METHODS AND COMPOSITIONS TO TREAT HEMORRHAGIC CONDITIONS OF THE BRAIN

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of priority of U.S. Provisional Application No. 61/306,758 filed February 22, 2010~~, which is incorporated by reference herein in its entirety~~.

FIELD OF THE INVENTION

[0002] The described invention relates to methods and compositions to treat hemorrhagic conditions of the brain.

BACKGROUND

[0003] The central nervous system is a bilateral and essentially symmetrical structure with seven main parts: the spinal cord, medulla oblongata, pons, cerebellum, midbrain, diencephalon, and the cerebral hemispheres. **Figure 1** shows a lateral view of the human brain from Stedman's Medical Dictionary, 27th Edition, plate 7 at A7 (2000).

[0004] The spinal cord, the most caudal part of the central nervous system, receives and processes sensory information from the skin, joints, and muscles of the limbs and trunk and controls movement of the limbs and the trunk. It is subdivided into cervical, thoracic, lumbar and sacral regions. The spinal cord continues rostrally as the brainstem, which consists of the medulla, pons, and midbrain. The brainstem receives sensory information from the skin and muscles of the head and provides the motor control for the muscles of the head. It also conveys information from the spinal cord to the brain and from the brain to the spinal cord, and regulates levels of arousal and awareness through the reticular formation. The brainstem contains several collections of cell bodies, the cranial nerve nuclei. Some of these receive information from the skin and muscles of the head; others control motor output to muscles of the face, neck and eyes.

transcription of a vast array of proteins involved in cell survival and proliferation, inflammatory response, and anti-apoptotic factors); (ii) the activation of MAPK pathways, including the JNK pathway, which is involved in cell differentiation, proliferation, and generally is pro-apoptotic; and (iii) the induction of death signaling.

[00064] Interleukin-6 (IL-6), a cytokine with both proinflammatory and antiinflammatory properties, is secreted by, among others, T cells and macrophages, to stimulate an immune response to trauma, and smooth muscle cells in the tunica media of many blood vessels. IL-6 is an important mediator of fever and the acute phase response. IL-6 signals through a cell-surface Type 1 cytokine receptor (consisting of IL-6Rα (ligand-biding chain) and gp130 (signal-transducing component). As IL-6 interacts with its receptor, it triggers the gp130 and IL-6R proteins to form a complex, thus activating the receptor. These complexes bring together the intracellular regions of gp130 to initiate a signal transduction cascade through certain transcription factors, Janus kinases (JAKs), and signal transducers and activators of transcription (STATs).

[00065] Interleukin 1β (IL-1β) is a cytokine that is produced by activated macrophages as a proprotein, which is processed proteolytically to its active form by caspase 1 (CASP/ICE). IL-1β is an important mediator of the inflammatory response, and is involved in several cellular activities, including, ~~but not limited to,~~ cell proliferation, differentiation and apoptosis.

[00066] Aquaporin 4 is an integral membrane protein that conducts water through the cell membrane. It is expressed constitutively in the basolateral cell membrane of principal collecting duct cells in the kidney. Aquaporin 4 also is expressed in astrocytes and is upregulated by direct insult to the central nervous system.

[00067] Vascular endothelial growth factor (VEGF) stimulates the growth of new blood vessels. All members of the VEGF family stimulate cellular responses by binding to tyrosine kinase receptors (VEGFRs) on the cell surface, causing them to dimerize and to become activated through transphosphorylation (although to different sites, times and extents).

usage of anticoagulant agents, antiplatelet agents, or chemotherapeutic agents; the presence of a cerebrospinal fluid shunt or of otherwise treated hydrocephalus; postoperative drainage of cerebrospinal fluid; and/or other causes for a decrease in size of the brain in relation to the fixed size of the cranium. The appearance of a chronic SDH on CT or magnetic resonance images (MRI) (layering hematoma compared to other types) and the method of treatment of a chronic SDH (burr hole, craniotomy, and twist drill trephination with or without irrigation) may influence the development of chronic SDH. Chronic SDH is a common disease in elderly persons and its incidence is highest (58 per 100,000 individuals) in persons older than 65 years of age. In approximately 60% to 80% of cases, a mild traumatic event is reported to have preceded the hemorrhage; however, a mild traumatic episode may sometimes go unrecognized. These putative risk factors for recurrence have been discussed in several reports in which controversial findings are not uncommon.

[00090] Surgery is the treatment of choice for chronic SDH. Several different modalities of surgery have been suggested: craniotomy, burr hole with or without irrigation and/or closed drainage system, and twist drill trephination directly into the hematoma at the site of its maximum thickness. However, concomitant diseases associated with chronic SDH can impair both its prognosis and surgical outcome. Further, the rate of recurrence of chronic SDH after surgery is between 3.7% and 30%. Recurrence increases the chance of death and morbidity from a chronic SDH.

[00091] The lack of an accurate and reproducible model system for chronic SDH has impaired efforts to research and develop new therapeutics and therapeutic methods for preventing the recurrence of chronic SDH. Prior attempts to develop animal models for chronic SDH have presented significant limitations, including, ~~but not limited to,~~ a lack of reproducibility.

5. Coagulation

[00092] Hemostasis is the cessation of blood loss from a damaged vessel. Platelets first

composition, that exerts a pharmacological, or any other beneficial activity.

[000139] The term "administer" as used herein means to give or to apply. The term "administering" as used herein includes *in vivo* administration, as well as administration directly to tissue *ex vivo*. Generally, compositions may be administered systemically either orally, buccally, parenterally, topically, by inhalation or insufflation (i.e., through the mouth or through the nose), or rectally in dosage unit formulations containing conventional nontoxic pharmaceutically acceptable carriers, adjuvants, and vehicles as desired, or may be locally administered by means such as, ~~but not limited to,~~ injection, implantation, grafting, topical application, or parenterally.

[000140] The term "agonist" as used herein refers to a chemical substance capable of activating a receptor to induce a full or partial pharmacological response. Receptors can be activated or inactivated by either endogenous or exogenous agonists and antagonists, resulting in stimulating or inhibiting a biological response. A physiological agonist is a substance that creates the same bodily responses, but does not bind to the same receptor. An endogenous agonist for a particular receptor is a compound naturally produced by the body which binds to and activates that receptor. A superagonist is a compound that is capable of producing a greater maximal response than the endogenous agonist for the target receptor, and thus an efficiency greater than 100%. This does not necessarily mean that it is more potent than the endogenous agonist, but is rather a comparison of the maximum possible response that can be produced inside a cell following receptor binding. Full agonists bind and activate a receptor, displaying full efficacy at that receptor. Partial agonists also bind and activate a given receptor, but have only partial efficacy at the receptor relative to a full agonist. An inverse agonist is an agent which binds to the same receptor binding-site as an agonist for that receptor and reverses constitutive activity of receptors. Inverse agonists exert the opposite pharmacological effect of a receptor agonist. An irreversible agonist is a type of agonist that binds permanently to a receptor in such a manner that the receptor is permanently activated. It is distinct from a mere agonist in that the association of an agonist to a receptor is reversible, whereas the binding of an

which are nontoxic and do not interact with other components.

[000165] The term "chemotherapeutic agent, in its most general sense, refers to a chemical substance or drug useful in the treatment or control of a disease. The term "cisterna" as used herein means a cavity or enclosed space serving as a reservoir.

[000166] The term "compatible" as used herein refers to the components of a composition are capable of being combined with each other in a manner such that there is no interaction that would substantially reduce the efficacy of the composition under ordinary use conditions.

[000167] The term "component" as used herein refers to a constituent part, element or ingredient.

[000168] The term "condition", as used herein, refers to a variety of health states and is meant to include disorders or diseases caused by any underlying mechanism or disorder, injury, and the promotion of healthy tissues and organs.

[000169] The term "contact" and all its grammatical forms as used herein refers to a state or condition of touching or of immediate or local proximity

[000170] The term "controlled release" is intended to refer to any drug-containing formulation in which the manner and profile of drug release from the formulation are regulated. This refers to immediate as well as non-immediate release formulations, with non-immediate release formulations including, ~~but not limited to,~~ sustained release and delayed release formulations.

[000171] The term "craniotomy" as used herein refers to a surgical removal of a section of a bone (e.g., bone flap) from the skull for the purpose of operating on the underlying tissues.

[000172] The term "cytokine" as used herein refers to small soluble protein substances secreted by cells which have a variety of effects on other cells. Cytokines mediate many

[000185] The term "hydrophilic" as used herein refers to a material or substance having an affinity for polar substances, such as water.

[000186] The terms "in the body", "void volume", "resection pocket", "excavation", "injection site", "deposition site" or "implant site" as used herein are meant to include all tissues of the body without limit, and may refer to spaces formed therein from injections, surgical incisions, tumor or tissue removal, tissue injuries, abscess formation, or any other similar cavity, space, or pocket formed thus by action of clinical assessment, treatment or physiologic response to disease or pathology as non-limiting examples thereof.

[000187] The term "injury," as used herein, refers to damage or harm to a structure or function of the body caused by an outside agent or force, which may be physical or chemical.

[000188] The term "interleukin" as used herein refers to a cytokine secreted by white blood cells as a means of communication with other white blood cells.

[000189] The term "isolated" is used herein to refer to material, such as, ~~but not limited to,~~ a nucleic acid, peptide, polypeptide, or protein, which is: (1) substantially or essentially free from components that normally accompany or interact with it as found in its naturally occurring environment. The terms "substantially free" or "essentially free" are used herein to refer to considerably or significantly free of, or more than about 95% free of, or more than about 99% free of. The isolated material optionally comprises material not found with the material in its natural environment; or (2) if the material is in its natural environment, the material has been synthetically (non-naturally) altered by deliberate human intervention to a composition and/or placed at a location in the cell (e.g., genome or subcellular organelle) not native to a material found in that environment. The alteration to yield the synthetic material may be performed on the material within, or removed, from its natural state.

[000190] The term "isomer" as used herein refers to one of two or more molecules having the same number and kind of atoms and hence the same molecular weight, but differing in

chemical structure. Isomers may differ in the connectivities of the atoms (structural isomers), or they may have the same atomic connectivities but differ only in the arrangement or configuration of the atoms in space (stereoisomers). Stereoisomers may include, ~~but are not limited to,~~ E/Z double bond isomers, enantiomers, and diastereomers. Structural moieties that, when appropriately substituted, can impart stereoisomerism include, ~~but are not limited to,~~ olefinic, imine or oxime double bonds; tetrahedral carbon, sulfur, nitrogen or phosporus atoms; and allenic groups. Enantiomers are non-superimposable mirror images. A mixture of equal parts of the optical forms of a compound is known as a racemic mixture or racemate. Diastereomers are stereoisomers that are not mirror images. The invention provides for each pure stereoisomer of any of the compounds described herein. Such stereoisomers may include enantiomers, diastereomers, or E or Z alkene, imine or oxime isomers. The invention also provides for stereoisomeric mixtures, including racemic mixtures, diastereomeric mixtures, or E/Z isomeric mixtures. Stereoisomers can be synthesized in pure form (Nógrádi, M.; Stereoselective Synthesis, (1987) VCH Editor Ebel, H. and Asymmetric Synthesis, Volumes 3 – 5, (1983) Academic Press, Editor Morrison, J.) or they can be resolved by a variety of methods such as crystallization and chromatographic techniques (Jaques, J.; Collet, A.; Wilen, S.; Enantiomer, Racemates, and Resolutions, 1981, John Wiley and Sons and Asymmetric Synthesis, Vol. 2, 1983, Academic Press, Editor Morrison, J). In addition the compounds of the described invention may be present as enantiomers, diasteriomers, isomers or two or more of the compounds may be present to form a racemic or diastereomeric mixture.

[000191] The term "labile" as used herein refers to subject to increased degradation.

[000192] The term "lipophilic" as used herein refers to preferring or possessing an affinity for a non-polar environment compared to a polar or aqueous environment.

[000193] The term "long-term" release, as used herein, means that the implant is constructed and arranged to deliver therapeutic levels of the active ingredient for at least 7 days, and potentially up to about 30 to about 60 days.

[000194] The term "minimizing progression" as used herein refers to reducing the amount, extent, size, or degree of development of a sequence or series of events.

[000195] The term "modulate" as used herein means to regulate, alter, adapt, or adjust to a certain measure or proportion. Such modulation may be any change, including an undetectable change.

[000196] The term "parenteral" as used herein refers to introduction into the body by way of an injection (i.e., administration by injection), including, for example, subcutaneously (i.e., an injection beneath the skin), intramuscularly (i.e., an injection into a muscle); intravenously (i.e., an injection into a vein), intrathecally (i.e., an injection into the space around the spinal cord or under the arachnoid membrane of the brain), intrasternal injection, or infusion techniques. A parenterally administered composition is delivered using a needle, e.g., a surgical needle. The term "surgical needle" as used herein, refers to any needle adapted for delivery of fluid (i.e., capable of flow) compositions into a selected anatomical structure. Injectable preparations, such as sterile injectable aqueous or oleaginous suspensions, may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents.

[000197] The term "particles" as used herein refers to an extremely small constituent, e.g., nanoparticles or microparticles) that may contain in whole or in part at least one therapeutic agent as described herein.

[000198] The term "improving patient outcome" as used herein refers to an absence of or diminutionf at least one side effect associated with the systemic administration of an anti-fibrinolytic agent. Examples of side effects include, ~~but are not limited to,~~ hypotension, cardiac arrythmias, edema, rhabdomyolysis,thrombosis, cerebral infarction or stroke and myocardial infarction or heart attack.

[000199] The term "pharmaceutical composition" is used herein to refer to a composition that is employed to prevent, reduce in intensity, cure or otherwise treat a target condition or

the results of which are judged to be desirable and beneficial. A therapeutic effect may include, directly or indirectly, the arrest, reduction, or elimination of a disease manifestation. A therapeutic effect may also include, directly or indirectly, the arrest reduction or elimination of the progression of a disease manifestation.

[000218] The term "therapeutically effective amount" or an "amount effective" of one or more of the active agents is an amount that is sufficient to provide the intended benefit of treatment. An effective amount of the active agents that can be employed ranges from generally 0.1 mg/kg body weight and about 50 mg/kg body weight. However, dosage levels are based on a variety of factors, including the type of injury, the age, weight, sex, medical condition of the patient, the severity of the condition, the route of administration, and the particular active agent employed. Thus the dosage regimen may vary widely, but can be determined routinely by a surgeon using standard methods.

[000219] The term "thickeners" as used herein refer to agents that make the composition of the described invention dense or viscous in consistency.

[000220] The term "transgenic" as used herein refers to an experimental strain of an animal that has been genetically engineered in the laboratory such that a specific exogenous gene is added to or deleted from the DNA of the animal. Common transgenic animal models include, ~~but are not limited to,~~ the mouse.

[000221] Traumatic brain injury (TBI) is caused by a head injury that can result in lasting damage to the brain and affects up to 10 million patients worldwide each year. The health effects of TBI can be debilitating, result in long term disability, and have significant financial burdens.

[000222] Traumatic brain injury is caused by an external mechanical force, such as a blow to the head, concussive forces, acceleration-deceleration forces, or a projectile. It may occur both when the skull fractures and the brain is directly penetrated (open head injury) and also when the skull remains intact but the brain still sustains damage (closed head injury).

to accomplishing one or more of the following: (a) reducing the severity of the disorder; (b) limiting development of symptoms characteristic of the disorder(s) being treated; (c) limiting worsening of symptoms characteristic of the disorder(s) being treated; (d) limiting recurrence of the disorder(s) in patients that have previously had the disorder(s); and (e) limiting recurrence of symptoms in patients that were previously symptomatic for the disorder(s).

[000228] The term "topical" refers to administration of a composition at, or immediately beneath, the point of application. The phrase "topically applying" describes application onto one or more surfaces(s) including epithelial surfaces. Although topical administration, in contrast to transdermal administration, generally provides a local rather than a systemic effect. The terms "topical administration" and "transdermal administration" as used herein, unless otherwise stated or implied, are used interchangeably.

[000229] The term "whole blood" as used herein refers to generally unprocessed or unmodified collected blood containing all of its components, including, ~~but are not limited to,~~ plasma, cellular components (e.g., red blood cells, white blood cells (including lymphocytes, monocytes, eosinophils, basophils, and neutrophils), and platelets), proteins (e.g., fibrinogen, albumin, immunoglobulins), hormones, coagulation factors, and fibrinolytic factors. The term "whole blood" is inclusive of any anticoagulant that may be combined with the blood upon collection.

[000230] The term "vascular malformation" as used herein refers to an abnormality in the development of blood vessels within the brain that result in an abnormal collection or pattern of blood vessels.

[000231] The term "xenogeneic" as used herein refers to being of different species.

I. Non-Human Animal Model for a Hemorrhagic Brain Condition

[000232] According to one aspect, the described invention provides a non-human animal model system for a hemorrhagic brain condition. According to some such embodiments, the

such embodiments, the volume of blood is about 8 ml. According to some such embodiments, the volume of blood is about 9 ml. According to some such embodiments, the initiating agent composition comprises at least one component of whole blood. Examples of components of whole blood include, ~~but are not limited to,~~ plasma, cellular components (e.g., red blood cells, white blood cells (including lymphocytes, monocytes, eosinophils, basophils, and neutrophils), and platelets), proteins (e.g., fibrinogen, albumin, immunoglobulins), hormones, coagulation factors, and fibrinolytic factors.

[000238] According to another embodiment, the initiating agent composition for inducing a hemorrhagic brain condition resulting in a hematoma in the non-human animal model comprises fluid obtained from a chronic SDH. According to some such embodiments, the fluid obtained from a chronic SDH is of a volume of about 1 µl to about 20 ml. According to some such embodiments, the fluid obtained from a chronic SDH is of a volume of about 100 µl to about 15 ml. According to some such embodiments, the fluid obtained from a chronic SDH is of a volume of about 500 µl to about 12.5 ml. According to some such embodiments, the fluid obtained from a chronic SDH is of a volume of about 1 ml to about 10 ml. According to some such embodiments, the volume of the fluid obtained from a chronic SDH is about 2 ml. According to some such embodiments, the volume of the fluid obtained from a chronic SDH is about 3 ml. According to some such embodiments, the volume of the fluid obtained from a chronic SDH is about 4 ml. According to some such embodiments, the volume of the fluid obtained from a chronic SDH is about 5 ml. According to some such embodiments, the volume of the fluid obtained from a chronic SDH is about 6 ml. According to some such embodiments, the volume of the fluid obtained from a chronic SDH is about 7 ml. According to some such embodiments, the volume of the fluid obtained from a chronic SDH is about 8 ml. According to some such embodiments, the volume of the fluid obtained from a chronic SDH is about 9 ml.

[000239] According to another embodiment, the initiating agent composition for inducing a hemorrhagic brain condition resulting in a hematoma in the non-human animal model comprises an antibody.

[000240] According to another embodiment, the initiating agent composition for inducing the hemorrhagic brain condition resulting in a hematoma in the non-human animal model is a monoclonal antibody. According to another embodiment, the initiating agent for inducing the hemorrhagic brain condition resulting in al hematoma in the non-human animal model is a polyclonal antibody.

[000241] According to another embodiment, the initiating agent composition for inducing the hemorrhagic brain condition resulting in the hematoma in the non-human animal model comprises a monospecific antibody directed against one blood coagulation factor, or against a specific epitope of the blood coagulation factor. According to another embodiment, the initiating agent composition for inducing the hemorrhagic brain condition resulting in the hematoma in the non-human animal model comprises an antibody that recognizes at least two blood coagulation factors. For example, an initiating agent composition may comprise antibodies against human plasmin or human plasminogen that cross-react with animal-derived plasmin or plasminogen. Alternately, an initiating agent composition may comprise antibodies against human thrombin that cross-react with animal-derived thrombin. Alternately, the initiating agent composition may comprise antibodies against vitamin K-dependent blood factors, such as, for example, factors of the prothrombin complex.

[000242] According to other embodiments, the initiating agent composition comprises antibodies against at least one procoagulant (including, ~~but not limited to,~~ blood coagulation factors II, V, VII, IX, X, XI, XII, prekallikrein, kininogen and tissue factor), antibodies against anti-coagulants (including, ~~but not limited to,~~ protein C, protein S, antithrombin III, heparin cofactor II), clot structure factors (including, ~~but not limited to,~~ fibrinogen and factor XIII), fibrinolysis factors (such as, ~~but not limited to,~~ plasminogen, t-PA, PAI-1 and α2-plasmin inhibitor) and phospholipids.

[000243] The suitability of the antibody preparation for this purpose can be judged on the basis of various tests. For example, an in vitro test may be carried out in which an antibody

antiserum from the immunized animal of (a), (c) optionally purifying an antibody fraction of the antiplasma or antiserum of (a), and (d) formulating a composition suitable for infusion into or proximal to the dura mater of a mammal.

[000249] According to another embodiment, the chronic SDH, or similar disorder, may be more precisely induced by preparing the initiating agent composition with antibodies specific for a certain blood factor that do not cross-react with other blood factors that may be contained in the material for immunization. Mammals in which immunization may be performed include, ~~but are not limited to,~~ sheep, goats, cows, pigs, rabbits, guinea pigs, horses, rats and mice. Mammals in which a chronic SDH may be induced include, ~~but are not limited to,~~ mice, rats, and other members of the order *Rodentia*.

[000250] According to another embodiment, the described invention provides methods for the use of antiplasma antibodies, for example in an infusion composition, for the treatment of a mammal as a model for a deficiency of blood factors by functionally inhibiting and/or eliminating several blood factors, so that the clotting time in vitro or ex vivo or the recurrence of chronic SDH in the mammal are changed. According to some embodiments, the antibodies against certain blood factors are absorbed in vivo by administering the blood factors to the animal.

[000251] According to some embodiments, a blood factor can be resubstituted and the changed clotting time and characteristics of the chronic SDH identified as being dependent upon the resubstituted blood factor.

[000252] According to another embodiment, the described invention further provides a method for determining characteristics of a recurrent chronic SDH, the method comprising the steps: (a) inducing a chronic SDH in a mammal; (b) collecting fluid obtained from the chronic SDH; (c) determining blood factor components of the fluid of step (b); and (d) determining the rate of expansion or decrease in size of the chronic SDH over time.

[000257] According to some embodiments, the mammal is a mouse. According to another embodiment, the mammal is a knockout mouse. According to another embodiment, the mammal is a rat. According to another embodiment, the mammal is a member of the Order *Rodentia*.

[000258] According to one embodiment, the hemorrhagic condition of the brain is a chronic SDH. According to one embodiment, the method further comprises the step of treating a mammal with an initiating agent composition for inducing a chronic SDH. According to another embodiment, the initiating agent composition for inducing a chronic SDH in the non-human animal model comprises whole blood. According to some embodiments, the whole blood is autologous. According to some embodiments, the whole blood is allogeneic. According to some embodiments, the whole blood is xenogeneic. According to some such embodiments, the blood is of a volume of about 1 μl to about 20 ml. According to some such embodiments, the blood is of a volume of about 100 μl to about 15 ml. According to some such embodiments, the blood is of a volume of about 500 μl to about 12.5 ml. According to some such embodiments, the blood is of a volume of about 1 ml to about 10 ml. According to some such embodiments, the volume of blood is about 2 ml. According to some such embodiments, the volume of blood is about 3 ml. According to some such embodiments, the volume of blood is about 4 ml. According to some such embodiments, the volume of blood is about 5 ml. According to some such embodiments, the volume of blood is about 6 ml. According to some such embodiments, the volume of blood is about 7 ml. According to some such embodiments, the volume of blood is about 8 ml. According to some such embodiments, the volume of blood is about 9 ml. According to some such embodiments, the initiating agent composition comprises at least one component of whole blood. Examples of components of whole blood include, ~~but are not limited to,~~ plasma, cellular components (e.g., red blood cells, white blood cells (including lymphocytes, monocytes, eosinophils, basophils, and neutrophils), and platelets), proteins (e.g., fibrinogen, albumin, immunoglobulins), hormones, coagulation factors, and fibrinolytic factors.

[000259] According to another embodiment, administering step (a) i.e., administering a substance to be evaluated to the mammal, comprises administering an initiating agent

chronic SDH is an antibody. According to another embodiment, the initiating agent composition for inducing a chronic SDH is a monoclonal antibody. According to another embodiment, the initiating agent composition for inducing a chronic SDH is a polyclonal antibody. According to some embodiments, the initiating agent composition is an anti-plasma antibody preparation.

[000263] According to some embodiments, the initiating agent composition comprises antibodies against at least one procoagulant (including, ~~but not limited to,~~ blood coagulation factors II, V, VII, IX, X, XI, XII, prekallikrein, kininogen and tissue factor), antibodies against anti-coagulants (including, ~~but not limited to,~~ protein C, protein S, antithrombin III, heparin cofactor II), clot structure factors (including, ~~but not limited to,~~ fibrinogen and factor XIII), fibrinolysis factors (such as, ~~but not limited to,~~ plasminogen, tissue-type plasminogen activator (t-PA), plasminogen activator inhibitor (PAI-1) and α2-plasmin inhibitor) and phospholipids.

[000264] According to some embodiments, a measurement of at least one parameter characteristic of the chronic SDH of a mammal with an induced chronic SDH is compared to a measurement of at least one parameter characteristic of the chronic SDH of a mammal which has been administered a compound or substance to be tested in order to determine the extent to which the substance to be tested can treat the induced chronic SDH. Examples of such a parameter include, ~~but are not limited to,~~ a bleeding behavior, a volume of blood in the chronic SDH, a size of the hematoma area, an expansion or a contraction of the hematoma area, expansion kinetics of the chronic SDH, and contraction kinetics of the chronic SDH. According to some embodiments, the compound or substance to be tested is administered prior to induction of the chronic SDH. According to some embodiments, the compound or substance to be tested is administered simultaneously with the initiating agent composition. According to some embodiments, the compound or substance to be tested is administered after induction of the chronic SDH.

[000265] According to another embodiment, the initiating agent composition is administered into a subcutaneous space of the dorsal surface of the mammal. According to

According to some such embodiments, the blood is of a volume of about 500 µl to about 12.5 ml. According to some such embodiments, the blood is of a volume of about 1 ml to about 10 ml. According to some such embodiments, the volume of blood is about 2 ml. According to some such embodiments, the volume of blood is about 3 ml. According to some such embodiments, the volume of blood is about 4 ml. According to some such embodiments, the volume of blood is about 5 ml. According to some such embodiments, the volume of blood is about 6 ml. According to some such embodiments, the volume of blood is about 7 ml. According to some such embodiments, the volume of blood is about 8 ml. According to some such embodiments, the volume of blood is about 9 ml. According to some such embodiments, the initiating agent composition comprises at least one component of whole blood. Examples of components of whole blood include, ~~but are not limited to,~~ plasma, cellular components (e.g., red blood cells, white blood cells (including lymphocytes, monocytes, eosinophils, basophils, and neutrophils), and platelets), proteins (e.g., fibrinogen, albumin, immunoglobulins), hormones, coagulation factors, and fibrinolytic factors.

[000271] According to another embodiment, the initiating agent composition for inducing an intracerebral hematoma comprises a collagenase. As used herein, one unit (U) of collagenase activity solubilizes 1 mg of collagen fibrils per hour at 37°C. According to some embodiments, the initiating agent composition comprises a collagenase of an amount of about 0.001 U/mg body weight to about 100 U/mg body weight. According to some embodiments, the initiating agent composition comprises a collagenase of an amount of about 0.01 U/mg body weight to about 100 U/mg body weight. According to some embodiments, the initiating agent composition comprises a collagenase of an amount of about 0.1 U/mg body weight to about 100 U/mg body weight. According to some embodiments, the initiating agent composition comprises a collagenase of an amount of about 1 U/mg body weight to about 100 U/mg body weight. According to some embodiments, the initiating agent composition comprises a collagenase of an amount of about 25 U/mg body weight to about 100 U/mg body weight. According to some embodiments, the initiating agent composition comprises a collagenase of an amount of about 50 U/mg body

weight to about 100 U/mg body weight. According to some embodiments, the initiating agent composition comprises a collagenase of an amount of about 75 U/mg body weight to about 100 U/mg body weight.

[000272] According to another embodiment, the initiating agent composition for inducing an intracerebral hematoma comprises at least one antibody. According to another embodiment, the initiating agent composition for inducing an intracerebral hematoma comprises at least one monoclonal antibody. According to another embodiment, the initiating agent composition for inducing an intracerebral hematoma comprises at least one polyclonal antibody. According to some embodiments, the initiating agent composition comprises an anti-plasma antibody preparation.

[000273] According to other embodiments, the initiating agent composition comprises antibodies against at least one procoagulant (including, ~~but not limited to,~~ blood coagulation factors II, V, VII, IX, X, XI, XII, prekallikrein, kininogen and tissue factor), antibodies against anti-coagulants (including, ~~but not limited to,~~ protein C, protein S, antithrombin III, heparin cofactor II), clot structure factors (including, ~~but not limited to,~~ fibrinogen and factor XIII), fibrinolysis factors (such as, ~~but not limited to,~~ plasminogen, t-PA, PAI-1 and α2-plasmin inhibitor) and phospholipids.

[000274] According to some embodiments, at least one parameter characteristic of the intracerebral hematoma of a mammal with an induced an intracerebral hematoma is compared to at least one parameter characteristic of the intracerebral hematoma of a mammal that has been administered a compound or substance to be tested in order to determine the extent to which the substance to be tested can treat the induced intracerebral hematoma. Examples of parameters characteristic of intracerebral hematoma include, ~~but is not limited to,~~ a bleeding behavior, a volume of blood in the intracerebral hematoma, a size of the hematoma area, an expansion or a contraction of the hematoma area, expansion kinetics of the intracerebral hematoma, and contraction kinetics of the intracerebral hematoma. According to some embodiments, the

activities, such as other related active agents. The applied dose may be adjusted based on the relative bioavailability and potency of the administered compound. Adjusting the dose to achieve maximal efficacy based on the methods described above and other methods as are well-known in the art is well within the capabilities of the ordinarily skilled artisan.

[000322] The formulations of therapeutic agent(s) may be administered in pharmaceutically acceptable solutions, which may routinely contain pharmaceutically acceptable concentrations of salt, buffering agents, preservatives, compatible carriers, adjuvants, and optionally other therapeutic ingredients.

[000323] According to some embodiments, the compositions of the described invention comprising a therapeutic agent(s) can further include one or more additional compatible active ingredients.

[000324] For use in therapy, an effective amount of the therapeutic agent(s) may be administered to a subject by any mode that delivers the therapeutic agent to the desired surface. Administering the pharmaceutical composition may be accomplished by any means known to the skilled artisan. Routes of administration include, ~~but are not limited to,~~ subdural, intracerebral, intrathecal, intra-arterial, parenteral (e.g. intravenous), or intramuscular. The therapeutics may be delivered to a subject during surgery to treat an underlying condition or side effect such as chronic SDH, ICH or during other procedures.

[000325] The therapeutic agent(s), when it is desirable to deliver it locally, may be formulated for parenteral administration by injection, e.g., by bolus injection or continuous infusion. Formulations for injection may be presented in unit dosage form, e.g., in ampoules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents. Pharmaceutical formulations for parenteral administration include aqueous solutions of the active compounds in water-soluble form. Additionally, suspensions of the active compounds may be prepared as appropriate oily

injection suspensions. Suitable lipophilic solvents or vehicles include fatty oils such as sesame oil, or synthetic fatty acid esters, such as ethyl oleate or triglycerides, or liposomes. Aqueous injection suspensions may contain substances which increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. Optionally, the suspension also may contain suitable stabilizers or agents which increase the solubility of the compounds to allow for the preparation of highly concentrated solutions. Alternatively, the active compounds may be in powder form for constitution with a suitable vehicle, e.g., sterile pyrogen-free water, before use.

[000326] The pharmaceutical compositions also may comprise suitable solid or gel phase carriers or excipients. Examples of such carriers or excipients include, ~~but are not limited to,~~ calcium carbonate, calcium phosphate, various sugars, starches, cellulose derivatives, gelatin, and polymers such as polyethylene glycols.

[000327] Suitable liquid or solid pharmaceutical preparation forms are, for example, microencapsulated, and if appropriate, with one or more excipients, encochleated, coated onto microscopic gold particles, contained in liposomes, pellets for implantation into tissue, or dried onto an object to be rubbed into tissue. Such pharmaceutical compositions also may be in the form of granules, beads, powders, tablets, coated tablets, (micro)capsules, suppositories, syrups, emulsions, suspensions, creams, drops or preparations with protracted release of active compounds, in whose preparation excipients and additives and/or auxiliaries such as disintegrants, binders, coating agents, swelling agents, lubricants, or solubilizers are customarily used as described above. The pharmaceutical compositions are suitable for use in a variety of drug delivery systems. For a brief review of methods for drug delivery, see Langer 1990 Science 249, 1527-1533~~, which is incorporated herein by reference~~.

[000328] The therapeutics may be administered in the form of a pharmaceutically acceptable salt. When used in medicine the salts should be pharmaceutically acceptable, but non-pharmaceutically acceptable salts may conveniently be used to prepare pharmaceutically

acceptable salts thereof. Such salts include, ~~but are not limited to,~~ those prepared from the following acids: hydrochloric, hydrobromic, sulphuric, nitric, phosphoric, maleic, acetic, salicylic, p-toluene sulphonic, tartaric, citric, methane sulphonic, formic, malonic, succinic, naphthalene-2-sulphonic, and benzene sulphonic. Also, such salts may be prepared as alkaline metal or alkaline earth salts, such as sodium, potassium or calcium salts of the carboxylic acid group. Pharmaceutically acceptable salts are well-known in the art. For example, P. H. Stahl, et al. describe pharmaceutically acceptable salts in detail in "Handbook of Pharmaceutical Salts: Properties, Selection, and Use" (Wiley VCH, Zurich, Switzerland: 2002). The salts may be prepared *in situ* during the final isolation and purification of the compounds described within the described invention or separately by reacting a free base function with a suitable organic acid. Representative acid addition salts include, ~~but are not limited to,~~ acetate, adipate, alginate, citrate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, camphorate, camphorsufonate, digluconate, glycerophosphate, hemisulfate, heptanoate, hexanoate, fumarate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethansulfonate(isethionate), lactate, maleate, methanesulfonate, nicotinate, 2-naphthalenesulfonate, oxalate, pamoate, pectinate, persulfate, 3-phenylpropionate, picrate, pivalate, propionate, succinate, tartrate, thiocyanate, phosphate, glutamate, bicarbonate, p-toluenesulfonate and undecanoate. Also, the basic nitrogen-containing groups may be quaternized with such agents as lower alkyl halides such as methyl, ethyl, propyl, and butyl chlorides, bromides and iodides; dialkyl sulfates like dimethyl, diethyl, dibutyl and diamyl sulfates; long chain halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides; arylalkyl halides like benzyl and phenethyl bromides and others. Water or oil-soluble or dispersible products are thereby obtained. Examples of acids which may be employed to form pharmaceutically acceptable acid addition salts include such inorganic acids as hydrochloric acid, hydrobromic acid, sulphuric acid and phosphoric acid and such organic acids as oxalic acid, maleic acid, succinic acid and citric acid. Basic addition salts may be prepared *in situ* during the final isolation and purification of compounds described within the invention by reacting a carboxylic acid-containing moiety with a suitable base such as the hydroxide, carbonate or bicarbonate of a pharmaceutically acceptable metal cation or with ammonia or an

organic primary, secondary or tertiary amine. Pharmaceutically acceptable salts include, ~~but are not limited to,~~ cations based on alkali metals or alkaline earth metals such as lithium, sodium, potassium, calcium, magnesium and aluminum salts and the like and nontoxic quaternary ammonia and amine cations including ammonium, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, triethylamine, diethylamine, ethylamine and the like. Other representative organic amines useful for the formation of base addition salts include ethylenediamine, ethanolamine, diethanolamine, piperidine, piperazine and the like. Pharmaceutically acceptable salts also may be obtained using standard procedures well known in the art, for example by reacting a sufficiently basic compound such as an amine with a suitable acid affording a physiologically acceptable anion. Alkali metal (for example, sodium, potassium or lithium) or alkaline earth metal (for example calcium or magnesium) salts of carboxylic acids may also be made.

[000329] The formulations may be presented conveniently in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing into association a therapeutic agent(s), or a pharmaceutically acceptable salt or solvate thereof ("active compound") with the carrier which constitutes one or more accessory agents. In general, the formulations are prepared by uniformly and intimately bringing into association the active agent with liquid carriers or finely divided solid carriers or both and then, if necessary, shaping the product into the desired formulation.

[000330] The pharmaceutical agent or a pharmaceutically acceptable ester, salt, solvate, functional derivative or prodrug thereof may be mixed with other active materials that do not impair the desired action, or with materials that supplement the desired action. Solutions or suspensions used for parenteral, intradermal, subcutaneous, subdural, intracerebral, intrathecal, or topical application may include, ~~but are not limited to,~~ for example, the following components: a sterile diluent such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl parabens; antioxidants such as ascorbic acid or sodium bisulfite;

chelating agents such as ethylenediaminetetraacetic acid; buffers such as acetates, citrates or phosphates and agents for the adjustment of tonicity such as sodium chloride or dextrose. The parental preparation may be enclosed in ampoules (or ampules), disposable syringes or multiple dose vials made of glass or plastic. Administered intravenously, particular carriers are physiological saline or phosphate buffered saline (PBS).

[000331] Pharmaceutical compositions for parenteral injection comprise pharmaceutically acceptable sterile aqueous or nonaqueous solutions, dispersions, suspensions or emulsions and sterile powders for reconstitution into sterile injectable solutions or dispersions. Examples of suitable aqueous and nonaqueous carriers, diluents, solvents or vehicles include water, ethanol, polyols (propylene glycol, polyethylene glycol, glycerol, and the like), suitable mixtures thereof, vegetable oils (such as olive oil) and injectable organic esters such as ethyl oleate. Proper fluidity may be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants.

[000332] These compositions also may contain adjuvants including preservative agents, wetting agents, emulsifying agents, and dispersing agents. Prevention of the action of microorganisms may be ensured by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, and the like. It also may be desirable to include isotonic agents, for example, sugars, sodium chloride and the like. Prolonged absorption of the injectable pharmaceutical form may be brought about by the use of agents delaying absorption, for example, aluminum monostearate and gelatin.

[000333] Suspensions, in addition to the active compounds, may contain suspending agents, as, for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar, tragacanth, and mixtures thereof.

[000334] Injectable depot forms may be made by forming microencapsulated matrices of the drug in biodegradable polymers such as, ~~but not limited to,~~ polyesters (polyglycolide,

polylactic acid and combinations thereof), polyester polyethylene glycol copolymers, polyamino-derived biopolymers, polyanhydrides, polyorthoesters, polyphosphazenes, sucrose acetate isobutyrate (SAIB), photopolymerizable biopolymers, naturally-occuring biopolymers, protein polymers, collagen, and polysaccharides. Depending upon the ratio of drug to polymer and the nature of the particular polymer employed, the rate of drug release may be controlled. Such long acting formulations may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt. Depot injectable formulations also are prepared by entrapping the drug in liposomes or microemulsions which are compatible with body tissues.

[000335] Polyglycolide (PGA) is a linear aliphatic polyester developed for use in sutures. Studies have reported PGA copolymers formed with trimethylene carbonate, polylactic acid (PLA), and polycaprolactone. Some of these copolymers may be formulated as microparticles for sustained drug release.

[000336] Polyester–polyethylene glycol compounds can be synthesized; these are soft and may be used for drug delivery.

[000337] Poly (amino)-derived biopolymers may include, ~~but are not limited to,~~ those containing lactic acid and lysine as the aliphatic diamine (see, for example, U.S. Patent 5,399,665), and tyrosine-derived polycarbonates and polyacrylates. Modifications of polycarbonates may alter the length of the alkyl chain of the ester (ethyl to octyl), while modifications of polyarylates may further include altering the length of the alkyl chain of the diacid (for example, succinic to sebasic), which allows for a large permutation of polymers and great flexibility in polymer properties.

[000338] Polyanhydrides are prepared by the dehydration of two diacid molecules by melt polymerization (see, for example, U.S. Patent 4,757,128). These polymers degrade by surface erosion (as compared to polyesters that degrade by bulk erosion). The release of the drug can be

controlled by the hydrophilicity of the monomers chosen.

[000339] Photopolymerizable biopolymers include, ~~but are not limited to,~~ lactic acid/polyethylene glycol/acrylate copolymers.

[000340] The term "hydrogel" refers to a substance resulting in a solid, semisolid, pseudoplastic or plastic structure containing a necessary aqueous component to produce a gelatinous or jelly-like mass. Hydrogels generally comprise a variety of polymers, including hydrophilic polymers, acrylic acid, acrylamide and 2-hydroxyethylmethacrylate (HEMA).

[000341] Naturally-occurring biopolymers include, ~~but are not limited to,~~ protein polymers, collagen, polysaccharides, and photopolymerizable compounds.

[000342] Protein polymers have been synthesized from self-assembling protein polymers such as, for example, silk fibroin, elastin, collagen, and combinations thereof.

[000343] Naturally-occurring polysaccharides include, ~~but are not limited to,~~ chitin and its derivatives, hyaluronic acid, dextran and cellulosics (which generally arenot biodegradable without modification), and sucrose acetate isobutyrate (SAIB).

[000344] Chitin is composed predominantly of 2-acetamido-2-deoxy-D-glucose groups and is found in yeasts, fungi and marine invertebrates (shrimp, crustaceous) where it is a principal component of the exoskeleton. Chitin is not water soluble and the deacetylated chitin, chitosan, only is soluble in acidic solutions (such as, for example, acetic acid). Studies have reported chitin derivatives that are water soluble, very high molecular weight (greater than 2 million daltons), viscoelastic, non-toxic, biocompatible and capable of crosslinking with peroxides, gluteraldehyde, glyoxal and other aldehydes and carbodiamides, to form gels.

[000345] Hyaluronic acid (HA), which is composed of alternating glucuronidic and glucosaminidic bonds and is found in mammalian vitreous humor, synovial fluid, unbiblical cords and rooster combs, from which it is isolated and purified, also can be produced by

fermentation processes.

[000346] The locally injectable formulations may be sterilized, for example, by filtration through a bacterial-retaining filter or by incorporating sterilizing agents in the form of sterile solid compositions that may be dissolved or dispersed in sterile water or other sterile injectable medium just prior to use. Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation also may be a sterile injectable solution, suspension or emulsion in a nontoxic, parenterally acceptable diluent or solvent such as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, U.S.P., phosphate-buffered saline (PBS), and isotonic sodium chloride solution. In addition, sterile, fixed oils conventionally are employed or as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid are used in the preparation of injectables.

[000347] Formulations for parenteral (including ~~but not limited to,~~ intracerebral, subdural, subcutaneous, intradermal, intramuscular, intravenous, intrathecal and intraarticular) administration include aqueous and non-aqueous sterile injection solutions that may contain anti-oxidants, buffers, bacteriostats and solutes, which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions, which may include suspending agents and thickening agents. The formulations may be presented in unit-dose or multi-dose containers, for example sealed ampules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example, saline, water-for-injection, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets of the kind previously described.

[000348] Another method of formulation of the compositions described herein involves

conjugating the compounds described herein to a polymer that enhances aqueous solubility. Examples of suitable polymers include ~~but are not limited to~~ polyethylene glycol, poly-(d-glutamic acid), poly-(l-glutamic acid), poly-(l-glutamic acid), poly-(d-aspartic acid), poly-(l-aspartic acid), poly-(l-aspartic acid) and copolymers thereof. Polyglutamic acids having molecular weights between about 5,000 to about 100,000, with molecular weights between about 20,000 and about 80,000 may be used and with molecular weights between about 30,000 and about 60,000 also may be used. The polymer may be conjugated via an ester linkage to one or more hydroxyls of a therapeutic agent using a protocol as essentially described by U.S. Pat. No. 5,977,163 ~~which is incorporated herein by reference~~.

[000349] Suitable buffering agents include: acetic acid and a salt (1-2% w/v); citric acid and a salt (1-3% w/v); boric acid and a salt (0.5-2.5% w/v); and phosphoric acid and a salt (0.8-2% w/v). Suitable preservatives include benzalkonium chloride (0.003-0.03% w/v); chlorobutanol (0.3-0.9% w/v); parabens (0.01-0.25% w/v) and thimerosal (0.004-0.02% w/v).

[000350] The pharmaceutical compositions within the described invention contain a therapeutically effective amount of at least one therapeutic agent and optionally other therapeutic agents included in a pharmaceutically-acceptable carrier. The components of the pharmaceutical compositions also are capable of being commingled in a manner such that there is no interaction which would substantially impair the desired pharmaceutical efficiency.

[000351] The therapeutic agent(s) also may be provided in particles, strings, or sheets.

[000352] According to one embodiment, the therapeutic agent(s) may be provided in particles. The particles may contain the therapeutic agent(s) in a core surrounded by a coating, or the therapeutic agent(s) may be dispersed throughout the particles, or the therapeutic agent(s) may be adsorbed into the particles. The particles may be of any order release kinetics, including zero order release, first order release, second order release, delayed release, sustained release, immediate release, etc., and any combination thereof. The particle may include, in addition to the therapeutic agent(s), any of those materials routinely used in the art of pharmacy and

medicine, including, ~~but not limited to,~~ erodible, nonerodible, biodegradable, or nonbiodegradable material or combinations thereof. The particles may be microcapsules, nanocapsules or in some instances larger that contain the therapeutic agent(s) in a solution or in a semi-solid state. The particles may be of virtually any shape. According to some embodiments the particle that may contain, in whole or in part, at least one therapeutic agent is a microparticle. According to some embodiments, the particle that may contain, in whole or in part, at least one therapeutic agent is a nanoparticle.

[000353] According to another embodiment, the therapeutic agent(s) may be provided in strings. The strings may contain the therapeutic agent(s) in a core surrounded by a coating, or the therapeutic agen(s) may be dispersed throughout the string, or the therapeutic agent(s) may be absorbed into the string. The string may be of any order release kinetics, including zero order release, first order release, second order release, delayed release, sustained release, immediate release, etc., and any combination thereof. The string may include, in addition to the therapeutic agent(s), any of those materials routinely used in the art of pharmacy and medicine, including, ~~but not limited to,~~ erodible, nonerodible, biodegradable, or nonbiodegradable material or combinations thereof.

[000354] According to another embodiment, the therapeutic agent(s) may be provided in at least one sheet. The sheet may contain the therapeutic agent(s) in a core surrounded by a coating, or the therapeutic agen(s) may be dispersed throughout the sheet, or the therapeutic agent(s) may be absorbed into the sheet. The sheet may be of any order release kinetics, including zero order release, first order release, second order release, delayed release, sustained release, immediate release, etc., and any combination thereof. The sheet may include, in addition to the therapeutic agent(s), any of those materials routinely used in the art of pharmacy and medicine, including, ~~but not limited to,~~ erodible, nonerodible, biodegradable, or nonbiodegradable material or combinations thereof.

[000355] Both non-biodegradable and biodegradable polymeric materials may be used in

the manufacture of particles for delivering the therapeutic agent(s). Such polymers may be natural or synthetic polymers. The polymer is selected based on the period of time over which release is desired. Bioadhesive polymers of particular interest include bioerodible hydrogels as described by Sawhney et al in Macromolecules (1993) 26, 581-587, ~~the teachings of which are incorporated herein~~. These include polyesters (polyglycolide, polylactic acid and combinations thereof), polyester polyethylene glycol copolymers, polyamino-derived biopolymers, polyanhydrides, polyorthoesters, polyphosphazenes, sucrose acetate isobutyrate (SAIB), and photopolymerizable biopolymers, naturally-occuring biopolymers, protein polymers, collagen, polysaccharides, photopolymerizable compounds, polyhyaluronic acids, casein, gelatin, glutin, polyanhydrides, polyacrylic acid, alginate, chitosan, poly(methyl methacrylates), poly(ethyl methacrylates), poly(butylmethacrylate), poly(isobutyl methacrylate), poly(hexylmethacrylate), poly(isodecyl methacrylate), poly(lauryl methacrylate), poly(phenyl methacrylate), poly(methyl acrylate), poly(isopropyl acrylate), poly(isobutyl acrylate), and poly(octadecyl acrylate). In some embodiments, the bioadhesive polymers of the described invention include hyaluronic acid. According to some such embodiments, the bioadhesive polymer include less than about 2.3 % of hyaluronic acid.

[000356] The therapeutic agent(s) may be contained in controlled release systems. In order to prolong the effect of a drug, it often is desirable to slow the absorption of the drug from subdural, intracerebral, subcutaneous, intrathecal, or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material with poor water solubility. The rate of absorption of the drug then depends upon its rate of dissolution which, in turn, may depend upon crystal size and crystalline form. For example, according to some embodiments, a SABER™ Delivery System comprising a high-viscosity base component, such as sucrose acetate isobutyrate (SAIB), is used to provide controlled release of the drug. (See U.S. Pat. No. 5,747,058 and U.S. Pat. No. 5,968,542, ~~incorporated herein by reference~~). When the high viscosity SAIB is formulated with drug, biocompatible excipients and other additives, the resulting formulation is liquid enough to inject easily with standard syringes and needles.

After injection of a SABER™ formulation, the excipients diffuse away, leaving a viscous depot.

[000357] As used herein, the term "controlled release" is intended to refer to any drug-containing formulation in which the manner and profile of drug release from the formulation are controlled. This refers to immediate as well as non-immediate release formulations, with non-immediate release formulations including, ~~but not limited to,~~ sustained release and delayed release formulations. The term "sustained release" (also referred to as "extended release") is used herein in its conventional sense to refer to a drug formulation that provides for gradual release of a drug over an extended period of time, and that preferably, although not necessarily, results in substantially constant blood levels of a drug over an extended time period. Alternatively, delayed absorption of a parenterally administered drug form is accomplished by dissolving or suspending the drug in an oil vehicle. The term "delayed release" is used herein in its conventional sense to refer to a drug formulation in which there is a time delay between administration of the formulation and the release of the drug there from. "Delayed release" may or may not involve gradual release of drug over an extended period of time, and thus may or may not be "sustained release."

[000358] Use of a long-term sustained release implant may be particularly suitable for treatment of chronic conditions. Long-term sustained release implants are well-known to those of ordinary skill in the art and include some of the release systems described above.

Delivery Systems

[000359] According to another aspect, the described invention provides a semisolid delivery system for therapeutic agents and a combination semisolid, multiparticulate, therapeutic delivery system for therapeutic agents. For example, the described invention provides a delivery system that utilizes a semisolid, biodegradable, biocompatible delivery system for injection, depositon or implantation within or upon the body so as to favorable local therapeutic effects. Alternatively, the described invention provides a biodegradable, biocompatible multiparticulate dispersed and suspended in a semisolid, biodegradable, biocompatible biodegradable delivery

produces a viscous liquid to a semisolid substance. The resulting substance is combined with GMO, whereby a product so formed swells and forms a highly viscous gel.

[000367] Without being limited by theory, for example, the therapeutic agent releases from the semisolid through diffusion, conceivably in a biphasic manner. A first phase involves, for example, a lipophilic drug contained within the lipophilic membrane diffuses therefrom into the aqueous channel. The second phase involves diffusion of the drug from the aqueous channel into the external environment. Being lipophilic, the drug may orient itself inside the GMO gel within its proposed lipid bi-layer structure. Thus, incorporating greater than approximately 7.5% of the drug by weight into GMO causes a loss of the integrity of the three-dimensional structure whereby the gel system no longer maintains the semisolid cubic phase, and reverts to the viscous lamellar phase liquid. According to some such embodiments, the therapeutic agent comprises tranexamic acid or an ester, salt, hydrate, solvate, functional derivative or prodrug thereof. According to some such embodiments, the therapeutic agent comprises aminocaproic acid or an ester, salt, hydrate, solvate, functional derivative or prodrug thereof. According to some such embodiments, the therapeutic agent comprises Factor VII or a recombinant Factor VII. According to some such embodiments, the therapeutic agent comprises aprotinin. According to another embodiment, about 1 to about 45% of therapeutic agent is incorporated by weight into a GMO gel at physiologic temperature without disruption of the normal three-dimensional structure. As a result, this system allows the ability of significantly increased flexibility with drug dosages. Because the delivery system is malleable, it may be delivered and manipulated in an implant site, for example, adjacent to or in a chronic SDH, so as to adhere and conform to contours of walls, spaces, or other voids in the body as well as completely fill all voids existing. The delivery system ensures drug distribution and uniform drug delivery throughout the implant site. Ease of delivery and manipulation of the delivery system within a space, for example, ~~but not limited to~~ the surface of the brain, is facilitated via a semisolid delivery apparatus. A semisolid delivery apparatus facilitates targeted and controlled delivery of the delivery system.

[000368] According to one embodiment, the multiparticulate component is comprised of

biocompatible, biodegradable, polymeric or non-polymeric systems utilized to produce solid structures including ~~but not limited to~~ nonpareils, pellets, strings, sheets, crystals, agglomerates, microparticles, or nanoparticles.

[000369] According to another embodiment, the multiparticulate component comprises of poly(lactic-co-glycolide) (PLGA's). PLGA's are biodegradable polymer materials used for controlled and extended therapeutic agent delivery within the body. Such delivery systems offer enhanced therapeutic efficacy and reduced overall toxicity as compared to frequent periodic, systemic dosing. Without being limited by theory, for example, PLGA's systems consisting of differing molar ratios of the monomeric subunits will facilitate greater flexibility in engineering precise release profiles for accommodating targeted therapeutic agent delivery through alterations in the rate of polymer degradation. According to one embodiment, the PLGA composition is sufficiently pure so as to be biocompatible and remains biocompatible upon biodegradation. According to one embodiment, the PLGA polymer is designed and configured into microparticles having a therapeutic agent or drug entrapped therein, whereby the therapeutic agent is subsequently released therefrom by a method to be described in greater detail below. According to some such embodiments, the therapeutic agent comprises aminocaproic acid or an ester, salt, hydrate, solvate, functional derivative or prodrug thereof. According to some such embodiments, the therapeutic agent comprises tranexamic acid or an ester, salt, hydrate, solvate, functional derivative or prodrug thereof. According to some such embodiments, the therapeutic agent comprises Factor VII or recombinant Factor VII. According to some such embodiments, the therapeutic agent comprises aprotinin.

[000370] According to another embodiment, the multiparticulate component is comprised of poly d,l(lactic-co-caprolactone). This provides a biodegradable polymer material used for controlled and extended therapeutic agent delivery within the body with a similar drug release mechanism to that of the PLGA polymers. According to one embodiment, the multiparticulate microparticles also are produced using biodegradable and/or biocompatible non-polymeric materials such as GMS.

[000371] According to another embodiment, the multiparticulate component is further modified by methods used to encapsulate or coat the multiparticulate components using polymers of the same composition with the same or different drug substances, different polymers with the same or different drug substances, or with multiple layering processes containing no drug, the same drug, a different drug, or multiple drug substances. This allows the production of a multi-layered (encapsulated) multiparticulate system with a wide range of drug release profiles for single or multiple drug agents simultaneously. According to another embodiment, coating materials which control the rate of physical drug diffusion from the multiparticulate may be utilized alone or in concert with the aforementioned preferred embodiments and envisioned embodiments.

[000372] According to another embodiment, the present invention provides a delivery system that utilizes PLGA. The PLGA polymer contains ester bonds, which are labile to hydrolysis. When H_2O penetrates the PLGA polymer, the ester bonds thereof are hydrolyzed, and monomers, being water soluble, are removed from the PLGA polymer, thus facilitating the physical release of the entrapped drug over time. According to some such embodiments, other classes of synthetic biodegradable, biocompatible polymers may be used for controlled and extended therapeutic agent delivery within the body, including polyanhydrides, poly(phosphates), polydioxanone, cellulosics and acrylics which are extended as non-limiting examples. According to some such embodiments, nonpolymeric materials may be utilized for controlled and extended therapeutic agent delivery within the body, including ~~but not limited to~~ sterols, sucrose fatty acid esters, fatty acids, and cholesteryl esters, which are extended as non-limiting examples.

[000373] According to another embodiment, the described invention provides a semisolid delivery system, which acts as a vehicle for local delivery of therapeutic agents, comprising a lipophilic, hydrophilic or amphophilic, solid or semisolid substance, heated above its melting point and thereafter followed by inclusion of a warm aqueous component so as to produce a gelatinous composition of variable viscosity based on water content. The therapeutic agent(s) is

effective amount is about 120 mg/kg body weight. According to some such embodiments, the therapeutically effective amount is about 130 mg/kg body weight. According to some such embodiments, the therapeutically effective amount is about 140 mg/kg body weight. According to some such embodiments, the therapeutically effective amount is about 150 mg/kg body weight. According to some such embodiments, the therapeutically effective amount is about 160 mg/kg body weight. According to some such embodiments, the therapeutically effective amount is about 170 mg/kg body weight. According to some such embodiments, the therapeutically effective amount is about 180 mg/kg body weight. According to some such embodiments, the therapeutically effective is about 190 mg/kg body weight. According to some such embodiments, the therapeutically effective amount is about 200 mg/kg body weight. According to some such embodiments, the therapeutically effective amount is about 250 mg/kg body weight. According to some such embodiments, the therapeutically effective amount is about 500 mg/kg body weight.

[000440] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although any methods and materials similar or equivalent to those described herein also can be used in the practice or testing of the described invention, the preferred methods and materials are now described. All publications mentioned herein ~~are incorporated herein by reference to~~ disclose and describe the methods and/or materials in connection with which the publications are cited.

[000441] Where a range of values is provided, it is understood that each intervening value, to the tenth of the unit of the lower limit unless the context clearly dictates otherwise, between the upper and lower limit of that range and any other stated or intervening value in that stated range is encompassed within the invention. The upper and lower limits of these smaller ranges which may independently be included in the smaller ranges is also encompassed within the invention, subject to any specifically excluded limit in the stated range. Where the stated range includes one or both of the limits, ranges excluding either both of those included limits are also

CLAIMS

What is claimed is:

1. Use of a flowable, site-specific sustained-release pharmaceutical composition in the manufacture of a medicament for treating hematoma expansion or recurrent bleeding resulting from a hemorrhagic condition in brain, wherein the pharmaceutical composition comprises:

(i) a therapeutic amount of at least one hemostatic agent; and

(ii) a pharmaceutically acceptable carrier, wherein the carrier comprises a plurality of microparticles, wherein the therapeutic agent is dispersed throughout each microparticle;

wherein the composition is formulated for administration locally in a cavity or space occupied by a hematoma or in a subdural space on the surface of the brain, and

characterized in that the therapeutic amount is effective to reduce hematoma expansion or recurrent bleeding, when compared to a nontreated control without entering systemic circulation in an amount to cause unwanted side effects.

2. The use according to claim 1, wherein the hemorrhagic condition results from traumatic brain injury (TBI), bleeding following a surgical evacuation of the hematoma, chronic subdural hematoma (SDH), intracerebral hematoma (ICH) or bleeding following a craniotomy procedure.

3. The use according to claim 2, wherein the intracerebral hematoma is a spontaneous intracerebral hematoma (ICH) or a traumatic intracerebral hematoma (ICH).

4. The use according to claim 2, wherein the craniotomy procedure is performed for treating a brain neoplasm a vascular malformation in brain or a brain aneurysm.

5. The use according to claim 1, wherein the hemostatic agent is an anti-fibrinolytic agent, Factor VII, or a recombinant Factor VII.

6. The use according to claim 1, wherein the pharmaceutically acceptable carrier is a controlled-release carrier or a sustained-release carrier.

7. The use according to claim 6, wherein the hemostatic agent is embedded in the sustained-release carrier or coated on the sustained-release carrier.

8. The use according to claim 6, wherein the sustained-release carrier is capable of releasing the hemostatic agent for at least 21 days post-administration.

9. The use according to claim 6, wherein the sustained-release carrier is capable of releasing the hemostatic agent for about 3 to 5 days post-administration.

10. The use according to claim 6, wherein the sustained-release carrier is a nanoparticle or a hydrogel.

11. The use according to claim 6, wherein the sustained-release carrier comprises a biodegradable polymer.

12. The use according to claim 11, wherein the biodegradable polymer is a synthetic polymer or a naturally occurring polymer.

13. The use according to claim 12, wherein the synthetic polymer 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, and a combination thereof.

14. The use according to claim 12, wherein the synthetic polymer is polyglycolic acid (PGA) or a copolymer of polyglycolic acid (PGA) formed with trimethylene carbonate, polylactic acid (PLA), or polycaprolactone.

15. The use according to claim 12, wherein the naturally occurring biopolymer is a protein polymer or comprises hyaluronic acid.

16. The use according to claim 15, wherein the naturally occurring polymer comprises less than 2.3 % of hyaluronic acid.

17. The use according to claim 1, wherein the distance proximal to the hematoma is from about 0.5 mm to about 10 mm.

18. The use according to claim 1, wherein the pharmaceutical composition exhibits a localized pharmacological effect in close proximity to the hematoma cavity or beyond the hematoma cavity.

19. A flowable site-specific, sustained-release pharmaceutical composition for treating hematoma expansion or recurrent bleeding resulting from a hemorrhagic condition in brain, the pharmaceutical composition comprising:

(a) a therapeutic amount of at least one hemostatic agent; and

(b) a pharmaceutically acceptable carrier, wherein the carrier comprises a plurality of microparticles, wherein the therapeutic agent is dispersed throughout each microparticle,

wherein the composition is formulated for administration locally in a cavity or space occupied by a hematoma or in a subdural space on the surface of the brain; and

characterized in that the therapeutic amount is effective to reduce hematoma expansion or recurrent bleeding, when compared to a nontreated control without entering systemic circulation in an amount to cause unwanted side effects.

20. The pharmaceutical composition according to claim 19, wherein the hemorrhagic brain condition is bleeding following traumatic brain injury, chronic subdural hematoma (SDH), intracerebral hematoma (ICH) or bleeding following a craniotomy procedure.

21. The pharmaceutical composition according to claim 20, wherein the intracerebral hematoma is a spontaneous intracerebral hematoma (ICH) or a traumatic intracerebral hematoma (ICH).

22. The pharmaceutical composition according to claim 20, wherein the craniotomy procedure is performed for treating a brain neoplasm.

23. The pharmaceutical composition according to claim 20, wherein the craniotomy procedure is performed for treating a vascular malformation in brain.

24. The pharmaceutical composition according to claim 20, wherein the craniotomy procedure is performed for treating a brain aneurysm.

25. The pharmaceutical composition according to claim 19, wherein the hemostatic agent is an anti-fibrinolytic agent, Factor VII or recombinant Factor VII.

26. The pharmaceutical composition according to claim 19, wherein the pharmaceutically acceptable carrier is a controlled-release carrier or a sustained-release carrier.

27. The pharmaceutical composition according to claim 26, wherein the hemostatic agent is embedded in the sustained-release carrier or coated on the sustained-release carrier.

28. The pharmaceutical composition according to claim 26, wherein the sustained-release carrier is capable of releasing the hemostatic agent for at least 21 days post-administration.

29. The pharmaceutical composition according to claim 26, wherein the sustained-release carrier is capable of releasing the hemostatic agent for about 3 to 5 days post-administration.

30. The pharmaceutical composition according to claim 26, wherein the sustained-release carrier comprises a nanoparticle, comprises a biodegradable polymer or is a hydrogel.

31. The pharmaceutical composition according to claim 30, wherein the biodegradable polymer is a synthetic polymer or a naturally occurring polymer.

32. The pharmaceutical composition according to claim 31, wherein the synthetic polymer 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, and a combination thereof.

33. The pharmaceutical composition according to claim 31, wherein the synthetic polymer is polyglycolic acid (PGA) or a copolymer of polyglycolic acid (PGA) formed with trimethylene carbonate, polylactic acid (PLA), or polycaprolactone.

34. The pharmaceutical composition according to claim 31, wherein the naturally occurring polymer is a protein polymer, a naturally occurring polysaccharide or a hyaluronic acid.

35. The pharmaceutical composition according to claim 34, wherein the protein polymer is synthesized from self-assembling protein polymers.

36. The pharmaceutical composition according to claim 34, wherein the naturally occurring polymer comprises less than 2.3 % of hyaluronic acid.

37. The use according to claim 5, wherein the anti-fibrinolytic agent is selected from the group consisting of ε-aminocaproic acid (AMICAR), tranexamic acid, aprotinin, aprotinin, 4-aminomethylbenzoic acid, fibrin fragment D, and a combination thereof.

38. The use according to claim 1, wherein the hemostatic agent is selected from the group consisting of antiplasmin, vitamin K, and a combination thereof.

39. The use according to claim 38, wherein the vitamin K is selected from the group consisting of vitamin K_1, vitamin K_2, and vitamin K_3.

40. The pharmaceutical composition according to claim 25, wherein the anti-fibrinolytic agent is selected from the group consisting of ε-aminocaproic acid (AMICAR), tranexamic acid, aprotinin, 4-aminomethylbenzoic acid, fibrin fragment D, and a combination thereof.

41. The pharmaceutical composition according to claim 19, wherein the hemostatic agent is antiplasmin, vitamin K, or a combination thereof.

42. The pharmaceutical composition according to claim 41, wherein the vitamin K is selected from the group consisting of vitamin K_1, vitamin K_2, and vitamin K_3.

CLAIMS

What is claimed is:

1. Use of a site-specific sustained-release pharmaceutical composition in the manufacture of a medicament for treating hematoma expansion or recurrent bleeding resulting from a hemorrhagic condition in brain, wherein the pharmaceutical composition comprises:

(i) a therapeutic amount of at least one anti-fibrinolytic agent; and

(ii) a pharmaceutically acceptable carrier, wherein the carrier comprises a plurality of microparticles,

wherein the composition is formulated for administration locally in a cavity or space occupied by a hematoma or in a subdural space on the surface of the brain,

the composition being characterized by:

(a) dispersal of the therapeutic amount of the anti-fibrinolytic agent throughout each microparticle, in a core of the microparticle surrounded by a coating, adsorbed into the particles, or a combination thereof;

(b) its deposition in or on a biodegradable implant at an implant site in a cavity or space within the brain occupied by a hematoma or in a subdural space on the surface of the brain;

(c) sustained release of the anti-fibrinolytic agent from the microparticles at the implant site to maintain a high concentration of the anti-fibrinolytic agent locally and lower concentrations in the rest of the body, thus decreasing risk of unwanted side effects;

(d) breakdown of the biodegradable carrier over time to effect release of the anti-fibrinolytic agent into the cerebrospinal fluid circulation to achieve tissue targeting of the therapeutic amount of the anti-fibrinolytic agent at a site of bleeding in or on the brain; and

(e) the therapeutic amount is effective to reduce hematoma expansion or recurrent bleeding, when compared to a nontreated control.

2. The use according to claim 1, wherein the hemorrhagic condition results from traumatic brain injury (TBI), bleeding following a surgical evacuation of the hematoma, chronic subdural hematoma (SDH), intracerebral hematoma (ICH) or bleeding following a craniotomy procedure.

3. The use according to claim 2, wherein the intracerebral hematoma is a spontaneous intracerebral hematoma (ICH) or a traumatic intracerebral hematoma.

4. The use according to claim 2, wherein the craniotomy procedure is performed for treating a brain neoplasm, a vascular malformation in brain or a brain aneurysm.

5. The use according to claim 1, wherein the pharmaceutically acceptable carrier is a controlled-release carrier or a sustained-release carrier.

6. The use according to claim 6, wherein the sustained-release carrier is capable of releasing the anti-fibrinolytic agent for at least 21 days post-administration.

7. The use according to claim 6, wherein the sustained-release carrier is capable of releasing the anti-fibrinolytic agent for about 3 to 5 days post-administration.

8. The use according to claim 6, wherein the sustained-release carrier is a nano-particle or a hydrogel.

9. The use according to claim 6, wherein the sustained-release carrier comprises a biodegradable polymer.

10. The use according to claim 11, wherein the biodegradable polymer is a synthetic polymer or a naturally occurring polymer.

11. The use according to claim 12, wherein the synthetic polymer 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, and a combination thereof.

12. The use according to claim 12, wherein the synthetic polymer is polyglycolic acid (PGA), or a copolymer of polyglycolic acid (PGA) formed with trimethylene carbonate, polylactic acid (PLA), or polycaprolactone.

13. The use according to claim 12, wherein the naturally occurring biopolymer is a protein polymer or comprises hyaluronic acid.

14. The use according to claim 15, wherein the naturally occurring biopolymer comprises less than 2.3% of hyaluronic acid.

15. The use according to claim 1, wherein the distance proximal to the hematoma is from about 0.5 mm to about 10 mm.

16. A site-specific, sustained-release pharmaceutical composition for treating hematoma expansion or recurrent bleeding resulting from a hemorrhagic condition in brain, the pharmaceutical composition comprising:

(a) a therapeutic amount of at least one anti-fibrinolytic agent; and

(b) a pharmaceutically acceptable carrier, wherein the carrier comprises a plurality of microparticles,

wherein the composition is formulated for administration locally in a cavity or space occupied by a hematoma or in a subdural space on the surface of the brain;

the composition being characterized by:

(i) dispersal of the therapeutic amount of the anti-fibrinolytic agent throughout each microparticle, in a core of the microparticle surrounded by a coating, adsorbed into the particles, or a combination thereof;

(ii) its deposition in or on a biodegradable implant at an implant site in a cavity or space within the brain occupied by a hematoma or in a subdural space on the surface of the brain;

(iii) sustained release of the anti-fibrinolytic agent from the microparticles at the implant site to maintain a high concentration of the anti-fibrinolytic agent locally and lower concentrations in the rest of the body, thus decreasing risk of unwanted side effects;

(iv) breakdown of the biodegradable carrier over time to effect release of the anti-fibrinolytic agent into the cerebrospinal fluid circulation to achieve tissue targeting of the therapeutic amount of the anti-fibrinolytic agent at a site of bleeding in or on the brain; and

(v) the therapeutic amount is effective to reduce hematoma expansion or recurrent bleeding, when compared to a nontreated control.

17. The pharmaceutical composition according to claim 19, wherein the hemorrhagic brain condition is bleeding following traumatic brain injury, chronic subdural hematoma (SDH), intracerebral hematoma (ICH) or bleeding following a craniotomy procedure.

18. The pharmaceutical composition according to claim 20, wherein the intracerebral hematoma is a spontaneous intracerebral hematoma (ICH) or a traumatic intracerebral hematoma (ICH).

19. The pharmaceutical composition according to claim 20, wherein the craniotomy procedure is performed for treating a brain neospasm.

20. The pharmaceutical composition according to claim 20, wherein the wherein the craniotomy procedure is performed for treating a vascular malformation in brain.

21. The pharmaceutical composition according to claim 20, wherein the craniotomy procedure is performed for treating a brain aneurysm.

22. The pharmaceutical composition according to claim 19, wherein the pharmaceutically acceptable carrier is a controlled-release carrier or a sustained-release carrier.

23. The pharmaceutical composition according to claim 26, wherein the sustained-release carrier is capable of releasing the anti-fibrinolytic agent for at least 21 days post-administration.

24. The pharmaceutical composition according to claim 26, wherein the sustained-release carrier is capable of releasing the anti-fibrinolytic agent for about 3 to 5 days post-administration.

25. The pharmaceutical composition according to claim 26, wherein the sustained-release carrier comprises a nanoparticle, comprises a biodegradable polymer or is a hydrogel.

26. The pharmaceutical composition according to claim 30, wherein the biodegradable polymer is a synthetic polymer or a naturally occurring polymer.

27. The pharmaceutical composition according to claim 31, wherein the synthetic polymer 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, and a combination thereof.

28. The pharmaceutical composition according to claim 31, wherein the synthetic polymer is polyglycolic acid (PGA) or a copolymer of polyglycolic acid (PGA) formed with trimethylene carbonate, polylactic acid (PLA), or polycaprolactone.

29. The pharmaceutical composition according to claim 31, wherein the naturally occurring polymer is a protein polymer, a naturally occurring polysaccharide or a hyaluronic acid.

30. The pharmaceutical composition according to claim 34, wherein the wherein the protein polymer is synthesized form self-assembling protein polymers.

31. The pharmaceutical composition according to claim 34, wherein the naturally occurring polymer comprises less than 2.3% of hyaluronic acid.

32. The use according to claim 1, wherein the anti-fibrinolytic agent is selected from the group consisting of ε-aminocaproic acid (AMICAR), tanexamic acid, aprotinin, 4-amionomethylbenzoic acid, fibrin fragment D, and a combination thereof.

33. The use according to claim 1, wherein the anti-fibrinolytic agent is selected from the group consisting of antiplasmin, vitamin K, and a combination thereof.

34. The use according to claim 38, wherein the vitamin K is selected from the group consisting of vitamin K_1, vitamin K_2 and vitamin K_3.

35. The pharmaceutical composition according to claim 19, wherein the anti-fibrinolytic agent is selected from the group consisting of ε-aminocaproic acid (AMICAR), tanexamic acid, aprotinin, 4-amionomethylbenzoic acid, fibrin fragment D, and a combination thereof.

36. The pharmaceutical composition according to claim 19, wherein the anti-fibrinolytic agent is antiplasmin, vitamin K, or a combination thereof.

37. The pharmaceutical composition according to claim 41, wherein the vitamin K is selected from the group consisting of vitamin K_1, vitamin K_2, and vitamin K_3.