at low flow rates such as those generated within a syringe. Therefore, improved systems, devices, and methods are desirable.

SUMMARY

[006] The instant disclosure provides a novel class of hemostats, and methods of manufacturing thereof, for use in methods for establishing local hemostasis. Disclosed ~~embodiments~~examples provide an essentially thrombin-free fibrin composition, and methods of manufacture and use thereof, said methods comprising heterogeneous catalysis.

[007] Use of heterogeneous instead of homogeneous catalysis enables the use of a single syringe or container, and eliminates the complications associated with managing parameters such as viscosity and back pressure. Through the use of disclosed ~~embodiments~~examples, mixing of fibrinogen and thrombin is no longer required, thus simplifying the administration of a fibrin glue such as TISSEEL® to a single syringe. Further, viscosity is no longer problematic, as fibrinogen can be directly diluted to obtain 50 mg/ml formulations. Because the solution viscosity is low, fibrin produced with heterogeneous catalysis can be easily sprayed and delivered, for example through a catheter. For example, ~~in embodiments,~~ the viscosity of the produced fibrin composition can be, for example, 90cps, 80cps, 70cps, 60cps, 50cps, 40cps, 30cps, 20cps, 10cps, 5cps, 1cps, or the like.

[007a] In one aspect, the present disclosure provides a method of preparing a liquid fibrin composition, said method comprising passing a fibrinogen solution over a dry solid phase substrate comprising thrombin, wherein the liquid fibrin composition has a viscosity of 50 cps or less.

[007b] In another aspect, the present disclosure provides a liquid hemostatic material comprising fibrin, wherein said composition comprises less than 2 IU thrombin per mL and has a viscosity of 50, 40, 30, 20, 10, 5 or 1 cps.

[007c] In another aspect, the present disclosure provides a liquid hemostatic material comprising fibrin, made by a process comprising heterogeneous catalysis comprising passing a liquid fibrinogen solution over a dry solid phase substrate, wherein the liquid hemostatic material has a viscosity of 50 cps or less.

[007d] In another aspect, the present disclosure provides a kit for use in establishing local hemostasis, comprising;

a fibrinogen composition;

a dry solid substrate comprising thrombin adsorbed to the surface of the substrate; and at least one administration device, buffer solution, syringe, tube, catheter, forceps, scissors, sterilizing pad or lotion.

[008] In ~~embodiments~~examples, adsorption of thrombin can be performed on the inner wall of ancillaries, for example devices and equipment such as tubes, pipes, vessels, and the like, that can be connected to a syringe, for example the luer of a syringe, containing the fibrinogen solution.

[009] In ~~embodiments~~examples, the need for calcium chloride in forming a fibrin clot is eliminated.

[010] ~~Embodiments~~Examples disclosed herein comprise methods of adsorbing thrombin on to a surface.

[011] ~~Embodiments~~Examples disclosed herein comprise methods of producing an essentially thrombin-free fibrin using heterogeneous catalysis.

[012] ~~Embodiments~~Examples disclosed herein comprise compositions comprising an essentially thrombin-free fibrin.

[013] ~~Embodiments~~Examples disclosed herein comprise compositions comprising an essentially thrombin-free fibrin made by a process comprising heterogeneous catalysis.

[014] ~~Embodiments~~Examples disclosed herein comprise thrombin formulations that are stable at room-temperature (RT). For example, in current formulations, thrombin in solution is not stable at RT because it is autocatalytic, degrading itself in a concentration-dependent manner. Hence, TISSEEL® must be used after thawing at RT within 48 to 72 hours, ARTISS® within 1-2 weeks and VISTASEAL™ within 24 hours. The surface-adsorbed thrombin of the current disclosure can be stored in a dry state which increases its stability.

[015] Disclosed ~~embodiments~~examples comprise methods of use comprising an essentially thrombin-free fibrin. For example, disclosed methods and devices can be used to reduce or stop bleeding, for example bleeding associated with surgical procedures, injuries, wounds, and the like. ~~Embodiments~~Examples can comprise treatment of various classes of bleeding, including:

a. **Class I** involves up to 15% of blood volume. There is typically no change in vital signs and fluid resuscitation is not usually necessary.
b. **Class II** involves 15-30% of total blood volume. A patient is often tachycardic (rapid heart beat) with a reduction in the difference between the systolic and diastolic blood pressures.
c. **Class III** involves loss of 30-40% of circulating blood volume. The patient's blood pressure drops, the heart rate increases, peripheral hypo-perfusion (shock) with diminished capillary refill occurs, and the mental status worsens.
d. **Class IV** involves loss of >40% of circulating blood volume. The limit of the body's compensation ability is reached and aggressive resuscitation is required to prevent death.

BRIEF DESCRIPTION OF THE DRAWINGS

[016] FIG. 1 shows neutralization of thrombin adsorbed on glass beads and in solution (control). The left hand graph shows that heparin with or without anti-thrombin (AT) does not neutralize the thrombin adsorbed on the glass beads. The right hand graph shows that the thrombin in solution is neutralized by the complex AT heparin.