SUMMARY

[000107a] In an aspect, there is provided the use of a microparticulate pharmaceutical composition for the manufacture of a medicament for reducing severity or incidence of a delayed complication associated with a brain injury in a mammal including interruption of at least one cerebral artery that deposits blood in the subarachnoid space, wherein the delayed complication is selected from the group consisting of a microthromboembolism, a cortical spreading ischemia, or a delayed cerebral ischemia (DCI) caused by formation of microthromboemboli or a cortical spreading ischemia (CSI), the composition comprising:

(a) a microparticulate formulation of a therapeutic amount of a voltage-gated calcium channel blocker, which microparticulate formulation comprises a suspension of microparticles of uniform size distribution formed from a polymer matrix impregnated with the voltage-gated calcium channel blocker; and

(b) a pharmaceutically acceptable carrier;

wherein

(i) the pharmaceutical composition is flowable;

(ii) the pharmaceutical composition is formulated for parenteral injection into a subarachnoid space of the brain;

(iii) the pharmaceutical composition has a release profile such that one half of the voltage-gated channel blocker is released from the composition from 1 day to 30 days *in vivo* after delivery;

(iv) the therapeutic amount of the voltage gated calcium channel blocker is effective to maintain cerebrospinal fluid (CSF) concentration of the voltage gated calcium channel blocker in therapeutic range to treat the delayed complication, while plasma concentration is below therapeutic range, thereby circumventing unwanted side effects associated with systemic delivery; and

(v) the therapeutic amount that contacts and flows around the cerebral artery in the subarachnoid space is effective in reducing signs or symptoms of the delayed complication associated with the brain injury.

[000108] According to one ~~aspect~~embodiment, the ~~described invention~~present disclosure provides a method for treating a delayed complication associated with a brain injury in a mammal in need thereof, wherein the brain injury includes interruption of at least one cerebral artery, the method comprising: (a) providing a pharmaceutical composition comprising (i) a microparticulate formulation of a voltage-gated calcium channel blocker; and optionally (ii) a pharmaceutically acceptable carrier; and (b) administering a therapeutic amount of the pharmaceutical composition by a means for administration of the therapeutic amount of the pharmaceutical composition at a site of administration, wherein the therapeutic amount is effective in reducing signs or symptoms of the at least one delayed complication associated with the brain injury, and wherein the at least one delayed complication is at least one of delayed cerebral ischemia (DCI), a plurality of microthromboemboli a cortical spreading ischemia (CSI), and an angiographic vasospasm.

[000109] According to one embodiment of the method, in step (b), the means for administration is a surgical injection apparatus and the site of administration is in close proximity to at least one cerebral artery affected by the brain injury. According to another embodiment, in step (b), the means for administration is a surgical injection apparatus and the site of administration is a cerebral ventricle. According to another embodiment, the surgical injection apparatus is a needle, a cannula, a catheter, or a combination thereof. According to another embodiment, According to another embodiment, the microparticulate formulation is carried by cerebrospinal fluid to contact the cerebral artery affected by the brain injury. According to another embodiment, the therapeutic amount is effective to increase the internal diameter of the cerebral artery affected by the brain injury, as compared to a control. According to another embodiment, the brain injury is a result of an aneurysm, sudden traumatic head injury, subarachnoid hemorrhage (SAH), or a combination thereof. According to another embodiment, the brain injury is a result of subarachnoid hemorrhage. According to another embodiment, the at least one delayed complication associated with the brain injury further comprises at least one of an intracerebral hematoma, an intraventricular hemorrhage, a fever, a behavioral deficit, a neurological deficit, a cerebral infarction, and neuronal cell death. According to another embodiment, the behavioral deficit is improved such that the improved behavioral deficit comprises an increase in appetite. According to

embodiment, the pharmaceutical composition does not comprise the pharmaceutically acceptable carrier. According to another embodiment, the pharmaceutically acceptable carrier does not comprise hyaluronic acid. According to another embodiment, the pharmaceutically acceptable carrier comprises hyaluronic acid. According to another embodiment, the pharmaceutically acceptable carrier ranges between 0 % to 5 % hyaluronic acid. According to another embodiment, the pharmaceutically acceptable carrier comprises less than 2.3 % hyaluronic acid. According to another embodiment, the pharmaceutically acceptable carrier comprises less than 5 % hyaluronic acid.

[000110] According to another ~~aspect~~embodiment, the ~~described invention~~present disclosure provides a semisolid multiparticulate delivery system for treating a delayed complication associated with a brain injury in a mammal in need thereof, wherein the brain injury includes interruption of at least one cerebral artery, the system comprising: (a) a pharmaceutical composition comprising (i) a microparticulate formulation of a voltage-gated calcium channel blocker; and optionally (ii) a pharmaceutically acceptable carrier; and (b) a means for administering a therapeutic amount of the pharmaceutical composition at a site for administration , wherein the therapeutic amount is effective in reducing signs or symptoms of the at least one delayed complication associated with the brain injury.

[000111] According to one embodiment, the at least one delayed complication is at least one of delayed cerebral ischemia (DCI), a plurality of microthromboemboli a cortical spreading ischemia (CSI), and an angiographic vasospasm. The system according to claim 31, wherein the means for administration is a surgical injection apparatus and the site of administration is in close proximity to at least one cerebral artery affected by the brain injury. According to another embodiment, the means for administration is a surgical injection apparatus and the site of administration is a cerebral ventricle. According to another embodiment, the surgical injection apparatus is a needle, a cannula, a catheter, or a combination thereof. According to another embodiment, the microparticulate formulation is capable of being carried by cerebrospinal fluid to contact the cerebral artery affected by the brain injury. According to another embodiment,= therapeutic amount is effective to increase the internal diameter of the cerebral artery affected by the brain injury,as compared to a control. According to another embodiment, the brain injury is a result of an aneurysm, sudden traumatic head injury, subarachnoid hemorrhage (SAH), or a combination thereof.