A method of controlling the moisture content of a spray dried product by measuring the drying gas flow exhaust temperature and adjusting the drying gas flow rate to maintain a predetermined exhaust temperature that results in the production of a spray dried product with a desired moisture content. A preferred product is spray dried human plasma.
Figure 13

- **Test Batch 1125**
- T5 Avg. = 125°C
- T8 Avg. = 55°C
- T6 Avg. = 52°C

- **Start-up** 
- **Plasma Spray Drying**

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- **Pressure (P7)**
- **Exhaust Gas Temp (T6)**
- **Collection Bag Inlet Temp (T8)**
- **Drying Gas Temp (T5)**
Figure 15

Test Batch 1125

Plasma Spray Drying

Start-up

T5 Avg. = 125°C

T8 Avg. = 55°C

T6 Avg. = 52°C

Pressure and Temperature (psig and degrees Celsius)

Time (min)

15

20

25

30

35

5

10

15

20

25

30

35

40

45

50

55

60

65

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100

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110

115

120

125

130

135

140

145

150

PROCESS CONTROL METHODS FOR
OBTAINING AND MAINTAINING A DESIRED
MOISTURE CONTENT OF SPRAY DRIED
PLASMA

GOVERNMENT SUPPORT

[0001] This invention was made with Government support under contract HS010001200005C awarded by the Bio-
medicul Advanced Research and Development Authority
(BARDA). TheGovernment has certain rights in the inven-
tion.

BACKGROUND

[0002] Making up about 55% of the total volume of whole
blood, blood plasma is a whole blood component in which
blood cells and other constituents of whole blood are sus-
pended. Blood plasma further contains a mixture of over 700
proteins and additional substances that perform functions
necessary for bodily health, including clotting, protein stor-
age, and electrolyte balance, amongst others. When
extracted from whole blood, blood plasma may be employed
to replace bodily fluids, antibodies and clotting factors.
Accordingly, blood plasma is extensively used in medical

[0003] Spray drying is a process wherein a liquid contain-
ing solutes such as proteins and salts is aerosolized into small
droplets. The moisture is then evaporated out of the aero-
solized droplets with heated air or other gas, allowing con-
stituents to precipitate into a powder or powder-like form.
The dried powder may contain from 2% to 10% or more moisture,
depending on the nature of the precipitant(s) and desired goal
of the process. Thus, “dried” or “dry” is a relative term and not
an absolute term. Over drying may damage the sought-after
precipitant(s) while under drying can leave the precipitant too
moist resulting in clumping or caking or degumming of the
precipitant(s) during storage. Consequently, problems asso-
ciated with the spray drying process include obtaining and
maintaining a suitable drying process to ensure the desired
dryness is obtained while not over drying or under drying the
sought-after precipitant. Current technologies utilize intricate
arrays of temperature and moisture sensors, the data from
which a person or computer analyzes before making any
necessary adjustments to the spray dry process. Constant
monitoring and adjustment is necessary because, throughout
the spray drying process, the temperature and moisture levels
in the drying chamber are constantly changing as moisture is
released from the aerosolized droplets. The relative complex-
ity of these systems can result in errors in analysis or errors in
the multitude of possible adjustments that can be made.

[0004] Accordingly, there is a need to develop simpler tech-
niques and processes for the control of the spray dry process,
especially for the spray drying of human plasma.

SUMMARY

[0005] A long-standing need and challenge to the blood
industry has been to provide safe, reliable and convenient
blood products while preserving the efficacy and safety of
those products in storage and when used in transfusion or as
a source a medical treatments. The efficient and efficacious
production of these products is the important first step in
meeting this need and challenge. The present invention pro-
vides for efficient methods and processes for the spray drying
of human plasma that are superior to the prior art methods
with regard to providing a consistent product with negligible
areas for generating process errors.

[0006] The present invention contemplates a spray drying
control process and procedure that solves the problems asso-
ciated with prior art spray drying control processes and pro-
cedures, especially with regard to the spray drying of human
plasma. The inventors of the present invention have discov-
ered that the spray drying process can be controlled effec-
tively, and spray dried plasma is collected in the collection chamber by measuring the exhaust gas temperature
of the spray dryer during the spray drying process, and adjust-
ing the flow rate of the drying gas to maintain the desired
exhaust gas temperature. In this regard, increasing the flow
rate of the drying gas puts more heat into the drying chamber,
increases the exhaust gas temperature and decreases the mois-
ture content of the spray dried plasma; and decreasing the
drying gas flow decreases the heat put into the drying cham-
ber, decreases the exhaust gas temperature and increases the
moisture content of the spray dried plasma. The inventors
have found that adjusting and maintaining the exhaust gas
temperature by changing the flow rate of the drying gas rather
than changing the temperature of the drying gas results in a
faster response rate since the flow of the drying gas can be
canceled almost instantaneously whereas changing the tem-
perature of the drying gas would require a time lag for warm-
ing or cooling the gas. Further, an exhaust gas temperature
of approximately 50°C to 65°C has been found to be suitable
for obtaining the desired spray dried plasma moisture content.
Further still, the exhaust gas temperature of approximately
55°C has been found to be most suitable for obtaining the
desired spray dried plasma moisture content. The desired
moisture content of the spray-dried plasma is about 4% to
about 10%.

[0007] The process and method of the present invention
may utilize electronic or computerized control mechanisms
for reading the exhaust gas temperature and calculating the
necessary adjustment to the drying gas flow rate. Embed-
ments of suitable software code will be apparent to those of
skill in the art in view of the teachings of this specification.
In still other embodiments, it is contemplated that the adjust-
ments are made manually by a trained operator.

[0008] The present invention contemplates a method of
controlling the moisture content of a spray dried plasma. The
method comprises: providing: (i) plasma and (ii) a spray drying
apparatus. The spray dry apparatus comprises a mechanism
for aerosolizing the plasma, a mechanism to deliver drying
gas at a controlled rate, a drying chamber, a collection cham-
ber and a sensor for measuring exhaust gas temperature as it
emerges from the drying process The method further com-
prises operating the spray drying apparatus to produce a
moisture controlled spray dried plasma, the operation com-
prising controlling the moisture content of the spray dried plasma collected in the collection chamber by measuring the
exhaust gas temperature with the sensor for measuring
exhaust gas temperature and adjusting the flow of the drying gas based on the exhaust gas temperature wherein the flow of the drying gas is increased to increase the exhaust gas temperature and decrease the moisture content of the spray dried plasma; and the drying gas flow is decreased to decrease the exhaust gas temperature and increase the moisture content of the spray dried plasma. This method produces a moisture controlled spray dried plasma having a moisture content of approximately 4 w/w % to approximately 10 w/w %.

[0009] The present invention further contemplates that the moisture content of the moisture controlled spray dried plasma is approximately 4 w/w % to approximately 8 w/w %.

[0010] The present invention still further contemplates that the exhaust gas temperature is maintained at a set point in the range of from approximately 45° C. to approximately 65° C.

[0011] The present invention still further contemplates that the exhaust gas temperature is maintained at a set point in the range of from approximately 50° C. to approximately 65° C.

[0012] The present invention still further contemplates that the exhaust gas temperature is maintained at a set point of approximately 55° C.

[0013] The present invention still further contemplates that the drying gas has a temperature of about 100° C.-150° C. when it starts to mix with the aerosolized plasma.

[0014] The present invention still further contemplates that the drying gas flow is maintained at approximately 500 L/min to approximately 1000 L/min during the process for producing the moisture controlled spray dried plasma.

[0015] The present invention still further contemplates that the drying process is controlled by a computer.

[0016] The present invention still further contemplates that the flow rate of the drying gas flow rate and percent moisture of the moisture controlled spray dried plasma is based on previously collected data.

[0017] The present invention still further contemplates that the plasma is whole blood (WB) plasma or citrate phosphate dextrose (CPD) plasma.

**BRIEF DESCRIPTION OF THE DRAWINGS**

[0018] The foregoing and other objects, features and advantages will be apparent from the following more particular description of the embodiments, as illustrated in the accompanying drawings in which like reference characters refer to the same parts throughout the different views. The drawings are not necessarily to scale, emphasis instead being placed upon illustrating the principles of the embodiments.

[0019] FIG. 1A is a schematic illustration of an embodiment of a spray dryer system of the present disclosure, including a spray dryer device 102 and a spray dryer assembly.

[0020] FIG. 1B is a schematic illustration of a plurality of the spray dryer systems of FIG. 1A for use with a pooled liquid source.

[0021] FIGS. 2A and 2B are schematic illustrations of the spray dryer assembly of FIG. 1A.

[0022] FIG. 3 is a schematic illustration detailing embodiments of a collection chamber of the spray dryer assembly of FIGS. 2A-2B.

[0023] FIG. 4 panels A-C are schematic illustrations depicting unfolding/refolding model of the vWF A2 domain and proteolysis by ADAMTS13. (A) Cartoon of the vWF A2 domain in its native folded state. (B) The first step of unfolding occurs from the C-terminal end of the vWF A2 domain, influenced by the presence of the vicinal disulfide bond (cysteines depicted by C). Initial unfolding occurs up to, or including, the central b4 sheet in which the scissile bond (YM) is contained. This unfolding intermediate step exposes the high-affinity ADAMTS13 spacer-binding site. (C) Once the stabilizing effect of the CBS is overcome this results in the complete unfolding of the vWF A2 domain and the positioning of the ADAMTS13 active site for nucleophilic attack of the Y1605-M1606 scissile bond.

[0024] FIG. 5 shows a schematic diagram of an embodiment of the computer hardware of the suitable for use in the present invention.

[0025] FIG. 6 shows a schematic diagram of an embodiment of the automation flow of the software of the present invention.

[0026] FIG. 7 shows a schematic diagram of an embodiment of the flow of the drying progress of the present invention.

[0027] FIG. 8 shows a schematic diagram of an embodiment of the product flow of the present invention up to the drying apparatus. Symbols and designations are explained in the Detailed Description, below.

[0028] FIG. 9 shows a schematic diagram of an embodiment of the product flow of the present invention from the drying apparatus. Symbols and designations are explained in the Detailed Description, below.

[0029] FIG. 10 shows a schematic diagram of an embodiment of a spray dryer with a mechanical collection filter for use in the present invention.

[0030] FIG. 11 shows a schematic diagram of two views of an embodiment of a spray dryer with a removable/disposable collection filter bag for use in the present invention. The left hand drawing indicates where various temperatures are measured. The right hand drawing indicates the designation of the various temperature sensors. Measurements are approximate.

[0031] FIG. 12 shows results of a study on degradation of protein activity in relation to spray dryer temperature. The X-axis is the collection chamber temperature (° C.). The Y-axis is normalized protein activity for fibrinogen and factor X.

[0032] FIG. 13 is a graphical representation of a product run showing consistent temperature readings at the dryer inlet, the collection bag inlet and the collection bag exhaust.

[0033] FIG. 14 is a graphical representation of a product run showing consistent temperature readings at the dryer inlet, the collection bag inlet and the collection bag exhaust.

[0034] FIG. 15 is a graphical representation of a product run showing consistent temperature readings at the dryer inlet, the collection bag inlet and the collection bag exhaust.

[0035] FIG. 16 shows the combined results of multiple product runs. Exhaust gas temperature is on the X-axis. Residual moisture is on the Y-axis. The graph shows that temperatures between about 50° C. and 60° C. produce product dried to about 4.8% to about 6.0% residual moisture with 55° C. producing product with about 5.0% residual moisture.

**DETAILED DESCRIPTION OF THE INVENTION**

[0036] Embodiments of the present disclosure are directed to systems and methods for spray drying a liquid sample. In certain embodiments, the liquid sample is plasma obtained from a blood donor. In a preferred embodiment, the blood donor is human. However, it may be understood that the disclosed embodiments may be employed to spray dry any biological mixture of solid particles and/or molecules in a continuous liquid medium, including, but not limited to, colloids, suspensions and sols.
Plasma is the fluid that remains after blood has been centrifuged (for example) to remove cellular materials such as red blood cells, white blood cells and platelets. Plasma is generally yellow-colored and clear to opaque. It contains the dissolved constituents of the blood such as dissolved proteins (6-8%); i.e., serum albumins, globulins, fibrinogen, etc.), glucose, clotting factors (clotting proteins), electrolytes (Na⁺, Ca²⁺, Mg²⁺, HCO₃⁻, Cl⁻, etc.), hormones, etc. Whole blood (WB) plasma is plasma isolated from whole blood with no added agents except anticoagulant(s). Citrate phosphate dextrose (CPD) plasma, as the name indicates, contains citrate, sodium phosphate and a sugar, usually dextrose, which are added for stability and as anticoagulants. The level of citrate in CPD plasma is typically about 20-30 mM.

The plasma of the present invention may be dried after pooling or unit-by-unit. Pooling of multiple plasma units has some benefits. For example, any shortfall in factor recovery on an equal-volume basis can be made up by adding volume from the pool to the finished product. There are negative factors as well. Making up volume from the pool to improve factor recovery is expensive. Importantly, pooled plasma must be constantly tested for pathogens as any pathogens entering the pool runs the risk of harming hundreds or thousands of patients if not detected. Even if detected, pathogen contamination of pooled plasma would render the whole pool valueless. Testing can be obviated by pathogen inactivation of the plasma by irradiation or chemically such as solvent detergent treatment; however, each such treatment adds cost and complexity to pooled plasma processing. In any event, pooled plasma processing is generally unsuitable to the blood centers and generally only really suitable to an industrial, mass production environment.

Conversely, unit-by-unit (unit) collection and processing is well-suited to the blood center and eliminates the risk of pooled plasma pathogen contamination by allowing for pre-processing testing for pathogens and tracking of the unit to ensure that each unit leaves the blood center site pathogen free. The inventors have discovered that efficient and effective preservation and recovery of clotting factors is the standard by which successful unit blood plasma processing should be measured. Such efficiency is also very helpful in the pooled plasma environment as well. The present invention is primarily directed towards unit-by-unit drying of plasma.

Clotting Factors

There are many blood plasma factors associated with clotting. The methods and compositions of the present invention include recovering amounts of active/undenatured FGN, FV, FVII, FIX and von Willebrand factor (vWF) from rehydrated plasma that has undergone the spray drying process. Such blood plasma factors are important in patient treatment, especially after trauma injuries, to promote clotting of wounds. Thus, rapid administration of plasma is often needed to be performed quickly. The spray dried plasma of the present invention is ideal in that it can be readily reconstituted in a few minutes at the location of the trauma event without moving the patient and without time delay. Further, the spray dried plasma of the present invention has high levels of functional protein that is stable for extended periods of time without refrigeration or freezing.

vWF has generally been difficult to recover and has become one indicator for preservation of all factors. In an embodiment, if vWF is preserved, the other factors are likely to be preserved as well. The present invention includes recovering amounts of active/undenatured clotting factors, such as vWF, in an amount in rehydrated spray dried plasma that is at least about 20 percentage points or greater (e.g., about 30, 40, 50, 60, 70, 80 percentage points or greater) as compared to amounts of active/undenatured clotting factors (i.e., vWF) of rehydrated spray dried plasma that do not undergo the processes of the present invention. The present invention includes recovering amounts of active/undenatured clotting factors, such as vWF, in an amount in rehydrated spray dried plasma that is at about 20 percentage points to about 40 percentage points or about 25 percentage points to about 35 percentage points as compared to amounts of active/undenatured clotting factors (i.e., vWF) of rehydrated spray dried plasma that do not undergo the processes of the present invention. vWF activity is typically assayed with an assay called the von Willebrand factor: Ristocetin cofactor [vWF:RCo] assay, as is known to those of skill in the art. The vWF:RCo assay measures the ability of a patient’s plasma to agglutinate platelets in the presence of the antibiotic Ristocetin. The rate of Ristocetin induced agglutination is related to the concentration and functional activity of the plasma von Willebrand factor. Another assay, the vWF antigen assay, measures the amount of vWF present in a sample.

vWF is a large adhesive glycoprotein with established functions in hemostasis. It serves as a carrier for factor VIII and acts as a vascular damage sensor by attracting platelets to sites of vessel injury. The size of vWF is important for this latter function, with larger multimers being more hemo- statically active. Functional imbalance in multimer size can variously cause microvascular thrombosis or bleeding. The regulation of vWF multimeric size and platelet-tethering function is carried out by ADAMTS13, a plasma metallopro- tease that is constitutively active. It is secreted into blood and degrades large vWF multimers, decreasing their activity. Unusually, protease activity of ADAMTS13 is controlled not by natural inhibitors but by conformational changes in its substrate, which are induced when vWF is subject to elevated rheologic shear forces. This transforms vWF from a globular to an elongated protein. This conformational transformation unfolds the vWF A2 domain and reveals cryptic exosites as well as the scissile bond. To enable vWF proteolysis, ADAMTS13 makes multiple interactions that bring the pro- tease to the substrate and position it to engage with the cleavage site as occurs by shear forces (See FIG. 4). ADAMTS 13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13), also known as von Willebrand factor-cleaving protease (vWFPCP), is a zinc-containing metalloprotease enzyme.

Temperature and Moisture Control of the Drying Process

During the spray drying process temperature and moisture are related parameters. Higher drying temperatures result in lower moisture levels and lower drying temperatures result in higher moisture levels. However, the use of temperatures that are too high, while resulting in drier spray dried powders (i.e., powders with lower moisture content), may cause irreversible damage to the constituents of the powder, especially proteins, thereby reducing recovery of active product. Conversely, the use of temperatures that are too low, while resulting in less damage to product, may leave the moisture content too high leading to clumping, caking and the degradation of constituents causing decreases in long term stability of the product. Thus, the optimal balance must be
obtained to provide a powder that is dry enough to reduce moisture related stability issues and temperatures that are low enough to permit the highest recovery of active product. This balancing act is complicated by the fact that moisture and temperature levels in the spray dryer are constantly in flux, at least to a small extent, as the liquid (e.g., plasma) to be dried and heated drying gas are forced into the dryer. This is particularly true during the start and end of the product run.

Prior art methods of dealing with the regulation of heat and moisture in a spray dryer often utilized multiple temperature, moisture and flow sensors. Data from these sensors would then be fed into either a computer that would change process parameters based on computer coding, or be fed to various readout devices such as charts and gauges, where an operator would make process adjustments based on written protocol and experience. Because of the large number of sensors used, the plethora of possible combinations of adjustments that could be made, many of which would counteract other adjustments, production errors could be frequent and could result in substandard, wasted product.

The present invention eliminates these concerns by using only one reading to regulate the spray dry process so that the desired product moisture level is obtained at the temperature that is most advantageous for the recovery and stability of active protein product. In the present invention, the exhaust temperature of the spray dry process is measured at the exit of the collection chamber (see, below for a description of an embodiment of a spray dryer apparatus suitable for spray drying human plasma). Based on this temperature, the drying gas flow rate is maintained, increased or decreased such that the target exhaust gas temperature is obtained. In this regard, any means known to those of ordinary skill in the art for the introduction and regulation of a flow of gas is contemplated for use with the present invention with regard to introducing and regulating the drying gas flow. In an embodiment, it is contemplated that the desired exhaust gas temperature is about 50°C to about 60°C. In an embodiment, it is contemplated that the exhaust gas temperature is about 55°C. It is further contemplated that the exhaust gas temperature is increased or decreased by changing the flow rate of the drying gas. An increase in the exhaust gas temperature is desired, the flow of the drying gas is increased. If a decrease of the temperature of the exhaust gas is desired, the flow rate of the drying gas is decreased. Increased flow rate of the drying gas results in a greater input of heated gas into the drying chamber of the spray dryer apparatus. This in turn results in a decrease in the moisture content of the spray dried product. Decreased flow rate of the drying gas results in a lower input of heated gas into the drying chamber of the spray dryer apparatus. This in turn results in an increase in the moisture content of the spray dried product. The desired moisture content of spray dried human plasma is about 3% to about 10% or about 4% to about 6%. The present invention has found that an exhaust gas temperature of about 55°C is suitable to obtain this level of moisture in the spray dried human plasma product.

In an embodiment, the drying gas flow is maintained at approximately 550 L/minute to approximately 750 L/minute during the process for producing the moisture controlled spray dried plasma.

In an embodiment, the regulation of the flow rate of the drying gas is controlled by an automated feedback control loop integrated with the temperature of the exhaust gas and the automated feedback control loop is controlled by a computer.

In an embodiment, the flow rate of the drying gas flow rate and percent moisture of the moisture controlled spray dried plasma is based on previously collected data.

In general, a spray dryer system (spray dryer device) is provided for spray drying a liquid sample such as blood plasma. In an embodiment, the spray dryer system of the present disclosure includes a spray dryer device and a spray dryer assembly. The spray dryer device is adapted, in an aspect, to receive flows of an aerosolizing gas, a drying gas and plasma liquid from respective sources and coupled with the spray dryer assembly. The spray dryer device may further transmit the received aerosolizing gas, drying gas and plasma to the spray dryer assembly. Spray drying of the plasma is performed in the spray dryer assembly under the control of the spray dryer device. Any suitable spray drying system may be used in the present invention. For exemplification, a suitable spray dryer is described below.

In certain embodiments, the spray dryer assembly includes a sterile, hermetically sealed enclosure body and a frame to which the enclosure body is attached. The frame defines first, second and third portions of the assembly, separated by respective transition zones. A drying gas inlet is provided within the first portion of the assembly adjacent to a first end of the enclosure body.

A spray drying head is further attached to the frame within the transition zone between the first and second portions of the assembly. This position also lies within the incipient flow path of the drying gas within the assembly. During spray drying, the spray drying head receives flows of an aerosolizing gas and plasma and aerosolizes the plasma with the aerosolizing gas to form aerosolized plasma. Drying gas additionally passes through the spray drying head to mix with the aerosolized plasma within the second portion of the assembly for drying. In the second portion of the assembly, which functions as a drying chamber, contact between the aerosolized plasma and the drying gas causes moisture to move from the aerosolized plasma to the drying gas, producing dried plasma and humid drying gas.

In alternative embodiments, the aerosolizing gas may be omitted and the spray dryer assembly head may include an aerosolizer that receives and atomizes the flow of plasma. Examples of the aerosolizer may include, but are not limited to, ultrasonic atomizing transducers, ultrasonic humidifier transducers, and piezo-ultrasonic atomizers. Beneficially, such a configuration eliminates the need for an aerosolizing gas, simplifying the design of the spray dryer device and assembly.

The spray drying head, in an embodiment, is adapted to direct the flow of drying gas within the drying chamber. For example, the spray drying head includes openings separated by fins which receive the flow of drying gas from the drying gas inlet. The orientation of the fins allows the drying gas to be directed in selected flow pathways (e.g., helical). Beneficially, by controlling the flow pathway of the drying gas, the path length over which the drying gas and aerosolized blood plasma are in contact within the drying chamber can be increased, reducing the time to dry the plasma.

The dried plasma and humid drying gas subsequently flow into the third portion of assembly, which houses a collection chamber. In the collection chamber, the dried plasma is isolated from the humid drying gas and collected using a filter. For example, the filter in an embodiment of the
invention is open on one side to receive the flow of humid air and dried plasma and closed on the remaining sides. The humid drying gas passes through the filter and is exhausted from the spray dryer assembly.

[0059] In alternative embodiments, the filter is adapted to separate the collection chamber into two parts. The first part of the collection chamber is contiguous with the drying chamber and receives the flow of humid drying gas and dried plasma. The dried plasma is collected in this first part of the collection chamber, while the humid air passes through the filter and is exhausted from the spray dryer assembly via an exhaust in fluid communication with the second part of the spray dryer assembly.

[0060] After collecting the dried plasma, the collection chamber is separated from the spray dryer assembly and hermetically sealed. In this manner, the sealed collection chamber is used to store the dried plasma until use. The collection chamber includes a plurality of ports allowing addition of water to the collection chamber for reconstitution of the blood plasma and removal of the reconstituted blood plasma for use. The collection chamber may further be attached to a sealed vessel containing water for reconstitution.

[0061] When handling transfusion products such as blood plasma, the transfusion products must not be exposed to any contaminants during collection, storage, and transfusion. Accordingly, the spray dryer assembly, in an embodiment, is adapted for reversible coupling with the spray dryer device. For example, the spray dryer assembly is coupled to the spray dryer device at about the drying gas inlet. Beneficially, so configured, the spray dryer assembly accommodates repeated or single use. For example, in one embodiment, the spray dryer assembly and spray drying head is formed from autoclavable materials (e.g., steels, alloys, etc.) that are sterilized prior to each spray drying operation. In an alternative embodiment, the spray dryer head and spray drying chamber is formed from disposable materials (e.g., polymers) that are autoclaved prior to each spray drying operation and disposed of after each spray drying operation.

[0062] Reference will now be made to FIG. 1A, which schematically illustrates one embodiment of a spray dryer system 100. The system 100 includes a spray dryer device 102 configured to receive a spray dryer assembly 104. A source of plasma 112, a source of aerosolizing gas 114, and a source of drying gas 116 are further in fluid communication with the spray dryer assembly 104. During spray drying operations, a flow of the drying gas 116A is drawn within the body of the assembly 104. Concurrently, a flow of a blood plasma 112A and a flow of aerosolizing gas 114A are each drawn at selected, respective rates, to a spray drying head 104A of the assembly 104. In the spray dryer assembly 104, the flow of blood plasma 112A is aerosolized in the spray dryer head 104A and dried in a drying chamber 104B, producing a dried plasma 112 that is collected and stored for future use in a collection chamber 104C. Waste water 122 removed from the blood plasma during the drying process is further collected for appropriate disposal.

[0063] The spray dryer device 102 further includes a spray dryer computing device 124.

[0064] The spray dryer computing device 124 is adapted to monitor and control a plurality of process parameters of the spray drying operation. The spray dryer computing device 124 further includes a plurality of user interfaces. For example, one user interface may allow an operator to input data (e.g., operator information, liquid sample information, dried sample information, etc.), command functions (e.g., start, stop, etc.). Another user interface may display status information regarding components of the spray dryer device (e.g., operating normally, replace, etc.) and/or spray drying process information (e.g., ready, in-process, completed, error, etc.).

[0065] The spray dryer device 102 records one or more parameters associated with a spray drying operation. Examples of these parameters includes, but are not limited to, bibliographic information regarding the blood plasma which is spray dried (e.g., lot number, collection date, volume, etc.), bibliographic information regarding the spray drying operation (e.g., operator, date of spray drying, serial number of the spray dryer assembly 104, volume of dried plasma, etc.), process parameters (e.g., flow rates, temperatures, etc.). Upon completion of a spray drying operation, the spray dryer device 102 communicates a selected portion or all the collected information to the blood bank computer system or other suitable computing device 150.

[0066] For example, a spray drying system 100 may be housed in a blood bank facility. The blood bank facility receives regular blood donations for storage. Liquid plasma is separated from whole blood donations, dried using the spray drying system 100 and subsequently stored until use.

[0067] In an alternative embodiment, illustrated in FIG. 1B, a plurality of spray dryer systems 100A, 100B . . . 100N can be used in combination with a pooled plasma source 112. In general, a pooled plasma source 112 is a bulk source of blood plasma having a volume larger than one blood unit, as known in the art (e.g., approximately 1 pint or 450 mL). Two or more of the spray dryer systems 100A, 100B . . . 100N can operate concurrently, each drawing blood for spray drying from the pooled plasma source 112, rather than a smaller, local blood source.

[0068] The spray dryer systems 100A, 100B . . . 100N in a pooled environment can operate under the control of a computing device 124. The computing device 124 is similar to computing device 124 discussed above, but adapted for concurrent control of each of the spray dryer systems 100A, 100B . . . 100N. The spray dryer computing device 124 further communicates with a remote computing device 150, as also discussed above.

[0069] The use of a pooled plasma source 112, provides advantages over a smaller, local plasma source, such as plasma source 112. When pooled prior to drying, the pooled liquid plasma can be treated for pathogen inactivation with UV light, a chemical, and the like. The pooled liquid plasma is dried using one or more spray drying systems 100 of the present invention and then the dried plasma can be collected in a single collection chamber or a plurality of collection chambers. If the pooled plasma is dried for human transfusion, then each collection container can be configured with an attached rehydration solution. If the pooled plasma is to be used for fractionation purposes, then it is collected in a configured without the rehydration solution. Further embodiments of a spray dryer device 102 for use with the disclosed spray dryer assembly 104 may be found in U.S. patent application Ser. No. 13/952,541, filed on Jul. 26, 2013 and entitled "Automated Spray dryer," the entirety of which is hereby incorporated by reference.

[0070] FIG. 2A and 2B illustrate embodiments of the spray dryer assembly 104 in greater detail. As illustrated in FIG. 2A, the spray dryer assembly 104 includes a frame 202. An
enclosure or body 204 having first and second ends 208A & 208B further extends about and encloses the frame 202. Thus, the body 204 adopts the shape of the frame 202. The enclosure 204 may further include a dual layer of film sealed together about the periphery of the frame 202.

In certain embodiments, the frame 202 may define a first portion 206A, a second portion 206B, and a third portion 206C of the assembly 104. The first portion of the assembly 206A is positioned adjacent the first end 208A of the body 204. The third portion of the assembly 206C is positioned adjacent to the second end 208B of the enclosure 204. The second portion of the assembly 206B is interposed between the first and third portions of the assembly 206A, 206C.

The frame 202 further defines first and second transition zones 210A, 210B between the first, second, and third portions of the assembly 206A, 206B, 206C. For example, the first transition zone 210A may be positioned between the first and second portions of the assembly 206A, 206B, and the second transition zone 210B may be positioned between the second and third portions of the assembly 206B, 206C. In certain embodiments, the frame 202 may narrow in width, compared to the width of the surrounding assembly within the transition zones 210A, and/or 210B. The relatively narrow transition zones 210A, 210B help to direct the flow of drying gas 116A through the assembly 104.

In further embodiments, the body 204 may include a drying gas inlet 212, adjacent to the first end 208A. The drying gas inlet 212 may be adapted to couple with the spray dryer device 102 to form a hermetic and sterile connection that allows the flow of drying gas 116A to enter the assembly 104. In one embodiment, illustrated in FIG. 2A, the drying gas inlet 212 is positioned within the first portion of the assembly 206A, at about the terminus of the first end of the body 208A. In this configuration, the flow of drying gas 116A is received within the assembly 104 in a direction approximately parallel to a long axis 250 of the assembly 104.

In an alternative embodiment of the spray dryer assembly 104, illustrated in FIG. 2B, the body 204 may include a drying gas inlet 212. The position of the drying gas inlet 212 is moved with respect to drying gas inlet 212. For example, the drying gas inlet 212 may be positioned within the first portion of the assembly 206A and spaced a selected distance from the terminus of the first end of the enclosure 208A. In this configuration, the flow of drying gas 116A may be received within the assembly 104 in a direction that is not parallel to the long axis 250 of the assembly 104. For example, in a non-limiting embodiment, the flow of drying gas 116A is received within the assembly 104 in a direction that is approximately perpendicular to the long axis 250 of the assembly 104.

In certain embodiments, the spray dryer assembly 104 may further include a removable cover 218. The cover 218 may be employed prior to coupling of the spray dryer assembly 104 with the spray dryer device 102 in order to inhibit contaminants from entering the spray dryer assembly. In certain embodiments, the cover 218 may be removed immediately prior to coupling with the spray dryer device 102 or frangible and penetrated by the spray dryer device 102 during coupling with the spray dryer assembly 104.

The drying gas 116A received by the assembly 104 is urged to travel from the first portion 206A, through the second portion 206B, to the third portion 206C, where it is removed from the assembly 104. As the drying gas 116A travels within the first portion of the assembly 206A towards the second portion of the assembly 206B, the drying gas 116A passes through a first filter 220A which filters the drying gas 116A entering the assembly 104 in addition to any filtering taking place within the spray dryer device 102 between the drying gas source 116 and the drying gas inlet 212. In certain embodiments, the first filter 220A is a 0.2 micron filter having a minimum BFE (bacterial filter efficiency) of 10%. The filter 220A further helps to ensure the cleanliness of the flow of drying gas 116A.

In an embodiment, during primary drying, the flow of drying gas BFE received by the spray dryer assembly BFE may possess a temperature between about 50°C and about 150°C, and a flow rate of between about 15 CFM to about 35 CFM. The flow of aerosolizing gas 116A can possess a flow rate of between about 5 L/min and about 20 L/min and a temperature between about 15°C to about 30°C (e.g., 24°C). The flow of liquid sample 112A may possess a flow rate of between about 3 ml/min to about 20 ml/min. As the plasma is dried, the flow of the aerosolizing gas 114A, the flow of drying gas 116C, or both may direct the flow of the dried sample 232 through at least a portion of the spray dryer assembly 104 (e.g., the drying chamber, the collection chamber or both).

In an embodiment, the assembly 104 may further include a spray drying head 104A, a drying chamber 1043, and a collection chamber 104C in fluid communication with one another. The spray drying head 104A may be mounted to the frame 202 and positioned within the first transition zone 210A. So positioned, the spray drying head 104A is also positioned within the flow of drying gas 116A traveling from the first portion of the assembly 206A to the second portion of the assembly 206B. The spray drying head 104A may be further adapted to receive the flow of plasma 112A and the flow of aerosolizing gas 114A through respective feed lines 214, 216 and output aerosolized plasma 230 to the drying chamber 1043.

In further embodiments, the drying chamber 1043 and collection chamber 104C may be positioned within the second and third portions of the assembly 206B, 206C, respectively. The drying chamber 1048 infuses the pressure of the flow of drying gas 116A and provides space for the aerosolized blood plasma 230 and the flow of drying gas 116A to contact one another. Within the drying chamber 1043, moisture is transferred from the aerosolized blood plasma 230 to the drying gas 116A, where the drying gas 116A becomes humid drying gas 234. The aerosolized flow of blood plasma 230 and the flow of drying gas 116A are further separated, within the drying chamber 1043, into dried plasma 232 and humid drying gas 234. In certain embodiments, the dried plasma 232 may possess a mean diameter of less than or equal to 25 µm.

The humid drying gas 234 and dried plasma 232 are further drawn into the collection chamber 104C through an inlet port 222A of the collection chamber 104C, positioned within the second transition zone 210B, connecting the collection chamber 104C and the drying chamber 1043. The collection chamber 104 includes a second filter 220B which allows through-passage of the humid drying gas 234 and inhibits through-passage of the dried plasma 232. As a result, the humid drying gas 234 passing through the filter 220B is separated from the dried plasma 232 and exhausted from the collection bag 104C through an exhaust port 222B of the collection chamber 104C that forms the second end 208B of the body 204. For example, a vacuum source (e.g., a vacuum
pump) may be in fluid communication with the exhaust port 222B of the collection chamber 104C to urge the humid drying gas 234 through exhaust port b. Concurrently, the dried plasma 232 is retained in a reservoir 228 of the collection chamber 104C. The collection chamber 104C is subsequently hermetically sealed at about the inlet and exhaust ports 222A, 222B, and detached (e.g., cut) from the spray dryer assembly 104, allowing the collection chamber 104C to function as a storage vessel for the dried plasma 232 until use.

With reference to FIG. 3, the collection chamber 104C further includes a plurality of one-way valves 702A, 702B positioned at about the inlet port 222A and the exhaust port 222B, respectively. The one-way valve 702A may function to permit gas flow from the drying chamber 104B to the collection chamber 104C and inhibit gas flow from the collection chamber 104C to the drying chamber 104B. The one-way valve 702B may function to permit gas flow from the collection chamber 104C while inhibiting gas flow into the collection chamber 104C via the exhaust port 222B.

The collection chamber 104C may be further configured for use in rehydrating the dried plasma 232. For example, the collection chamber 104C may include a rehydration port 224, a plurality of spikes ports 226, and a vent port 228. The rehydration port 224 may be used to communicate with a source of rehydration solution, allowing the rehydration solution to come in contact with the dried plasma 232 within the collection chamber 104C to form reconstituted plasma. The reconstituted plasma may be subsequently drawn from the collection chamber 104C through the spike ports 226.

The temperature of the collection chamber 104C may be regulated by measuring the temperature of the humid exhaust gas 234A as it exits the collection chamber 104C. One or more of the flow rate of the drying gas 116A, and the temperature of the drying gas 116A may be adjusted, based upon the temperature of the humid exhaust gas 234A, to maintain the collection chamber 104C at temperatures less than about 70° C, and preferably at about 50° C to about 60° C, or about 55° C.

Control of the Spray Drying Process via Control of the Exhaust Temperature

Spray Drying System
The purpose of this section is to describe the design of the process flow and software for the Velco Spray Dry Plasma (SpDP) system and derive the software-specific requirements from higher-level requirements. This description is exemplary only and those of ordinary skill in the art will be able to develop variations and improvements based on the teachings of this application.

Architecture

Hardware Description: See, FIG. 5. The Spray-Dry Plasma (SpDP) control system runs on a small computer capable of running, for example, the open-source Linux operating system. This computer is connected to a LabJack U6/I/O controller via USB. This computer is connected via Ethernet to all external systems including a computer used to provide the web-based user interface.

Automation Software: The automation software is responsible for controlling the spray-dry process. The master state machine controls the sequence of operations required to conduct the drying process. There are individual controllers for the subsystems that require active feedback to achieve specific set points during the drying process.

The update cycle runs at approximately 10 Hz. During each update the values of the sensors are read, the control system computations are executed, and the new output values are written out. Data is logged to an internal database which may be accessed by the blood center computer systems and/or the web user interface described next.

User Interface Software: The user interface to the spray-dry instrument is implemented as web pages served by the automation computer. Any computer running a web browser may be used to access the user interface pages provided the user authentication is successful.

Automation Software Design

Main State Machine, see FIG. 6

Off/On—These states do not have any software associated with them.

Self-Test—In the self-test state the operating system is booted up and diagnostic tests are performed to ensure that the hardware is functioning correctly.

Ready—In this state the system is ready to dry and waiting for the disposable to be loaded.

Disposable Integrity Test—Once the disposable (the disposable comprises a self-contained spray dry chamber and product collection bag) has been loaded the system conducts an integrity test to ensure that the disposable is loaded properly and not leaking.

Drying, see FIG. 7

Startup—In this state the air dryers are started with the drains open and the aerosol controller is started.

Starting Dryers—This state waits for a specific period of time to allow the aerosol compressed air to come up to pressure and the dryers to start operating. Once this period of time has elapsed...

The dryer drains are closed. The drying gas flow rates is set for drying and the controller is enabled. The heater controller set point is set for drying and the controller is enabled. The aerosol gas flow rate is set for drying.

Starting Drying Gas—In this state the drying gas is coming up to speed and temperature. The criteria for moving on to the next state are:

Drying gas temperature more than 85% of the target temperature for drying. Drying gas flow rate more than 85% of the target flow rate for drying. Start-up exhaust temperature observed by T5 more than 65° C.

Once these conditions are satisfied, the peristaltic pump flow rate is set to half of the value which will be used for drying. Fluid Half-Speed—In this state the fluid is running at half the rate which will be used for drying. To move onto the next state the drying gas temperature must be at the target set point for drying.

Fluid Full-Speed—This is the primary state for drying the full unit of plasma. The scale value is monitored and when the full unit has been processed the state moves forward to the Finished state.

Finished—This state is entered upon successful completion of drying the full unit of plasma.

Aborted—This state is entered if any of the consistency checks performed during the drying process fail and the unit must be discarded.

Stopping—This state turns off the drying equipment as follows:

Air dryers are powered off

Drying gas pump is stopped

Heater power is turned off
The peristaltic pump is switched to reverse to back the plasma away from the spray nozzle and prevent dripping of liquid plasma into the dry product.

Stopped—This state completes the shut-down process by turning off the peristaltic pump and shutting down its controller.

Controllers—All of the controllers except the peristaltic pump controller use a PID (Proportional/Integral/Derivative) control loop with the gains chosen to provide the performance required by the spray-dry system. The peristaltic pump has its own controller so the set point is just transformed to an analog set point value.

Aerosol—The aerosol controller maintains a flow set point by monitoring the flow sensor F1 and controlling the PWM and cycle of the variable valve V2. The aerosol controller also maintains pressure in the pneumatic reservoir by controlling the aerosol gas pump and the soft-start valve V5. A feed-forward term is used to compensate for the changing pressure observed at P1, which goes up quickly when the aerosol gas pump is running and drops slowly when the aerosol gas pump is off.

Drying Gas—The drying gas controller maintains a flow set point by monitoring the flow sensor F2 and controlling the analog voltage to the drying gas pump motor controller.

Heater—The heater controller maintains a temperature set point for the drying gas by monitoring the temperature sensor T5 and modulating the power to the heater. The heater power is modulated with a duty cycle of approximately 1 Hz to provide reasonably good time resolution with the heater power switching on zero crossings at the 60 Hz (or 50 Hz) power line frequency.

Peristaltic Pump—The peristaltic pump controller transforms the commanded flow rate into a analog voltage command for the pump controller. There are also two digital lines for forward/reverse and brake. The forward/reverse line is controlled based on the sign of the flow rate. A negative flow rate can be used to back up the pump and prevent liquid from dripping out of the spray nozzle at the end of the drying cycle. The brake is set when the flow rate is zero to completely stop the pump.

Exhaust Gas—The exhaust gas controller maintains a set exhaust temperature by monitoring the temperature sensor T6 and adjusting the set point of the drying gas flow controller. A higher flow rate results in a higher exhaust temperature. The flow rate is controlled rather than the drying gas temperature because it is much quicker to respond as necessary to maintain the exhaust gas temperature set point.

The error value used by this controller is the difference between the exhaust gas temperature observed at T6 and the set point (°C). The controller determines an offset to apply to the drying gas flow rate set point. The gains used by the controller are:

- Proportional gain: -40.0
- Integral gain: -0.1
- Derivative gain: 0.0 (the derivative gain is not used)

The output of this controller is limited to the range -150.0 L/min to +150.0 L/min adjustment to the commanded flow rate. The error integrator is saturated at a value that would maximize the controller output. This prevents the integrator from winding up significantly when the controller is unable to achieve the set point.

Data Logging—The following data is logged to a database on the automation computer:

- Date and time the spray-dry process is initiated
- Any data configured for capture by the blood center, possibly including any or all of the following:
  - Operator ID
  - Donation ID
  - Disposable ID
  - Moisture barrier bag ID
  - All sensor values at 1 Hz during the drying process

Success or failure of the drying process

User Interface Software Design

Web Pages and Data Flow—The user interface web pages are generated by CGI programs written in C++. Communication between these user interface web pages and the automation software is accomplished using POSIX queues. The automation software creates the queues and publishes the data while the system is running to the monitor queues. It also listens for input from the user interface on the command queues.

Automated Drying—The automated drying user interface contains the minimal controls and status information required by an operator to conduct the drying process.

Diagnostics—The diagnostics user interface shows all of the sensor values and controller set points in real time while the system is operating. This facilitates process development and diagnosis of hardware issues.

Data Access—The data access user interface allows downloading of data stored in the automation computer database.

Drying Gas Control, See, FIG. 8

The drying gas control system takes air from outside environment and conditions it for use as drying gas. The air is filtered, dehumidified and heated as it is pumped at a controlled flow rate through the system. P.S.—pressure sensor; T.S.—temperature sensor; N.O.—valve. The specific components in this flow path are:

- P3: Ambient pressure (absolute)
- HEPA: High-efficiency filter
- P4 Pressure after the filter, used to compute the pressure drop across the filter and determine when it must be changed.
- T1, H1: relative humidity and temperature of the incoming air flow
- AD1: dehumidifier to remove moisture from the incoming air flow
- F2: This flow sensor is used to control the pump speed for a fixed drying gas flow rate
- T2: Temperature before the pump
- P5: Pressure before the pump; this is used to determine the pressure drop across the dehumidifier and the pressure increase by the pump
- P6: Pressure after the pump
- T3: Temperature after the pump. There is a significant temperature increase due to compression by the pump.

HEPA: this 0.2 um filter removes any particulate that may have been generated by the pump

P10: Pressure after first HEPA filter.

HEPA: this 0.2 um filter provides additional filtration of the drying gas. There should be no particulate from the pump by this point because it should be removed by the first HEPA filter after the pump.
This valve can block the drying gas flow path at the end of the drying process to facilitate removal of air from the drying chamber. This is the pressure presented to the head of the drying disposable. This valve is used for consistency checking to ensure proper performance of the disposable during the drying process. Temperature prior to entering the heater. This heater brings the drying gas up to the correct temperature. This temperature sensor is used to control the heater and achieve the correct drying gas temperature. The spray-dry process requires consistent flow and temperature of the drying gas so both of these attributes are actively controlled. The drying gas flow rate is measured by the flow sensor F2 and a feedback loop controls the motor speed to achieve the correct drying gas flow rate. The temperature is measured by the temperature sensor T5 and a feedback loop controls the heater power to achieve the correct drying gas temperature.

The drying gas leaving the disposable contains all of the moisture that was evaporated from the plasma. The exhaust gas management system incorporates a secondary dehumidifier to remove this moisture. The exhaust gas management system also incorporates a back-up filter and instrumentation to monitor the performance of the drying process. N.C. = control valves; RSH = humidity sensor; F.S. = flow sensor. The specific components in this flow path are:

Temperature of the drying gas as it leaves the disposable. This value is used to monitor the performance of the drying process.

Pressure leaving the disposable: this is used to compute the pressure drop across the full HEPA filter to determine when it needs to be replaced.

Venturi vacuum: once the drying process is complete, the valve N.O. is closed and then the vacuum pump may be used to evacuate the air from the disposable.

This valve is used to close off the disposable from the system exhaust as noted earlier.

These valves control access from the flow path to the venturi vacuum pump. These valves are closed during normal operation and disposable integrity testing, and are opened to facilitate evacuation of the air from the drying chamber and the collection filter bag.

This 0.1 um filter ensures that any biohazard material that escapes from a failed disposable collection filter cannot leave the system.

This is the final pressure, used to compute the pressure drop across the HEPA filter and also the pressure drop across the final air dryer.

This dehumidifier removes the water which was evaporated from the plasma.

These sensors monitor the final humidity and temperature of the exhaust gas prior to release from the system.

This exhaust flow sensor is used to cross-check with the drying gas inlet and aerosol gas flow sensors.

Process development experiments conducted by the inventors have shown that the temperature of the drying gas as it passes through the collection bag is a key parameter with respect to preservation of the coagulation factor proteins. The system design addresses this issue by creating an outer control loop to maintain the temperature of the drying gas as it leaves the collection bag. The control loop feeds back this temperature and increases the drying gas flow to bring the final temperature up or reduces the flow to bring the final temperature down.

Mechanical, See, FIGS. 10 and 11

Operator Interface—The spray-dry unit has mechanical features to facilitate hanging the incoming plasma unit, mounting the drying disposable, loading and clamping the plasma tube in the peristaltic pump, and removing the disposable components after the drying process is completed.

Disposable Mounting and Constraint—The disposable drying chamber has connections at the top for the plasma feed, aerosol gas feed, and drying gas feed. It has a connection at the bottom for the exhaust gas. The system constrains the disposable so it may inflate only to the volume required by the drying process. This minimizes the mechanical strength required of the disposable, allowing the use of a relatively thin material which may soften somewhat during the drying process without losing its integrity and leaking.

Heater Connections—The heater assembly is comprised primarily of stainless steel for strength and heat resistance. This structure has a relatively large thermal mass so it takes some time to come up to operating temperature or cool back down to the temperature of the ambient environment. This heat-up and cool-down time is decoupled from the processing cycle by leaving the heater assembly hot while the disposable is changed between cycles. There is a thermal break between the heater and the disposable interface so the operator is not exposed to hot surfaces that are unsafe to touch between cycles.

Drying Instrument Filters—The filters incorporated into the drying instrument provide an additional level of protection for the plasma being processed.

The air used for drying gas is cleaned before it enters the disposable. The drying disposable incorporates its own additional filtering. The region of the instrument where the disposable docking is performed is additionally protected by filtered laminar air flow to significantly reduce any bio-burden that might be introduced while docking the disposable.

Service Interface—The system is designed to facilitate routine maintenance by trained personnel at the customer facility.

Filters—The HEPA filters which are incorporated into the device are designed to be changed by trained service personnel as necessary. The drying system monitors pressure drops across the filters and reports to the operator when a filter needs to be changed.

SUMMARY


Ranges of values include all values within the range not specifically mentioned. For example, a range of “20% or
greater” includes all values from 20% to 100% including 35%, 41.6%, 67.009%, etc., even though those values are not specifically mentioned.

The term “about,” such as “about 20%” or “about pH 7.6,” shall mean ±1%, ±2%, ±5%, or ±10% of the value given.

Example 1

Plasma Protein Activity Correlated with Drying Gas Exhaust Temperature

We found that the most important parameter with respect to protein viability in dried plasma was the drying gas exhaust temperature. If dried plasma is exposed to an exhaust temperature higher than 60°C, even briefly, plasma protein activity degrades. Please note, during the drying process the surface of the wet plasma droplets is exposed to 125°C but the droplet remains cool due to the evaporation process. A significant improvement in process consistency was achieved by actively controlling the exhaust temperature by varying the speed of the drying gas pump and, thus, the flow rate of the drying gas through the spray drying apparatus.

When bleeding occurs, the body causes coagulation factors, such as Fibrinogen and/or Factor V, to combine and produce a clot which stops bleeding. Insufficient protein activity may impair clot formation, resulting in excessive bleeding. Accordingly, it is desirable that the protein activity of dried plasma is relatively unchanged as compared to its liquid state. When these blood proteins are damaged, such as by exposure to elevated temperature during plasma drying, measured protein activity is reduced.

Residual moisture and protein activity generally decreased as exhaust temperature increased. Our data indicate that Fibrinogen and Factor V are the elements most sensitive to temperature, with activity reductions of 40% and 19%, respectively, when the exhaust temperature was 70°C. FIG. 12 represents the ratio of the protein activity of dried plasma to the protein activity of the liquid plasma and may vary between 1.0 to 0. High values of normalized protein activity, approaching 1.0, indicate that the proteins within the dried plasma are relatively undamaged, as compared to the liquid plasma. In contrast, low values of normalized protein activity, approaching 0, indicate that the proteins within the dried plasma are relatively damaged, as compared to the liquid plasma.

With exhaust temperatures in the range of 55-60°C, all protein activity measurements were within 15% of native plasma, with moisture content at about 4.5%. FIG. 12 plots the normalized protein activity as a function of temperature within the range between 55°C to 70°C. As noted below, collection chamber temperature correlates with collection bag exhaust temperature and is about 3°C higher than the exhaust temperature. Thus, collection bag temperature and collection bag exhaust temperature are proxies for each other. FIG. 12 shows that protein activity increases for each of Fibrinogen and Factor V as the collection chamber temperature decreases from about 70°C to about 55°C. For example, the normalized activity of Fibrinogen increases from about 0.60 to about 0.925, while the normalized activity of Factor V increases from about 0.83 to about 0.97 over this range. Accordingly, embodiments of the drying processes discussed herein should be performed such that the temperature of the collection chamber is about 55°C.

Example 2

Controlling Exhaust Gas Temperature Maintains Consistent Spray Drier Temperature

In this study, 220 mL of plasma was spray dried on the Velico Medical Alpha 1 spray drier apparatus using the configuration shown in FIG. 8. Input parameters were as follows: Plasma flow fluid rate: 10 mL/minute; Aerosol gas flow rate: 20 L/minute; Drying gas initial temperature: 125°C; Drying gas flow rate 550-750 L/minute; Drying gas exhaust temperature: 52°C. The exhaust gas temperature was maintained at about 52°C by varying the drying gas flow rate.

To map the gradient in the spray drier during spray drying, temperature probes were placed at the drying head, the inlet of the collection filter bag and at the exhaust of the collection filter bag. In FIG. 9, temperature sensor T5 measures the inlet drying gas temperature; temperature sensor T6 measures the inlet collection filter bag temperature; temperature sensor T7 measures the exhaust gas temperature as it leaves the collection filter bag. Pressure sensor P7 measures the pressure generated during the spray drying process. The temperature difference between the T5 and T8 temperature sensors shows the temperature drop caused by the drying process and released of moisture from the aerosolized plasma droplets.

FIGS. 13, 14 and 15 show the results of three separate experiments. The results show that by maintaining the exhaust gas temperature as a constant 52°C, the temperature at the drying gas inlet and at the inlet of the collection filter bag were also constant.

Example 3

Plasma Powder Moisture Correlated with Exhaust Gas Temperature

The correlation between spray drier exhaust gas temperature and moisture content of the spray dried plasma was determined. Spray dryer parameters used were

- Drying Gas Flow Rate: 600-850 L/min
- Drying Gas Initial Temperature: 125-135°C
- Drying Gas Exhaust Temperature: 30-70°C
- Fluid Flow Rate: 8-10 ml/min

Velico Medical Alpha 1 Spray Dryer

Exhaust gas temperature was controlled at various temperatures from 30°C to 70°C. Residual moisture in the dried plasma was measured by the Karl Fischer method for dried plasma collected in the collection filter. FIG. 16 shows the residual moisture content of the dried plasma ranged from about 15% when the exhaust temperature was maintained at about 30°C to about 4.0% when the exhaust temperature was maintained at about 70°C. As indicated above, when the spray drier was operated to keep the exhaust gas temperature from about 55-60°C, the plasma protein activity was measured to be within 15% of the native protein. Likewise, preferred residual moisture content of from about 4% to about 6% was obtained when the exhaust gas temperature was maintained from about 60°C to about 52°C, respectively. Thus, the present invention contemplates operating the spray drier apparatus so that the exhaust gas temperature ranges from about 52°C to about 60°C with the preferred exhaust gas temperature being from 54°C to 58°C or about 55°C.

When taken together, the results of Examples 1, 2 and Example 3 show that maintaining the exhaust gas temperature at a predetermined temperature (temperature range)
results in a suitably dried plasma powder with acceptable plasma protein activity recovery.

We Claim:

1. A method of controlling the moisture content of a spray dried plasma, the method comprising:
   a) providing: i) plasma, and ii) a spray drying apparatus, comprising, a mechanism for aerosolizing the plasma, a mechanism to deliver drying gas at a controlled rate, a drying chamber, a collection chamber and a sensor for measuring exhaust gas temperature as it emerges from the drying process;
   b) operating the spray drying apparatus to produce a moisture controlled spray dried plasma, said operation comprising controlling the moisture content of the spray dried plasma collected in the collection chamber by measuring the exhaust gas temperature with the sensor for measuring exhaust gas temperature and adjusting the flow of the drying gas based on the exhaust gas temperature wherein the flow of the drying gas is increased to increase the exhaust gas temperature and decrease the moisture content of the spray dried plasma; and the drying gas flow is decreased to decrease the exhaust gas temperature and increase the moisture content of the spray dried plasma, thereby producing a moisture controlled spray dried plasma, wherein the moisture content of the moisture controlled spray dried plasma is approximately 4 w/w % to approximately 10 w/w %.

2. The method of claim 1, wherein said moisture content of the moisture controlled spray dried plasma is approximately 4 w/w % to approximately 8 w/w %.

3. The method of claim 1, wherein said exhaust gas temperature is maintained at a set point in the range of from approximately 45° C. to approximately 65° C.

4. The method of claim 1, wherein said exhaust gas temperature is maintained at a set point in the range of from approximately 50° C. to approximately 60° C.

5. The method of claim 1, wherein said exhaust gas temperature is maintained at a set point of approximately 55° C.

6. The method of claim 1, wherein said drying gas has a temperature of about 100° C. to 150° C. when it starts to mix with the aerosolized plasma.

7. The method of claim 1, wherein said drying gas flow is maintained at approximately 500 L/min to approximately 1000 L/min during the process for producing the moisture controlled spray dried plasma.

8. The method of claim 1, wherein said drying process is controlled by a computer.

9. The method of claim 1, wherein the flow rate of the drying gas flow rate and percent moisture of the moisture controlled spray dried plasma is based on previously collected data.

10. The method of claim 1, wherein said plasma is whole blood (WB) plasma or citrate phosphate dextrose (CPD) plasma.

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