventricularly or (iii) intrathecally is from 200 mg to about 1,000 mg; and

(d) the site-specific, sustained release, targeted delivery is effective to achieve avoidance of hypotension, hypoxia and other factors that adversely affect cerebral blood flow.

2. The use 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.

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

4. The use according to claim 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.

5. The use according to claim 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.

6. The use according to claim 5, wherein the dihydropyridine is nimodipine.

7. The use according to claim 1, wherein the hyaluronic acid has an average molecular weight of about 500 kDa.

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

9. The use according to claim 1, wherein the flowable particulate composition is formulated for administration intraventricularly in a lateral ventricle, a third ventricle, a fourth ventricle, or a combination thereof.

10. The use according to claim 1, 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.

11. The use according to claim 1, wherein the lactide to glycolide ratio of the poly(lactide-co-glycolide) polymer is 85:15, 75:25, 65:35 or 50:50.

12. The use according to claim 1, 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.

13. The use according to claim 1, wherein the pharmaceutical carrier comprises aqueous channels.

14. The use according to claim 6, wherein

(a) concentration of the 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.

15. The use according to claim 6, wherein

(a) concentration of the 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.

16. The use 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.

17. The use 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.

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

19. The use according to claim 1, wherein the mean particle diameter is about 70 μm.

20. The use according to claim 6, wherein each microparticle is loaded with an initial drug load of at least 65% (wt/wt) nimodipine and 35% polymer.