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 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 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, 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 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 examples, the need for calcium chloride in forming a fibrin clot is eliminated.

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

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

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

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

[014] 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 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. 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.