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(54) **SPRAY-DRIED BLOOD PRODUCTS AND METHODS OF MAKING SAME**

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(52) **U.S. Cl.**

CPC ***A61K 9/1688*** (2013.01); ***A61F 13/00063*** (2013.01); ***A61K 9/0026*** (2013.01); ***A61K 35/16*** (2013.01); ***A61K 35/19*** (2013.01); ***A61L 15/40*** (2013.01); ***A61L 26/0047*** (2013.01); ***A61L 26/0057*** (2013.01); ***A61L 26/0076*** (2013.01); *A61F 2013/00306* (2013.01); *A61F 2013/00472* (2013.01); *A61F 2013/00927* (2013.01)

(58) **Field of Classification Search**

CPC A61K 35/19; A61K 35/16; A61K 9/1688; A61F 13/0063; A61F 2013/0306; A61F 2013/0472; A61F 2013/0927

See application file for complete search history.

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(57) **ABSTRACT**

The present invention is directed to a method of preparing dehydrated blood products, comprising the steps of: (a) providing a hydrated blood product; (b) spray-drying the hydrated blood product to produce a dehydrated blood product, as well as dehydrated blood products made by the method. The present invention is directed to a method of treating a patient suffering from a blood-related disorder, comprising the steps of: (a) rehydrating a therapeutic amount of the dehydrated blood products to produce a rehydrated therapeutic composition; and (b) administering the rehydrated therapeutic composition to the patient. The present invention is directed to a bandage or surgical aid comprising the dehydrated blood products described above.

6 Claims, 5 Drawing Sheets

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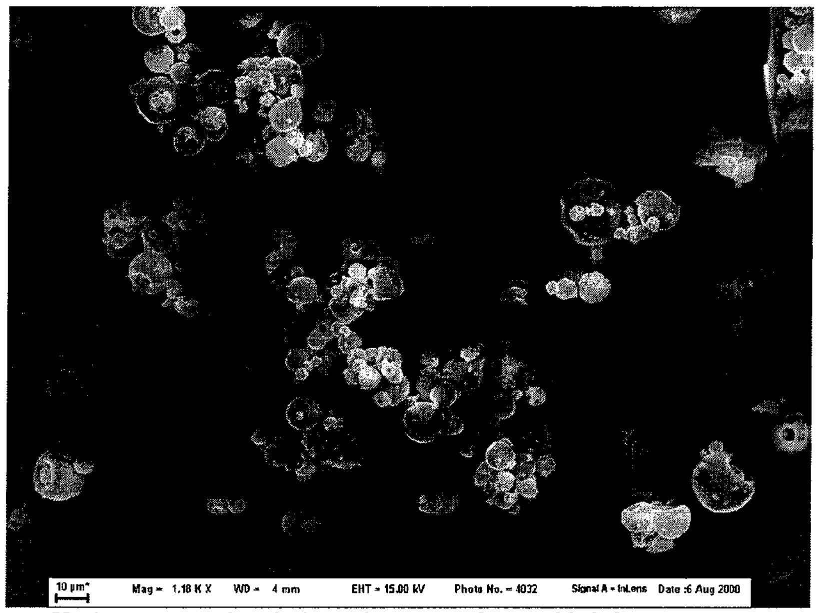
Microspheres of Spray-Dried Plasma



20 microns **scanning electron microscopy of spray-dried plasma**

Figure 1

Spray-Drying Minimally Affects Coagulation Protein Profile

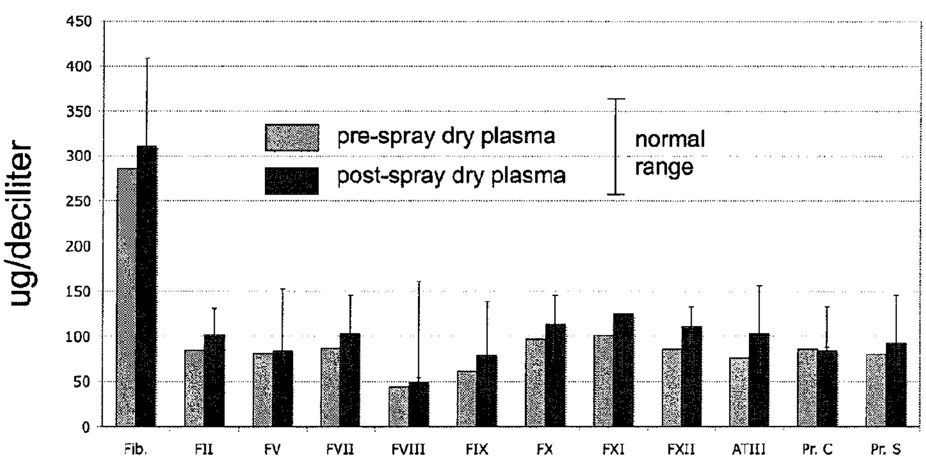


Figure 2

Native Coagulation Pathway Turnover with Spray-Dried Plasma

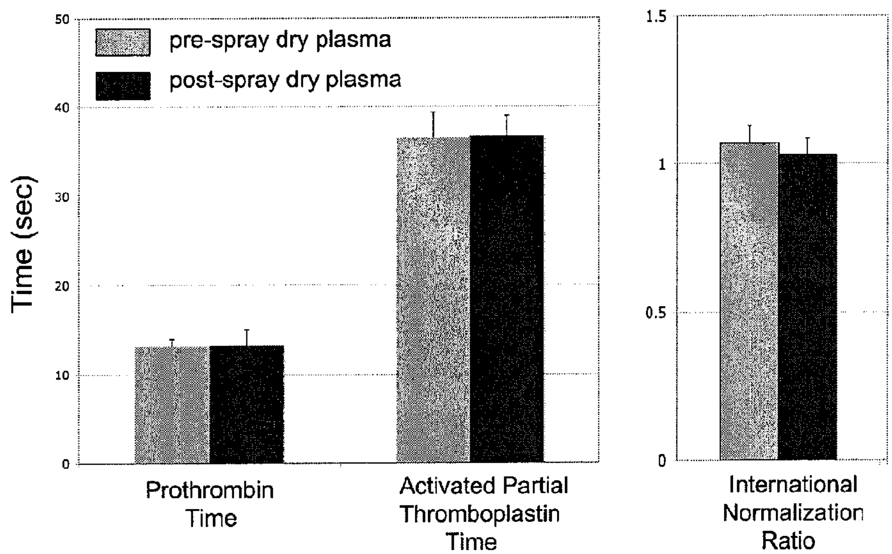
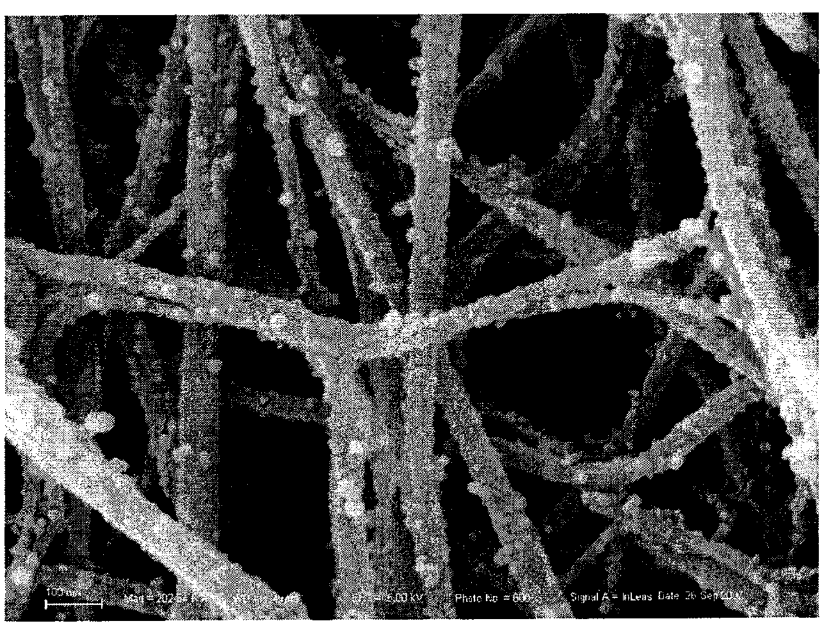


Figure 3

Fibrin Ultrastructure from Spray-Dried Plasma



—— 100 nanometers **Scanning Electro-microgram of Fibrin Clot**

Figure 4

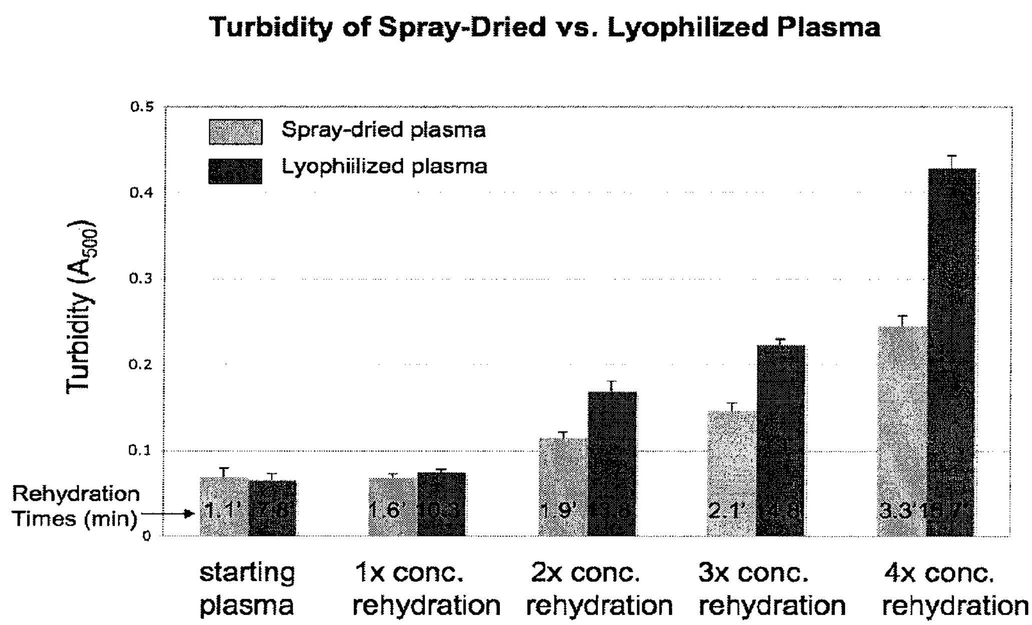

Turbidity of Spray-Dried vs. Lyophilized Plasma
Spray-dried plasma
Lyophilized plasma
Turbidity (A_{500})
0.5
0.4
0.3
0.2
0.1
0
Rehydration Times (min)
1.1'
1.6'
1.9'
2.1'
3.3'
starting plasma
1x conc. rehydration
2x conc. rehydration
3x conc. rehydration
4x conc. rehydration

Figure 5

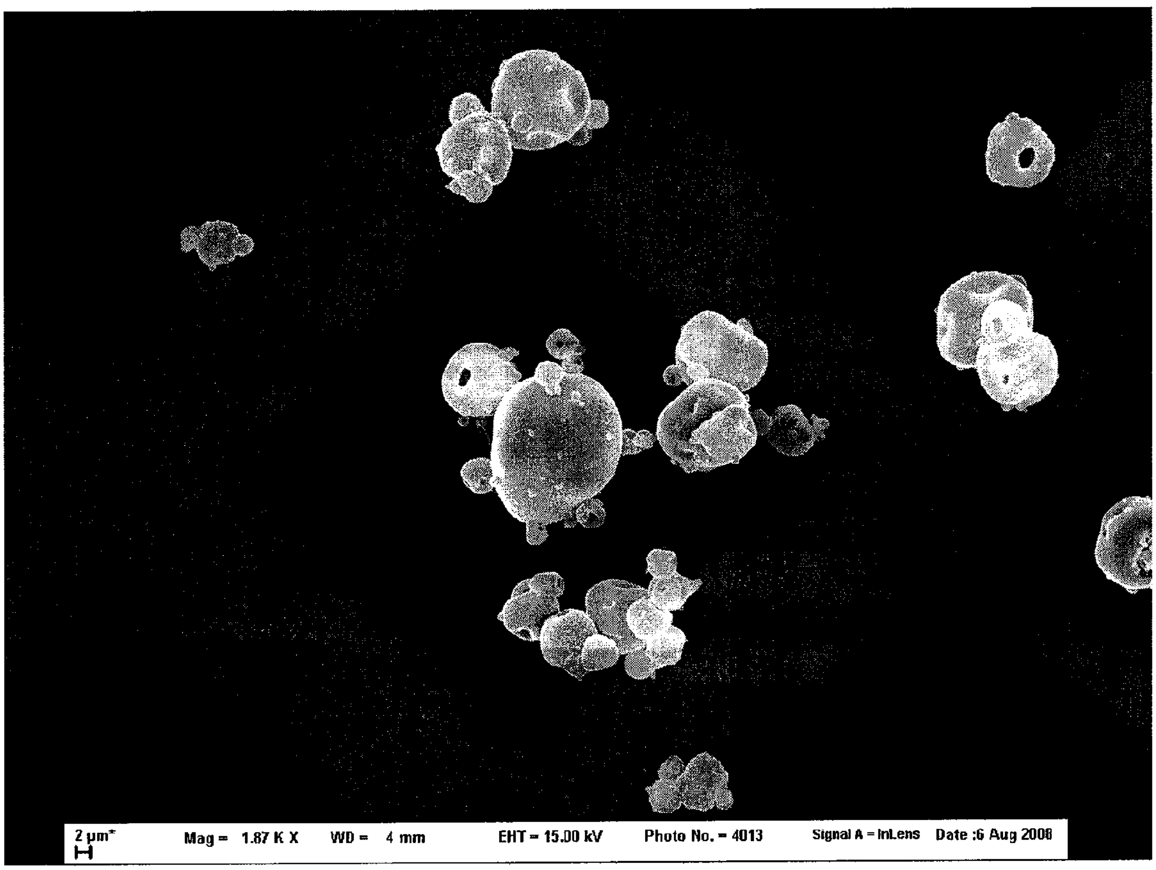

2 μm*
Mag = 1.87 K X
WD = 4 mm
EHT = 15.00 kV
Photo No. = 4013
Signal A = InLens
Date :6 Aug 2008

Figure 6

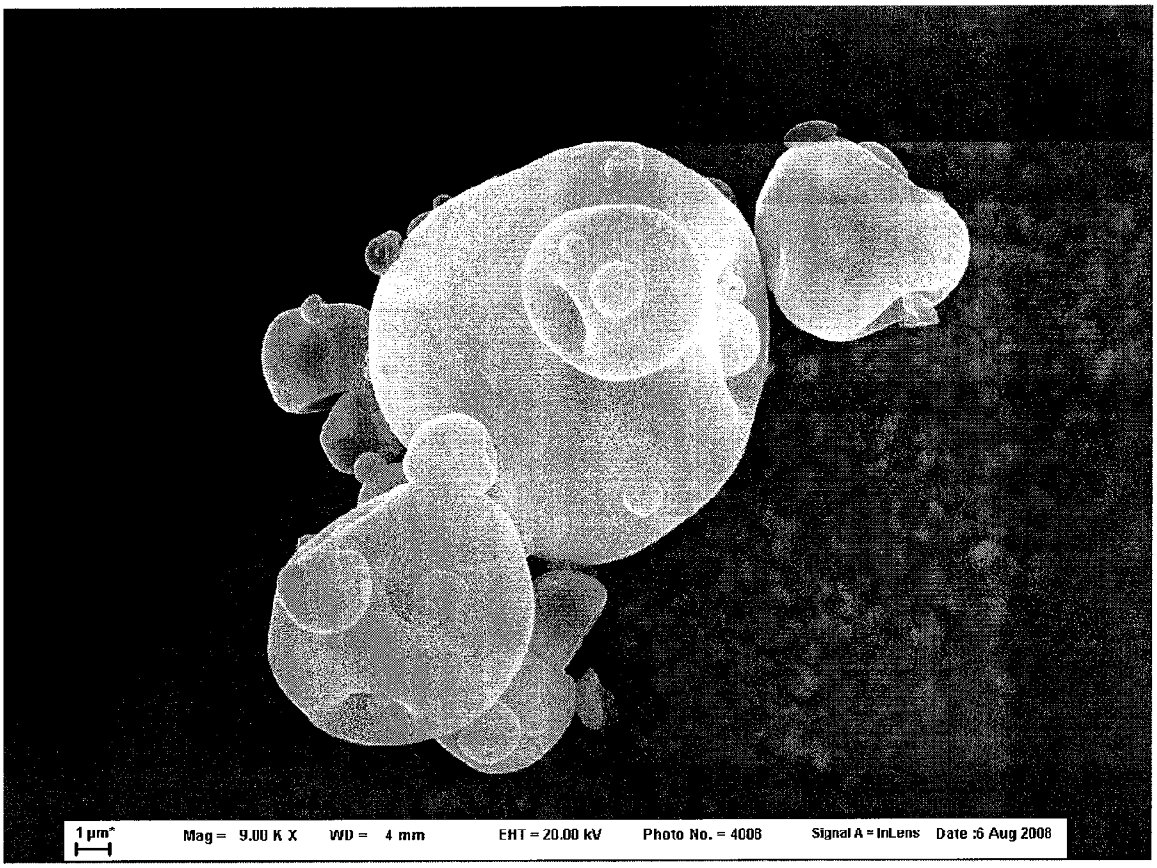


Figure 7

Ristocetin Agglutination of Spray-Dried RL Platelets
Visible Microscopy

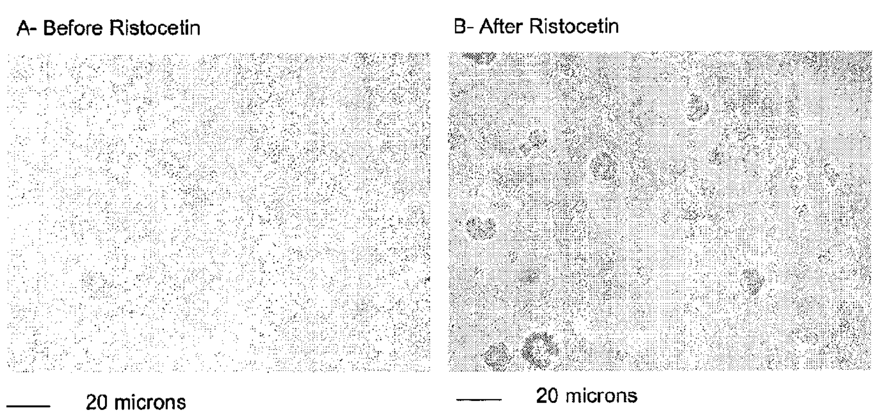


Figure 8

SPRAY-DRIED BLOOD PRODUCTS AND METHODS OF MAKING SAME

CROSS REFERENCE TO RELATED APPLICATIONS

This application is a continuation of 35 U.S.C. § 371 U.S. National Phase application Ser. No. 13/262,931 filed Oct. 13, 2011, which claims the benefit of International Application No. PCT/US2010/030031 having an international filing date of Apr. 6, 2010, which claims the benefit of U.S. Provisional Patent Application No. 61/212,321 filed Apr. 9, 2009, each of which is incorporated herein by reference in its entirety.

BACKGROUND OF THE INVENTION

Field of the Invention

The present invention is directed to methods of preparing dried blood products using spray-drying as an alternative to conventional lyophilization (freeze-drying), and products made by the method. Using the method of the invention, increased recovery rates of dried product are possible. The final product displays at least three-fold concentration over native plasma, as well as increased reconstitution rates when mixed with liquids.

Brief Description of the Related Art

Spray-drying is a technology in which a solution is atomized in a stream of flowing gas for rapid solvent vaporization (e.g., dehydration). The result is the formation on a sub-second timescale of microparticles composed of the residual solute. Spray-drying has been used as a industrial process in the material,[4] food[5] and pharmaceutical[6, 7] industries for decades. (e.g., see Bergsoe[8] for an earlier review). More recently, spray-drying has facilitated the preparation of protein therapeutics as microparticles for inhalation,[9] the formulation of advanced carrier-therapeutic microstructures,[10-12] and new classes of micromaterials.[13-15] The role of kinetic, phase transition, mass transfer, heat transfer, and other physical processes in determining ultimate particle size and composition are well-understood (e.g., see Vehring[16] for a recent review), and research in spray-drying is an extremely active area in materials science research. An important finding from this body of research is that in aqueous systems the heat of vaporization reduces the temperature of the particles during the volatilization process. Thus, thermal denaturation of proteins can be minimized for preservation of protein activities.

During World War II, the benefits of whole blood transfusion were appreciated, but logistical difficulties related to collection, transport, outdating and typing mismatch for transfusion reactions limited widespread utilization[17]. Dried plasma was thus developed as a surrogate for whole blood[18]. American, British and Canadian military transfusion services extensively utilized dried plasma[1] during World War II with a very favorable safety profile. The methods for preparing U.S. Army-Navy dried plasma were originally scaled to commercial volumes by Sharp and Dohme, Inc. (and later by a larger industrial consortium) with lyophilization technologies analogous to today's freeze-drying protocols[19]. The dried U.S. Army-Navy plasma was anticoagulated with 0.67% (w/v) sodium citrate, and after 1942 was rehydrated with 0.1% (w/v) citric acid. Rehydration with citric acid was found to result in a final product pH of 7.4-7.6 for a more favorable preservation of thrombin generation[20].

Dried U.S. Army-Navy plasma was placed in widespread civilian use after 1945, and used in the initial phases of the Korean War. However, despite nascent development of ultraviolet irradiation microbial decontamination methods[21], the production of dried plasma was suspended in 1953, the stated reason being hepatitis contamination. However, civilian use of plasma, mostly as fresh frozen plasma, has greatly expanded, with over 13 million units being collected in 2005[22]. In current medical practice plasma is used for a variety of indications, one of the most important being as a component of resuscitation mixtures in trauma with massive blood loss. Plasma contains components, such as the coagulation factors and fibrinogen, which are frequently diminished in hemorrhagic shock-related coagulopathies (e.g., see Hardy et al.[23]).

Several medical findings point towards the utility of a hyper-concentrated plasma product. The desirability of low volume resuscitation, as facilitated by products such as hyper-concentrated plasma, is becoming increasingly accepted since the initial observations of adverse outcomes related to standard resuscitation.[24-26] Incidences of transfusion associated cardiac overload and fluid overload-associated acute respiratory distress syndrome might be avoided with low volume resuscitation.[27, 28] Administration of reduced volumes can also be desirable if ongoing hemorrhage is exacerbating dilutional coagulopathies (e.g. see Stern for a review[29]). The development of advanced resuscitation products, such as hemoglobin-based oxygen carriers (HBOCs),[30] facilitate the ability to achieve adequate tissue oxygenation without infusion of large volumes of fluids. However, the introduction of HBOCs is anticipated to create a need for low volume products to supplement hemostatic systems, such as concentrated plasma.

Dried blood products are known in the art, and the predominant technique for achieving the dried product is lyophilization (freeze-drying). For example, U.S. Pat. Nos. 4,287,087 and 4,145,185 to Brinkhous et al. disclose dried blood platelets that have been fixed with a crosslinking reagent such as formaldehyde. U.S. Pat. Nos. 5,656,498, 5,651,966; 5,891,393; 5,902,608; and 5,993,804 disclose additional dried blood products. Such products are useful for therapeutic purposes because they are stable, have long shelf life, and can be used potentially in powder form to arrest bleeding in patients undergoing severe trauma. However, such products must be manufactured under strict sterile conditions in order to avoid contamination.

With current transfusion practices, plasma is frequently provided as a thawed single donor "fresh frozen" product. However, since refrigeration is difficult to provide in forward military applications, underdeveloped countries, and in wilderness medicine situations, this form factor can be logistically problematic. Thus, the elimination of freezing (lyophilization) via a dried plasma product would be a significant advantage. In addition, the dried plasma product is significantly easier to pathogen reduce than is fresh frozen plasma. The present invention is believed to be an answer to that need.

SUMMARY OF THE INVENTION

In one embodiment, the present invention is directed to a method of preparing dehydrated blood products, comprising the steps of: (a) providing a hydrated blood product; (b) spray-drying the hydrated blood product to produce a dehydrated blood product, as well as dehydrated blood products made by the method.

In another embodiment, the present invention is directed to a method of treating a patient suffering from a blood-related disorder, comprising the steps of: (a) rehydrating a therapeutic amount of the dehydrated blood products to produce a rehydrated therapeutic composition; and (b) administering the rehydrated therapeutic composition to the patient.

In another embodiment, the present invention is directed to a bandage or surgical aid comprising the dehydrated blood products described above.

In yet another embodiment, the present invention is directed to a method of preparing dehydrated fixed blood platelets, comprising the steps of: (a) providing hydrated fixed blood platelets; and (b) spray-drying the hydrated fixed blood platelets to produce a dehydrated fixed blood platelets, as well as dehydrated fixed blood platelets made by the method.

In yet another embodiment, the present invention is directed to a method of treating a patient suffering from a blood-related disorder, comprising the steps of: (a) rehydrating a therapeutic amount of the dehydrated fixed blood platelets to produce a rehydrated therapeutic composition; and (b) administering the rehydrated therapeutic composition to the patient.

In yet another embodiment, the present invention is directed to a bandage or surgical aid comprising the dehydrated fixed blood platelets described above.

In yet another embodiment, the present invention is directed to spray dried fixed blood platelets having spherical-dimpled geometry, wherein when said spray dried fixed blood platelets are rehydrated to form a rehydrated fixed blood platelet composition, the composition has a turbidity (A_{500}) value less than that of a comparable rehydrated lyophilized composition of fixed blood platelets.

These and other embodiments will become evident on reading the following detailed description of the invention.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** is an electron micrograph of microspheres of spray-dried plasma produced according to the present invention;

FIG. **2** is a graph showing coagulation factor levels in various samples;

FIG. **3** depicts graphs showing native coagulation pathway turnover with spray dried plasma produced according to the method of the invention;

FIG. **4** is an electron micrograph showing fibrin ultrastructure from spray dried plasma produced according to the method of the invention;

FIG. **5** is a graph depicting the turbidity and rehydration rate of spray-dried vs. lyophilized plasma at several concentrations;

FIG. **6** is an electron micrograph of rehydrated spray-dried derivatized blood platelets;

FIG. **7** is another electron micrograph of rehydrated spray-dried derivatized blood platelets; and

FIG. **8** are electron micrographs illustrating ristocetin agglutination of spray-dried rehydrated platelets made according to the method of the invention.

DETAILED DESCRIPTION OF THE INVENTION

As indicated above, the present invention is directed to methods of preparing dehydrated blood products, and dehydrated blood products made by the method. Useful hydrated blood products that may be dehydrated by the method of the invention include, but are not limited to, whole blood, blood plasma, blood platelets, red blood cells, blood serum, plasma, and combinations of these. One particularly useful blood product that is suitable for the method of the present invention is blood platelets that have been fixed with a fixative agent, such as formaldehyde or paraformaldehyde. Additionally, the blood products may be modified with additional diagnostic or therapeutic agents, such as imaging agents, concentration factors, performance enhancement drugs, antimicrobial and antiviral reagents, universal donor solutions, and the like, as well as combinations of these. One example of a useful modified product is STASIX (derivatized dried blood platelets) available from Entegrion, Inc. (Research Triangle Park, NC).

The technique of spray-drying is used in the method of the invention as an alternative to conventional drying techniques known in the art, such as lyophilization (freeze drying). Spray drying is a method of transforming material in a fluid state into a dried particulate form by spraying a feed of a material into a warm drying medium. Spray drying involves evaporation of moisture from an atomized feed by mixing the spray and the drying medium in a controlled fashion. The drying medium is typically air, although other gases such as nitrogen may also be used. The drying proceeds until the desired moisture content is reached in the sprayed particles and the product is then separated from the drying medium.

The complete process of spray drying basically consists of a sequence of four processes. The dispersion can be achieved with a pressure nozzle, a two fluid nozzle, a rotary disk atomizer or an ultrasonic nozzle. Selection upon the atomizer type depends upon the nature and amount of feed and the desired characteristics of the dried product. The higher the energy for the dispersion, the smaller are the generated droplets. The manner in which spray contacts the drying air is an important factor in spray dryer design, as this has great bearing on dried product properties by influencing droplet behavior during drying. In one embodiment, the material is sprayed in the same direction as the flow of hot air through the apparatus. The droplets come into contact with the hot drying gas when they are the most moist. In another embodiment, the material is sprayed in the opposite direction of the flow of hot gas. The hot gas flows upwards and the product falls through increasingly hot air into the collection tray. The residual moisture is eliminated, and the product becomes very hot. This method is suitable only for thermally stabile products. In yet another embodiment, the advantages of both spraying methods are combined. The product is sprayed upwards and only remains in the hot zone for a short time to eliminate the residual moisture. Gravity then pulls the product into the cooler zone. This embodiment is particularly advantageous because the product is only in the hot zone for a short time, and is less likely to be affected by heat.

In the spray drying method, air is mostly used as drying medium, but other gases such as nitrogen may also be used. The gas stream is heated electrically or in a burner and after the process exhausted to atmosphere. If the heating medium is recycled and reused, typically an inert gas such as nitrogen, is used instead of air. Use of nitrogen is advantageous when flammable solvents, toxic products or oxygen sensitive products are processed.

During the spray drying process, as soon as droplets of the spray come into contact with the drying gas, evaporation takes place from the saturated vapor film which is quickly established at the droplet surface. Due to the high specific surface area and the existing temperature and moisture gradients, heat and mass transfer results in efficient drying. The evaporation leads to a cooling of the droplet and thus to a small thermal load. Drying chamber design and air flow rate provide a droplet residence time in the chamber, so that the desired droplet moisture removal is completed and product removed from the dryer before product temperatures can rise to the outlet drying air temperature. Hence, there is little likelihood of heat damage to the product.

Two systems are used to separate the product from the drying medium. First, primary separation of the drying product takes place at the base of the drying chamber, and second, total recovery of the dried product in the separation equipment. In one embodiment, a cyclone is used to collect the material. Based on inertial forces, the particles are separated to the cyclone wall as a down-going strain and removed. Other systems such as electrostatic precipitators, textile (bag) filters or wet collectors like scrubbers, may also be used to collect the dried product.

As used in the present invention, spray drying offers advantages over other drying methods such as lyophilization (freeze drying). Use of spray drying produces a product that is more consistent, less clumpy, and better dispersed than freeze drying methods. The highly dispersed particles produced by spray drying also allow for a rapid rehydration rate, which is likely a result of a larger available surface area. By contrast, the clumped nature of a freeze dried product, results in substantially longer rehydration times for the blood products that are dried in the method of the invention. Since many transfusions and other uses of blood products can be highly time-sensitive, this higher rate of rehydration can be a significant advantage in battlefield or emergency treatment situations. As explained in more detail below, spray dried fixed blood platelets of the invention can be rehydrated to form a rehydrated fixed blood platelet composition, and the composition has a turbidity (A_{500}) value less than that of a comparable rehydrated lyophilized composition of fixed blood platelets.

The spray-dried products of the method of the invention may be used as topical treatments in treating wounds. In one embodiment, the products may be used directly on a wound to assist clotting, or may be applied to a bandage or surgical aid or covering to assist in wound healing. In an alternative embodiment, the rehydrated forms of the spray-dried products of the method of the invention may be administered via intravenous injection as therapeutic treatments to patients afflicted with blood-related disorders such as thrombocytopenia (including washout thrombocytopenia), hemorrhagic platelet dysfunction, and trauma victims experiencing severe bleeding.

EXAMPLES

General Design and Methods

Spray-dried Plasma Concentration. Human pooled solvent-detergent treated plasma (Kedrion S.p.A., Barga, Italy) and porcine plasma from a pool of ten animals (donated by the Francis Owen Blood Research Laboratory, University of North Carolina at Chapel Hill) can be spray-dried over a range of instrumental run parameters or freeze-dried with a standard lyophilization cycle to obtain different sized dehydrated microparticles. The products are then rehydrated with different volumes of sterile water that contain a low concentration of glycine at pH=2.4 to compensate for the loss of protons during the dehydration process and compared to establish the upper limit for concentration. Details of the experiments follow:

Plasma dehydration. Porcine and human plasma can be spray-dried in a Buchi B-270 research spray-dryer at a flow rate of 415 liters N_2 per hour at 140° C., 130° C., 120° C., 110° C., and lower if dehydration can be obtained. Runs are preferably performed three times at each temperature and with each type (i.e., porcine and human) plasma. The final product can be analyzed for moisture content and microparticles imaged with scanning electron microscopy. Portions of pig and human plasma may also be lyophilized at −20° C. for three days from a 4 mm layer to obtain a "lyophilization control" cake. As shown in the accompanying Figures, spray-dried material is observed to be a fine powder, and appear as microspheres under the microscope, while lyophilized material forms a cake.

Plasma rehydration. Spray-dried and lyophilization control lots (each in triplicate) are rehydrated with the appropriate volume of sterile water with glycine for 1×, 2×, 3×, 4× and possibly higher hyper-concentration of the plasma. Rehydration can be with glycine solutions at pH=2.4 for a product with a final rehydrated pH=7.4 as follows: 1×—20 mM glycine, 2×—40 mM glycine, 3×—60 mM glycine, 4×—80 mM glycine, etc.

Physical and chemical analysis. The following analysis may be performed with each triplicate sample of starting plasma (pre-spray dry), each lot spray-dried material and the lyophilized control plasma. Comparisons can be made with the Wilcoxon Signed Rank Test, and directionality will be assessed using the Sign test.

Turbidity and rate of solubilization—Optical measurement of the light absorption at 700 nm can assess turbidity as a function of time after initiation of the rehydration reaction.

Viscosity can be estimated with a falling ball viscometer.

Coagulation factor levels (including FII, FV, FVII, FVIII, FIX, FX, FXII, FXII, FXIII, protein S, protein C, von Willebrand factor) are measured with ELISA analysis.

Coagulation pathway turnover—Prothrombin times and activated partial thromboplastin times are measured with concentrated plasmas after dilution of the hyper-concentrated solutions to 1×. Final clots are examined with scanning electron microscopy to assess fiber thickness and density.

A concentrated solution preferably will have the appropriate rheology for standard transfusion practice in which coagulation factor levels and activities are within normal intra- and inter-individual ranges of variation. This solution can be utilized for the "most concentrated" infusions in porcine studies described below.

Safety evaluation of concentrated plasma products in pigs. The goal of these studies is to identify a maximum tolerated dose for hyper-concentrated plasma preparations in injured pigs. Animals are subjected to hepatic injuries for blood loss and induction of compensated hemorrhagic shock. Animals are then be infused with hyper-concentrated plasma porcine preparations until an adverse hemodynamic response is noted. At the termination of the experiment animals is sacrificed and subjected to post-mortem analysis for histological evidence of prothrombotic complications. The endpoint of this analysis will be the definition of the relationship between maximum tolerated dose and degree of plasma concentration.

Induction of Shock in Pigs and Infusion of hyper-concentrated plasma. 40 to 50 kg pigs (obtained from the Division of Laboratory Animal Medicine (UNC) breeding colony) are anesthetized.

Analysis of hemodynamic and vasoactive processes. Several sensors are placed to follow hemodynamic and vasoactive processes: a pulmonary artery thermo dilution catheter is inserted via the external jugular vein into a pulmonary artery; micromanometer-tipped catheters are positioned via the left femoral vessels into the right atrium and thoracic aorta; a 0.22 gauge catheter is inserted into the left femoral artery and connected to a withdrawal pump. Patterns of blood flow are measured by placing Doppler flow probes on the cephalic and mesenteric arteries; this procedure can be supported by carotid artery cut down and laparotomy.

Induction of shock and infusion of hyper-concentrated plasma. Hemorrhagic shock can be induced by withdrawing 40% of total blood volume over a one-hour period. After withdrawal of blood and verification of hemorrhagic shock (mean arterial blood pressure<40 mm Hg, shift in cephalic, splanchnic blood flow pattern), the animals are infused with multiple doses of 1× spray-dried plasma or hyper-concentrated spray-dried plasma at an intermediate and high level of concentration (to be determined as described above). Each infusion is preferably a volume equivalent to 1/10th of the animal's blood volume, and is preferably performed over a three minute period with a Harvard syringe pump. Hemodynamic and other physiological parameters can be measured, and infusions can be stopped when two successive boluses result in worsening hemodynamic stability. Animals are then be sacrificed for autopsy and histological analysis. The number of animals and the infused products used in this Example are shown in Table 1.

TABLE 1

Infused Product	Number of Animals
1x Plasma	3
Intermediate Concentration (e.g., 2x)	3
High Concentration (e.g., 4x)	3
Total Animals	9

Microvasculopathologies and hemolytic disorders. After sacrifice, selected renal, hepatic, pulmonary, splenic, lung and other tissue are prepared for light microscopic analysis. The histological analysis focuses on identifying signs of macroscopic or disseminated intravascular coagulation or premature induction of selected organ failure.

Data analysis. Comparisons between plasma groups are made with the Wilcoxon Signed Rank Test, and directionality assessed using the Sign test.

Example 1: Spray-Drying of Plasma and Preservation of Coagulation Protein Activities

The following series of experiments demonstrate that plasma can be spray-dried to obtain dehydrated microparticles, and then rehydrated to the original volume for plasma with native coagulation factor levels and coagulation parameters. Solvent-detergent pooled plasma was subjected to standard spray-drying (415 liters N_2 per hour at 120° C. in Butchi, Inc. B-270) to obtain the product depicted in FIG. **1**. The spherical-dimpled geometry of the resulting microparticles is similar to the shapes obtained when other proteins are spray-dried, indicating that a protein surface shell forms as a result of the initial kinetics of water removal and concentration (e.g., see Vehring[16]). However, this geometry is distinctive over lyophilized plasma which displays a jagged surface texture.

Upon rehydration with 20 mM glycine, pH=2.4 to compensate for proton loss during the drying process for the original protein concentration, the coagulation factor levels were found to be essentially the same as in the original plasma before spray drying as shown in FIG. **2**. Spray-drying also had an insignificant effect on the kinetics of plasma coagulation (FIG. **3**). There was a statistical trend (that was not significant in this analysis) towards enhanced coagulation protein molecular turnover after spray-drying, an effect that might be related to differences in the association states of proteins in plasma samples. The fibrin strands after spray-dried plasma fibrinogen polymerization had normal morphology (FIG. **4**).

In contrast to the methods of the present invention, freezing and lyophilized plasma results in a product that contains microscopic and macroscopic domains of varying composition due to phase separation. The result is that rehydration at super-physiological concentrations is time consuming and results in a turbid suspension. This point is demonstrated by the data presented in FIG. **5** which shows A_{500} (turbidity) for several concentrations of rehydrated plasma. The solvent-detergent treated plasma product was subjected to spray-drying or lyophilization, then rehydrated for native (1×), 2×, 3× or 4× final concentration. Rehydration times, based on the time for macroscopic dissolution to occur, was dramatically faster with the spray-dried material due to the massive surface area of the microparticle formulation, and results in a significantly less turbid suspension as shown by lower A_{500} values in FIG. **5**.

In addition to the plasma described above, other blood products may be dried and rehydrated in accordance with the description above. Virtually any treated or untreated blood product may be used in the method of the invention. Examples of blood products include whole blood, blood plasma, blood platelets, red blood cells, blood serum, as well as combinations of these. The blood products may be used in the method of the invention in their naturally occurring state, or may be modified in any way. Examples of modifications of these blood products include fixation with a fixing agent such as formaldehyde or paraformaldehyde as described in U.S. Pat. Nos. 5,651,966; 5,891,393; 5,902,608; and 5,993,804; addition of imaging agents, concentration factors, performance enhancement drugs, antimicrobial and antiviral reagents and universal donor solutions. One example of a useful modified product is STASIX (derivatized dried blood platelets) available from Entegrion, Inc. (Research Triangle Park, NC). The following is a general protocol for rehydration of spray-dried STASIX particles.

Example 2: Rehydration of Spray Dried Derivatized Blood Platelets

The goal of this example is to rehydrate spray-dried derivatized blood platelets (sold under the tradename STASIX and available from Entegrion, Inc., NC) so that the concentration of all components (platelet particles, buffer salts, bulking agents (e.g., human serum albumin)) are the same as the suspension that went into the spray-drier. This was achieved in three stages.

First, a "reference A_{280} value" for the bulking medium used for the pre-spray-dried suspension is obtained. This is an A_{280} nm value for the pre-spray-dry after the platelets are spun out, reflecting the supernatant protein concentration, which is largely human serum albumin bulking agent. Second, a trial rehydration with the post-spray-dried powder is performed at 10% (w/v), then the optical density at 280 nm (A_{280}) of the bulking agent (human serum albumin) is measured. Third, the pre-spray-dried supernatant A_{280} and 10% supernatant A_{280} values are compared (ratioed) to determine how far off the 10% rehydration approximation was. This ratio is then used to calculate the exact weight percentage of dried powder that is needed to match the bulking agent protein concentration of the pre-spray dried suspension.

The platelet count of the post-rehydration particles are then measured two ways. First with a Hiska cell counter and second by measuring the optical turbidity. These values, and related rehydration volumes, form the starting point for all the particle characterization assays.

Procedure

1. Measure the optical density of the pre-spray dry to obtain the reference A_{280} value.

a) Thaw the liquid pre-spray dry sample and spin out the particles by centrifuging on a desktop microfuge at a setting of five for two minutes. Retain the supernatant.

b) Dilute the supernatant 1/10 into citrated saline in triplicate and measure A_{280} values with the nanodrop spectrometer.

2. Measure protein optical density of 10% (w/v) suspension

a) Weigh out several (approximately 4) 20-50 mg particle portions in microfuge tubes. Record the mass. Rehydrate one tube with distilled water for a 10% (w/v) suspension. Save the remaining tubes for future analysis.

b) Spin out particles as above and retain supernatant.

c) Dilute each rehydrated sample supernatant 1/10 into citrated saline in triplicate and measure the A_{280} values.

3. Calculate the rehydration weight percentage to match the pre-spray dried value as follows.

a) Divide the A_{280} values from the diluted pre-spray dry supernatant by the dilution factor (1/10) and average the three values to obtain a theoretical reference A_{280} value or $A_{280,\ ref}$.

b) Divide the A_{280} values form the 10% rehydration supernatant by the dilution factor (1/10) and average the three values to obtain a theoretical undiluted A_{280} value, referred to as $A_{280,\ 10\%}$.

c) Ratio $A_{280,\ 10\%}$ to the $A_{280,\ ref}$ value according to Equation 1 to obtain the proper rehydration mass (w/v) of post spray-dry powder so that the rehydrated sample will have the same A_{280} value as the reference A_{280} value.

$$\text{Weight percentage (w/v)*}=10\%\ (\text{w/v})\times A_{280,ref}/A_{280,10\%} \quad \text{(Equation 1)}$$

*weight percentage can be in units of mg/ml, e.g., 8.9% (w/v) is equivalent to 89 mg/ml.

Measurement of STASIX Particle Counts

a) Dilute the 10% rehydration suspension (don't perform the cell spin out) **1/10** with citrated saline in triplicate.

b) Measure the turbidity at A_{500} of each sample.

c) Measure the direct cell count with the Hiska hematological analyzer.

d) Calculate and factor in yield loss.

Electron micrographs of rehydrated spray-dried derivatized blood platelets (rehydrated STASIX) are shown in FIG. **6** and FIG. **7**.

Example 3: Single Dose Range-Finding Intravenous Toxicity Study in Cynomolgus Monkeys

A study was designed to assess the toxicity of spray-dried derivatized dried blood platelets (spray-dried Stasix as described above, then rehydrated) when administered via intravenous infusion (over approximately 5 minutes) to monkeys as a single dose. A recovery subgroup of the animals was observed for 7 days.

Five groups of monkeys were used—Group 1—vehicle (buffer) control; Group 2—1× therapeutic STASIX dose; Group 3—5× therapeutic STASIX dose; Group 4-10× therapeutic STASIX dose; and Group 5—human serum albumin (500 mg/kg). Dosages were respectively 0.0, 2.1×10^{9}, 1.05×10^{10}, 2.1×10^{10}, and 0.0 platelets/kg in group 1, 2, 3, 4, and 5. A 1× dose is the estimated therapeutic STASIX dose in a human patient, i.e., an additional 30,000 platelet particles per microliter of blood.

No adverse effects either symptomatic or micro-pathologic were seen in any of the monkeys used in this experiment. Since 2 male monkeys and 2 female monkeys all tolerated a 10× therapeutic dose of STASIX infused over the very brief time period of only 5 minutes, the no observable adverse effect level (NOAEL) is at least 10× the therapeutic dose. In a human clinical setting, STASIX doses would be infused at a much slower time rate of 20 minutes.

Necropsy of the 14 study monkeys comprising the 5 dosing groups was conducted at either Day 2 or Day 8 following infusion, and showed no evidence of the development of microthrombi in either the heart or lungs. In summary, in a detailed animal study conducted by a major outside research laboratory under all appropriate animal use and handling regulations, STASIX was shown to display no harmful effects at either a macroscopic or microscopic level at doses up to 10 times the intended human therapeutic dose.

Example 4: Spray-Drying of Aldehyde Stabilized Platelets

The utility of spray-drying as an alternative to lyophilization for the dehydration of aldehyde-stabilized platelets is examined in this example. Human apheresis platelets were stabilized using the procedure of Read et al. described in U.S. Pat. No. 5,651,966, which is herein incorporated by reference in its entirety.

Spray-drying (415 liters N_2 per hour at 120° C.) of the final aldehyde-stabilized platelet suspension at 2.0 million platelets/microliter in 5% (w/v) human serum albumin as described above resulted in a fine powder that, upon examination, consisted of spherical particles with 3 to 30 micron diameters similar to those shown in FIGS. **6** and **7**.

Seventeen independent dried platelet preparations were prepared with spray-drying and then rehydrated for the original pre-dehydration volumes. The yield (post-rehydration/pre-spray drying) of countable platelets was 96.8%+/−7.0% (standard deviation) for these seventeen runs.

FIG. **8** depicts spray-dried platelets after rehydration, exchange into normal human plasma (as a von Willebrand factor source) and addition of ristocetin to 1 mg/ml (Panel B) or a corresponding volume of control buffer (Panel A). Large aggregates were noted with ristocetin addition, indicating that spray-drying preserved glycoprotein 1B—von Willebrand factor receptor functions.

Cynomolgus monkeys (1 or 2/sex/group) received a single 5-minute intravenous infusion of the spray-dried platelets at doses of 2.1×10^{9}, 1.05×10^{10}, or 2.1×10^{10} platelets/kg. Control animals (2/sex) received vehicle (5.375 mM sodium citrate and 2 mM cysteine in physiological saline) and an additional group received 500 mg/kg human serum albumin (HSA). The dose volume was 2 mL/kg/min for all groups. Animals were observed for 1 or 7 days post-dose. One day after dose administration, 1 animal/sex/group was euthanized and necropsied. One animal per sex from the control and high-dose (2.1×10^{10} platelets/kg) groups were held for 7 days prior to necropsy. Parameters evaluated during the study were viability, clinical observations, body weights, clinical pathology (pretest, day 2 and day 8), organ weights, macroscopic observations and microscopic pathology.

Administration of all doses of spray-dried platelets (up to 2.1×10^{10} platelets/kg) was well tolerated. Hematology changes were limited to a decrease in the number of platelets and an increase in mean platelet volume in one of the two high-dose (2.1×10^{10} platelets/kg) animals (the female) on the day following dose administration. There were no observed changes in coagulation or clinical pathology parameters. Increases in spleen weight, relative to control values, were seen in all test article- and HSA-treated animals. Microscopic observations showed slight to moderate increases in the size of germinal centers in the spleen in mid- and high-dose (1.05×10^{10} or 2.1×10^{10} platelets/kg) females and the HSA-treated female on day 2 and the high-dose female (only group necropsied) on day 8 that correlated with macroscopic observations of tan discoloration and surface abnormalities of the spleen in some animals. Germinal center enlargement in females was considered a possible response to HSA. Similar findings were not seen in the vehicle treated control, which had smaller germinal centers. However, because active germinal centers are a common finding in monkey spleens, and because the sample size was small, this finding may be within normal background range. The persistence of splenic germinal center enlargement after 7 days in one animal suggests lack of recovery, which would be consistent with germinal center reaction to antigenic stimulation, but this finding may also reflect normal background variation.

Example 5: Spray-Drying of Plasma and Testing in Pigs

Plasma separated from fresh porcine blood was either stored as fresh frozen plasma (FFP) or preserved as freeze dried plasma (FDP) or spray-dried plasma (SDP, prepared as detailed in previous examples). For in-vitro testing: SDP was reconstituted in distilled water which was either equal (1×SDP) or one-third (3×SDP) the original volume of FFP. Analysis included measurements of prothrombin time (PT), partial thromboplastin time (PTT), fibrinogen levels, and activity of selected clotting factors. For in-vivo testing swine were subjected to polytrauma (femur fracture, grade V liver injury) and hemorrhagic shock (60% arterial hemorrhage, with the "lethal triad" of acidosis, coagulopathy and hypothermia), and treated with FFP, FDP, or 3×SDP (n=4-5/group). Coagulation profiles (PT, PTT, thromboelastography) were measured at baseline (BL), post-shock (PS), post crystalloid (PC), treatment (MO), and during 4 hours of monitoring (M 1-4).

In-vitro testing revealed that clotting factors were preserved after spray-drying. The coagulation of FFP and 1×SDP were similar, with 3×SDP showing a prolonged PT/PTT. Polytrauma/hemorrhagic shock produced significant coagulopathy, and 3×SDP infusion was as effective as FFP and FDP in reversing it. These results show that plasma can be spray-dried, and reconstituted to one-third its original volume without compromising the coagulation properties in-vivo. This shelf-stable, low-volume, hyperoncotic, hyperosmotic plasma is a logistically attractive option for the treatment of trauma-associated and other coagulopathies.

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What is claimed is:

1. A method of treating a patient suffering from a blood-related disorder, comprising the steps of:

a. preparing a dehydrated plasma blood product through a method comprising the steps of:
   1. providing hydrated plasma having clotting factors with measurable clotting factor levels of concentration and activity; and
   2. spray-drying said hydrated plasma at a temperature between about 110° C. to about 140° C. to produce a dehydrated plasma blood product wherein said clotting factors are preserved;
   3. measuring said clotting factor levels after said spray-drying; and
   4. comparing said clotting factor measurements, wherein said clotting factor levels of concentration and activity of said hydrated plasma and of said dehydrated plasma are essentially the same;

b. rehydrating a therapeutic amount of the dehydrated plasma blood product to produce a rehydrated therapeutic composition; and

c. administering said rehydrated therapeutic composition to said patient.

2. The method of claim **1**, wherein said hydrated plasma is physically or chemically modified.

3. The method of claim **2**, wherein said modification is chemical fixation.

4. The method of claim **2**, wherein said modification comprises additional diagnostic or therapeutic reagents.

5. The method of claim **4**, wherein said diagnostic or therapeutic reagents are selected from the group consisting of imaging agents, concentration factors, performance enhancement drugs, antimicrobial and antiviral reagents, universal donor solutions, and combinations thereof.

6. Spray dried plasma formed by the process of:

a) providing hydrated plasma; and

b) spray-drying said hydrated plasma directly by a spray dryer, wherein when said spray dried plasma has clotting factor levels of concentration and activity that are essentially the same as said hydrated plasma.

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