evacuation of a hematoma, tumor or vascular malformation in the brain. This provides high concentrations of the drug at the site where activity is needed, and lower concentrations in the rest of the body, thus decreasing the risk of unwanted systemic side effects.

[000119] Site-specific delivery systems, for example, include use of microparticles (of about 1 μm to about 100 μm in diameter), thermoreversible gels (for example, PGA/PEG), and biodegradable polymers (for example, PLA, PLGA) that may be in the form of a film.

[000120] The delivery characteristics of the drug and the polymer degradation in vivo also can be modified. For example, polymer conjugation can be used to alter the circulation of the drug in the body and to achieve tissue targeting, reduce irritation and improve drug stability.

[000121] While all these possibilities exist, no one has applied such polymers to deliver therapeutic agents locally within the human brain to treat hemorrhagic brain conditions.

[000122] The described invention provides therapeutic compositions, methods for identifying therapeutic agents for treating hemorrhagic conditions of the brain, methods for treating hemorrhagic conditions of the brain, and an accurate and reproducible model system for chronic SDH and for ICH.

SUMMARY

[000122a] According to one aspect, there is provided the use of a pharmaceutical composition in the manufacture of a medicament for treating hematoma expansion or recurrent bleeding resulting from a hemorrhagic condition in brain, the pharmaceutical composition comprising: a pharmaceutically acceptable carrier comprising a biodegradable polymer comprising a matrix; wherein the polymer can be formed to produce a solid structure selected from the group consisting of: nonpareils, pellets, strings, sheets, crystals, an agglomerate, microparticles, and nanoparticles, wherein (a) the solid structure contains a therapeutic amount of at least one anti-fibrinolytic agent selected from the group consisting of aminocaproic acid (AMICAR), tranexamic acid, Factor VII, aprotinin, an antiplasmin, fibrin fragment D, a vitamin K, and 4-aminomethylbenzoic acid; (b) the solid structure is dispersed in the matrix, (c) the pharmaceutical composition is to be delivered by implantation to a fluid-filled space or cavity selected from a subarachnoid space, a subdural

cavity of a chronic subdural hematoma (SDH), or a cavity left after surgical evacuation of a hematoma, tumor or vascular malformation in the brain, (d) the anti-fibrinolytic agent is gradually released over an extended period of time that results in substantially constant blood levels of the anti-fibrinolytic agent over the extended time period into the fluid-filled space or cavity, and (e) site-specific activity provides high concentrations of the therapeutic agent at the site where therapeutic activity is needed and lower concentrations in the rest of the body, thus decreasing the risk of unwanted systemic side effects such as hypotension, cardiac arrhythmias, edema, rhabdomyolysis, thrombosis, cerebral infarction and myocardial infarction associated with systemic administration of the antifibrinolytic agent.

[000123] According to one embodiment, the disclosure provides a method for treating hematoma expansion or recurrent bleeding resulting from a hemorrhagic condition in brain, the method comprising: (a) providing a pharmaceutical composition comprising (i) a therapeutically effective amount of an anti-fibrinolytic agent and (ii) a pharmaceutically acceptable carrier; (b) administering the pharmaceutical composition into or at a distance proximal to the hematoma in brain; and (c) improving patient outcome. According to one embodiment, the hemorrhagic condition results from traumatic brain injury (TBI). According to another embodiment, the hemorrhagic condition is rebleeding following a surgical evacuation of a hematoma. According to another embodiment, the hemorrhagic condition is a chronic subdural hematoma. According

CLAIMS

What is claimed is:

1. Use of a pharmaceutical composition in the manufacture of a medicament for treating hematoma expansion or recurrent bleeding resulting from a hemorrhagic condition in brain, the pharmaceutical composition comprising:
a pharmaceutically acceptable carrier comprising a biodegradable polymer comprising a matrix; wherein the polymer can be formed to produce a solid structure selected from the group consisting of: nonpareils, pellets, strings, sheets, crystals, an agglomerate, microparticles, and nanoparticles,

wherein

(a) the solid structure contains a therapeutic amount of at least one anti-fibrinolytic agent selected from the group consisting of aminocaproic acid (AMICAR), tranexamic acid, Factor VII, aprotinin, an antiplasmin, fibrin fragment D, a vitamin K, and 4-aminomethylbenzoic acid;

(b) the solid structure is dispersed in the matrix,

(c) the pharmaceutical composition is to be delivered by implantation to a fluid-filled space or cavity selected from a subarachnoid space, a subdural cavity of a chronic subdural hematoma (SDH), or a cavity left after surgical evacuation of a hematoma, tumor or vascular malformation in the brain,

(d) the anti-fibrinolytic agent is gradually released over an extended period of time that results in substantially constant blood levels of the anti-fibrinolytic agent over the extended time period into the fluid-filled space or cavity, and

(e) site-specific activity provides high concentrations of the therapeutic agent at the site where therapeutic activity is needed and lower concentrations in the rest of the body, thus decreasing the risk of unwanted systemic side effects such as hypotension, cardiac arrhythmias, edema, rhabdomyolysis, thrombosis, cerebral infarction and myocardial infarction associated with systemic administration of the antifibrinolytic agent.

2. The use according to claim 1, wherein the hemorrhagic condition

a. results from traumatic brain injury (TBI); or

b. is rebleeding following a surgical evacuation of the hematoma; or

c. is a chronic subdural hematoma (SDH); or

d. is an intracerebral hematoma (ICH); or

e. is rebleeding following a craniotomy procedure.

3. The use according to claim 2, wherein the craniotomy procedure is performed

(a) for treating a brain cancer; or

(b) for treating a vascular malformation in brain; or

(c) for treating a brain aneurysm.

4. The use according to claim 1, wherein the composition releases the anti-fibrinolytic agent for at least 21 days post-administration.

5. The use according to claim 1, wherein the composition releases the anti-fibrinolytic agent for about 3 to 5 days post-administration.

6. The use according to claim 1, wherein the carrier comprises

(a) a biodegradable polymer; or

(b) a synthetic polymer; or

(c) a naturally occurring polymer; or

(d) a nonpolymeric material;

7. The use according to claim 6, wherein the synthetic polymer

(a) is selected from the group consisting of a polyester, a polyester polyethylene glycol polymer, a polyamino-derived biopolymer, a polyanhydride, a polyorthoester, a polyphosphazene, a sucrose acetate isobutyrate (SAIB), a photopolymerizable biopolymer, a polyglycolic acid (PGA), a polylactic acid (PLA); a poly (lactic-co-glycolide) (PLGA), a polycaprolactone; or

(b) a copolymer containing polyglycolic acid formed with trimethylene carbonate, polylactic acid (PLA), or polycaprolactone; or

(c) a poly d, L (lactic co-caprolactone) copolymer; or

(d) a thermoreversible gel.

8. The use according to claim 7, wherein

(a) the thermoreversible gel exhibits differing phases at room temperature and at physiologic temperature and pH; or

(b) at body temperature, the thermoreversible gel comprises a semisolid viscous gel; or

(c) the thermoreversible gel is a hydrogel.

9. The use according to claim 1, wherein the polymer is formed into an implant.

10. The use according to claim 1, wherein the polymer is malleable such that it can be delivered and manipulated in an implant site to adhere and conform to contours of walls, spaces or other voids.

11. The use according to claim 1, wherein the solid structure contains microparticles of about 1 μm to about 100 μm in diameter.

12. The use according to claim 1, wherein the carrier comprises a multilayered multiparticulate system.