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(54) Title: SPRAY-DRYING PROCESS

(57) Abstract: The process comprises delivering a spray solution comprising an active agent and a matrix material in an organic solvent to a spray-drying apparatus, atomizing the spray solution into droplets within the spray-drying apparatus to remove at least a portion of the organic solvent from the droplets to form a plurality of particles, and collecting the particles. The spray solution may be formed by forming a feed suspension comprising the active agent, the matrix material, and the organic solvent, wherein the feed suspension is at a temperature T_1, and directing the feed suspension to a heat exchanger, thereby increasing the temperature of the feed suspension to a temperature T_2, wherein T_2 is greater than T_1, and the spray solution is at a pressure greater than the vapor pressure of the organic solvent at T_2, such that the active agent and matrix material are soluble in the organic solvent at T_2.

SPRAY-DRYING PROCESS

CROSS REFERENCE TO RELATED APPLICATION

The present application claims the benefit of United States Provisional Patent Application No. 61/164,353, filed March 27, 2009, which is incorporated herein in its entirety by reference.

BACKGROUND

A novel spray-drying process is disclosed. The process can lead to spray-dried products with improved properties, as well as increased throughput relative to conventional spray-drying processes.

The use of spray drying to produce powders from fluid feed stocks is well known, with applications ranging from powdered milk to bulk chemicals and pharmaceuticals. See U.S. Patent No. 4,187,617 and Mujumbar et al., *Drying* 91, pages 56-73 (1991). See also Masters, *Spray Drying Handbook*, pages 263-268 (4th edition, 1985). The use of spray drying to form solid amorphous dispersions of drugs or active agents and concentration-enhancing polymers is also known. See commonly owned U.S. Patent Nos. 6,763,607 and 6,973,741.

When it is desired to form a spray-dried product in which the drug or active agent is amorphous, it is desirable to have the active agent fully dissolved in the spray solution when it is atomized into droplets. Specifically, when it is desired to form a spray-dried product in which the amorphous active agent is dispersed in one or more other materials, termed matrix material, it is generally desired to have at least a part and often all of the matrix material also dissolved in the spray solution. In such cases, the throughput of a conventional spray-drying process is often limited by the amount of active agent and matrix material that can be dissolved in the spray solution. It is generally known that the solubility of many substances, such as active agents and matrix materials, often increases as the temperature of the solvent is increased. However, industry avoids using elevated temperatures when using organic solvents, due to the inherent dangers and safety concerns when processing organic solvents, which are often flammable at high temperatures. In addition, conventional spray-drying processes avoid use of elevated temperatures out of

concern for the thermal stability of the active agent and matrix material—degradation of the active agent and/or the matrix material can lead to unwanted breakdown products in the particles produced.

Because of this, conventional spray-drying solutions are generally kept at or near room temperature when entering the spray nozzle. This limits the throughput of the process due to the often low solubility of active agents and matrix materials in the solvents used. In addition, when the solubility of the active agent in the spray solution is low, the active agent is often dissolved to near its solubility limit to achieve as high a throughput as possible. The spray-dried products obtained from such solutions are often not homogeneous. Finally, conventional spray-dried processes often produce products that suffer from not being homogeneous because the rate of solvent removal is not sufficiently fast, and broad ranges of particle sizes are produced because the atomization means produces a wide range of droplet sizes.

U.S. Patent Application Publication No. 2008/0248114A1 describes the production of solid solutions containing poorly-soluble active substances using a spray-drying process utilizing short-term heating and rapid drying. The process avoids organic solvents by utilizing a feed stream that is an aqueous suspension of the active. The aqueous suspension is heated to allow dissolution of the active in the spray solution. However, this process is limited to actives that have a high solubility in water at elevated temperature.

What is needed is a spray-drying process that results in improved properties of the spray-dried product, such as a higher degree of homogeneity and more uniform particle size, and that improves the throughput of spray-drying equipment while spraying solutions of an active agent and the matrix material, and provides a safe, reproducible process to produce high-quality product. Such a process promises to increase the quality and decrease manufacturing costs for spray-dried products.

SUMMARY

A process for increasing the throughput of a spray drier comprises (a) delivering a spray solution comprising an active agent and a matrix material in an organic solvent to a spray-drying apparatus, (b) atomizing the spray solution into droplets within the spray-drying apparatus to remove at least a portion of the organic

solvent from the droplets to form a plurality of particles, and (c) collecting the particles. The spray solution is formed by forming a feed suspension comprising the active agent, the matrix material, and the organic solvent, wherein the feed suspension is at a temperature T_1, and directing the feed suspension to a heat exchanger, thereby increasing the temperature of the feed suspension to a temperature T_2, wherein (i) temperature T_2 is greater than temperature T_1, and (ii) the spray solution is at a pressure that is greater than the vapor pressure of the solvent at temperature T_2, such that substantially all of the active agent in the spray solution and at least a portion of the matrix material are soluble in the solvent at temperature T_2.

In one embodiment, temperature T_2 is greater than the ambient-pressure boiling point of the organic solvent.

In another embodiment, the nozzle used for atomization of the spray solution is a pressure nozzle. In another embodiment, the nozzle used for atomization of the spray solution in the spray-drying apparatus is a flash nozzle. A flash nozzle utilizes a pressure drop that induces cavitation in the spray solution prior to exiting the nozzle orifice to induce droplet formation. A sweep gas around the orifice is used to eliminate or reduce solids build-up during operation.

In another aspect, the matrix material comprises a polymer.

In still another aspect, the particles comprise a solid amorphous dispersion of the active agent and a polymer.

The disclosed processes provide one or more advantages over a conventional spray-drying process. Certain embodiments of the disclosed processes can increase the throughput of a spray dryer by forming a spray solution that has a higher concentration at a higher temperature than conventional processes. Additionally, certain embodiments of the disclosed processes allow spray-drying solutions wherein ratio of the concentration of active agent in the spray solution to the solubility of the active agent in the organic solvent at the atomization temperature is significantly less than one, preferably less than 0.5, and even more preferably less than 0.3. Operating in this regime generally leads to spray-dried products that are more homogeneous and more uniform. In addition, the disclosed processes result in rapid evaporation of the organic solvent, and shorter times to solidification than

conventional processes. Furthermore, in some embodiments, the process results in improved atomization of the spray solution relative to conventional processes due to the temperature of the spray solution when it is atomized being above the boiling point of the solvent at the pressure of the drying chamber.

BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWINGS

FIG. 1 is a schematic of a spray-drying apparatus suitable for use in performing the process of the invention.

FIG. 2 is a schematic of a flash nozzle, suitable for use in performing the process of the invention.

FIG.3 is a figure showing the results of powder X-ray diffraction of the samples of Example 1, Control 1, and Control 2.

DETAILED DESCRIPTION

A spray-drying process for producing a composition comprising an active agent and a matrix material is described. The spray-drying process, suitable apparatus for carrying out the process, and suitable active agents and matrix materials are described in detail below.

Unless otherwise indicated, all numbers expressing quantities of components, molecular weights, percentages, temperatures, times, and so forth, as used in the specification or claims are to be understood as being modified by the term "about." Accordingly, unless otherwise indicated, implicitly or explicitly, the numerical parameters set forth are approximations that may depend on the desired properties sought and/or limits of detection under standard test conditions/methods. When directly and explicitly distinguishing embodiments from discussed prior art, the embodiment numbers are not approximates unless the word "about" is recited.

Spray-Drying Process

The term spray drying is used conventionally and broadly refers to processes involving breaking up liquid mixtures into small droplets (atomization) and rapidly removing solvent from the mixture in a container (drying chamber) where there is a strong driving force for evaporation of solvent from the droplets. The strong driving

force for solvent evaporation is generally provided by maintaining the partial pressure of solvent in the spray-drying apparatus well below the vapor pressure of the solvent at the temperature of the drying droplets. This is accomplished by (1) mixing the liquid droplets with a warm drying gas, (2) maintaining the pressure in the spray-drying apparatus at a partial vacuum (e.g., 0.01 atm to 0.50 atm), or (3) both.

Generally, the temperature and flow rate of the drying gas is chosen so that the droplets of spray solution are dry enough by the time they reach the wall of the apparatus that they are essentially solid, form a fine powder, and do not stick to the apparatus wall. The actual length of time to achieve this level of dryness depends on the size of the droplets and the conditions at which the process is operated. Droplet sizes may range from 1 μm to 500 μm in diameter, the size being dependent on the desired particle size of the spray dried powder. The large surface-to-volume ratio of the droplets and the large driving force for evaporation of solvent lead to actual drying times of a few seconds or less, and often less than 0.1 second. Solidification times should be less than 100 seconds, and often less than a few seconds.

Turning to the drawings, wherein the same numerals refer to like elements, there is shown in FIG. 1 an apparatus 10 suitable for performing embodiments of the disclosed processes. In the following discussion it is assumed that the spray-drying apparatus is cylindrical. However, the dryer may take any other cross-sectional shape suitable for spray drying a spray solution, including square, rectangular, and octagonal, among others. The spray-drying apparatus is also depicted as having one nozzle. However, multiple nozzles can be included in the spray-drying apparatus to achieve higher throughput of the spray solution.

The apparatus shown in FIG. 1 includes a feed suspension tank 20, a heat exchanger 30, a drying chamber 40, a nozzle 50, and a particle-collection means 60. In one embodiment, the process is performed as follows. An active agent and a matrix material are combined with an organic solvent in the feed suspension tank 20 to form a feed suspension. The feed suspension is at a temperature T_1, which is below the ambient-pressure boiling point of the organic solvent. Temperature T_1 is also below either T_A, the temperature at which the active agent solubility equals the active agent concentration in the organic solvent, or T_M, the temperature at which

the matrix material solubility equals the matrix material concentration in the organic solvent. At least a portion of the active agent, a portion of the matrix material, or a portion of both the active agent and the matrix material are suspended, that is not dissolved, in the organic solvent. An optional mixing means 22 may be used to keep the feed suspension homogeneous while processing. When the organic solvent is flammable, oxygen is normally excluded from all parts of the drying apparatus. In particular, an inert gas, such as nitrogen, helium, argon, and the like, is often used to fill the void space in the feed suspension tank for safety reasons.

As used herein, the term "feed suspension" means a composition comprising an active agent, a matrix material, and an organic solvent, wherein at least a portion of the active agent, a portion of the matrix material, or a portion of both active agent and matrix material are suspended or not dissolved in the organic solvent. In one embodiment, the feed suspension consists essentially of an active agent, a matrix material, and an organic solvent. In still another embodiment, the feed suspension consists of an active agent, a matrix material, and an organic solvent. In yet another embodiment, the feed suspension consists of particles of active agent suspended in a solution of matrix material dissolved in the organic solvent. It will be recognized that in such feed suspensions, a portion of the active agent and the matrix material may dissolve up to their solubility limits at the temperature of the feed suspension.

As used herein, the term "organic solvent" means an organic compound that can be used to dissolve the active agent and the matrix material at elevated temperature. In one embodiment, the solvent is volatile, having an ambient-pressure boiling point of 150°C or less. In another embodiment, the solvent has an ambient-pressure boiling point of 100°C or less. Suitable solvents include alcohols such as methanol, ethanol, n-propanol, isopropanol, and butanol; ketones such as acetone, methyl ethyl ketone and methyl isobutyl ketone; esters such as ethyl acetate and propyl acetate; and various other solvents, such as tetrahydrofuran, acetonitrile, methylene chloride, toluene, and 1,1,1-trichloroethane. Lower volatility solvents such as dimethylacetamide or dimethylsulfoxide can also be used, generally in combination with a volatile solvent. Mixtures of solvents, such as 50% methanol and 50% acetone, can also be used, as can mixtures with water. In one embodiment, the organic solvent contains less than 50 wt% water. In another embodiment, the

organic solvent contains less than 25 wt% water. In still another embodiment, the organic solvent contains less than 10 wt% water. In yet another embodiment, the organic solvent contains less than 5 wt% water. In another embodiment, the organic solvent contains essentially no water.

For convenience, the feed suspension is often maintained at near-ambient temperatures; however, this is not a limitation of the disclosed processes. Generally, the temperature of the feed suspension, T_1, can range from 0°C to 50°C or even higher. Temperatures of less than 0°C may also be utilized, especially when there are stability concerns about the active agent.

The feed suspension in the feed suspension tank 20 is delivered to a pump 24, which directs the feed suspension to a heat exchanger 30. The heat exchanger has a feed suspension inlet 26, a spray solution outlet 36, a heating fluid inlet 32, and a heating fluid outlet 34. In the heat exchanger 30, the feed suspension enters through the feed suspension inlet 26 at temperature T_1, and exits as the spray solution through the spray solution outlet 36 at temperature T_2. Spray solution temperature T_2 is greater than feed suspension temperature T_1. To prevent unwanted vaporization/boiling of the organic solvent in the spray solution, pump 24 increases the pressure of the spray solution such that the pressure of the spray solution at spray solution outlet 36 is greater than the vapor pressure of the organic solvent at temperature T_2. The temperature of the spray solution when it enters the nozzle 50 is generally near T_2. Preferably it is within 30°C of temperature T_2. In addition, T_2 is greater than or equal to the lesser of T_A and T_M. In one embodiment, T_2 is greater than or equal to the greater of T_A and T_M. When it is the object of the process to form a solid amorphous dispersion of the active agent and the matrix material, T_2 is greater than or equal to T_A. Preferably, T_2 is at least 10°C greater than T_A. In one embodiment, the spray solution temperature T_2 is greater than the ambient-pressure boiling point of the organic solvent.

The spray solution exiting the heat exchanger may be at any temperature, T_2, which is greater than T_1, as long as T_2 is greater than or equal to the lesser of T_A and T_M. Temperature T_2 may be at least 10°C greater than T_1, at least 20°C greater than T_1, at least 30°C greater than T_1, at least 40°C greater than T_1, or even at least 50°C greater than T_1. In one embodiment, temperature T_2 is at least 50°C. In another

embodiment, temperature T_2 is at least 70°C. In another embodiment, temperature T_2 is at least 80°C. In another embodiment, temperature T_2 is at least 90°C. In another embodiment, T_2 is at least 100°C. In still another embodiment, T_2 is at least 120°C.

The active agent and the matrix material are both soluble in the organic solvent at temperature T_2. By "soluble" is meant that essentially all of the active agent and matrix material are dissolved in the organic solvent at temperature T_2. In the case of the active agent, the term "dissolved" has the conventional meaning, indicating that the active agent has gone into solution. In the case of matrix materials, the term "dissolved" can take a broader definition. For some matrix materials, such as polymers, the term dissolved can mean the polymer has gone into solution, or it can mean the polymer is dispersed or highly swollen with the organic solvent such that it acts as if it were in solution. In contrast, at temperature T_1, at least one of the active agent and the matrix material are present as a suspension in the organic solvent. Any suitable technique may be used to determine if the active agent and matrix material are soluble in the organic solvent at temperature T_2. Examples include dynamic or static light scattering analysis, turbidity analysis, and visual observations. In one embodiment, the spray solution comprises the active agent and the matrix material dissolved in the organic solvent at temperature T_2.

In one embodiment, temperature T_2 is greater than the temperature at which the active agent and matrix material are soluble in the organic solvent. That is, T_2 is greater than or equal to the greater of T_A and T_M. It may be desirable that temperature T_2 be much greater than the greater of T_A and T_M. Thus, temperature T_2 may be at least 10°C greater than the greater of T_A and T_M, at least 20°C greater than the greater of T_A and T_M, or even at least 30°C greater than the greater of T_A and T_M. Spray-dried products made by embodiments of the disclosed processes are typically more uniform and homogeneous when temperature T_2 is greater than the greater of T_A and T_M.

In one embodiment, the pump 24 increases the pressure of the spray solution to a pressure ranging from 2 atm to 400 atm. In another embodiment, the pressure of the spray solution as it exits the heat exchanger 30 is greater than 10 atm.

The heat exchanger 30 may be of any design wherein heat is transferred to the feed suspension resulting in an increase in temperature. In one embodiment, the heat exchanger 30 is an indirect heat exchanger, wherein a heating fluid is in contact with the feed suspension through a heat-transfer surface. Exemplary indirect heat exchangers include tube-in-tube devices and tube-in-shell devices, both well-known in the art. The heat exchanger 30 may also be a direct heat exchanger, in which a heating fluid, such as steam, is injected directly into the feed suspension, resulting in an increase in the temperature of the feed suspension. In yet another embodiment, the feed suspension flows over a hot surface, such as a resistance heating element, resulting in an increase in temperature of the feed suspension. Other heating sources may also be used, such as microwaves and ultrasonic devices that can increase the temperature of the feed suspension.

The concentration of active agent and matrix material in the spray solution can be virtually any value. In one embodiment, the concentration of total solids (that is, active agent and matrix material) in the organic solvent is at least 0.5 wt%. The concentration of total solids in the organic solvent may be at least 1 wt%, at least 5 wt%, or even at least 10 wt% or more. In another embodiment, the concentration of active agent in the organic solvent is at least 1.25-fold the solubility of the active agent in the organic solvent at temperature T_1. The concentration of active agent in the organic solvent may be at least 1.5-fold, at least 2.0-fold, or even 2.5-fold or more the solubility of the active agent in the organic solvent at temperature T_1.

In one embodiment, the residence time of the feed suspension in the heat exchanger 30 is minimized so as to limit the time the suspension/solution is exposed to elevated temperatures. The residence time of the suspension/solution in the heat exchanger may be less than 30 minutes, less than 20 minutes, less than 10 minutes, less than 5 minutes, or even less than 1 minute.

The spray solution at the spray solution outlet 36 is directed to a drying chamber 40, where it enters a nozzle 50 for atomizing the spray solution into droplets 44. The temperature of the spray solution when it enters the nozzle 50 is the spray temperature, designated as T_3. When it is desired to keep the active agent and matrix material dissolved in the spray solution, it is often desirable for T_3 to be

at or near T_2. However, there are sometimes advantages to having T_3 significantly less than T_2. For example, degradation of the active agent may be reduced or atomization in certain nozzles may be more effective when T_3 is significantly less than T_2. In some cases, it is even desirable for T_3 to be sufficiently low that the active agent, the matrix material, or both the active agent and the matrix material are not soluble in the solvent. In such cases, the solution may be below the point at which the solutes are soluble for a sufficiently short time such that all the solutes remain in solution until the solution is atomized. Alternatively, the solution may be below the point at which the solutes are soluble for a sufficiently long time that one or more of the matrix material or the active agent may precipitate or crystallize from solution. In one embodiment, temperature T_3 is less than 5°C less than T_2. In another embodiment, temperature T_3 is less than 20°C less than T_2. In another embodiment, temperature T_3 is less than 50°C less than T_2. In still another embodiment, both temperatures T_2 and T_3 are greater than the greater of T_A and T_M. In one embodiment, temperatures T_2 and T_3 are at least 5°C greater than the greater of T_A and T_M. In another embodiment, temperatures T_2 and T_3 are at least 20°C greater than the greater of T_A and T_M. In yet another embodiment, temperatures T_2 and T_3 are at least 50°C greater than the greater of T_A and T_M.

In one embodiment, the apparatus 10 is designed such that the time the spray solution is at a temperature greater than T_3 is minimized. This may be accomplished by locating the spray solution outlet 36 as close as possible to the nozzle 50. Alternatively, the size of the tubing or fluid connections between the spray solution outlet 36 and the nozzle 50 may be small, minimizing the volume of spray solution and reducing the time the spray solution is at a temperature greater than T_3. The time the spray solution is at a temperature greater than T_3 may be less than 30 minutes, less than 20 minutes, less than 10 minutes, less than 5 minutes, or even less than 1 minute.

Virtually any nozzle can be used to atomize the spray solution into droplets. The inventors have found that pressure nozzles are effective in embodiments of the disclosed processes. In another embodiment, a flash nozzle is used, as described below.

The drying chamber 40 also has a source of heated drying gas 42 which is combined with the droplets 44 in the drying chamber 40. In the drying chamber 40, at least a portion of the solvent is removed from the droplets to form a plurality of particles comprising the active agent and the matrix material. Generally, it is desired that the droplets are sufficiently dry by the time they come in contact with the drying chamber surface that they do not stick or coat the chamber surfaces.

The particles, along with the evaporated solvent and drying gas, exit the drying chamber at outlet 46, and are directed to a particle-collection means 60. Suitable particle-collection means include cyclones, filters, electrostatic particle collectors, and the like. In the particle-collection means 60, the evaporated solvent and drying gas 62 are separated from the plurality of particles 66, allowing for collection of the particles.

The particles may be of any desired size. In one embodiment, the particles have an average diameter ranging from 0.5 μm to 500 μm. In another embodiment, the particles have a diameter ranging from 0.5 μm to 100 μm. In another embodiment, the particles have an average diameter of greater than 10 μm. In still another embodiment, the particles have an average diameter of greater than 20 μm. In still another embodiment, the particles have an average diameter of greater than 30 μm. In yet another embodiment, the particles have a mass median aerodynamic diameter ranging from 0.5 μm to 10 μm. In still another embodiment, the particles have a mass median aerodynamic diameter ranging from 1 μm to 5 μm.

In one embodiment, the concentration of solvent remaining in the particles when they are collected (that is, the concentration of residual solvent) is less than 10 wt% based on the total weight of the particles. In another embodiment, the concentration of residual solvent in the particles when they are collected is less than 5 wt%. In yet another embodiment, the concentration of residual solvent in the particles is less than 3 wt%. In another embodiment, a drying process subsequent to the spray-drying process may be used to remove residual solvent from the particles. Exemplary processes include tray drying, fluid-bed drying, vacuum drying, and the drying processes described in WO2006/079921 and WO2008/012617.

In one embodiment, nozzle 50 is a flash nozzle 50a. There is shown in FIG. 2 a cross-sectional schematic of a flash nozzle 50a. Flash nozzle 50a consists

of a central tube 51 and an outer tube 53. Central tube 51 is in fluid communication with the inflowing spray solution 55, while outer tube 53 is in fluid communication with a sweep gas 52. The flash nozzle 50a has an inlet end, represented by A, and an outlet end, represented by B. The spray solution 55 from the heat exchanger 30 (not shown in FIG. 2) enters central tube 51 at A. A sweep gas 52 enters outer tube 53 at A. As spray solution 55 travels through the central tube 51 from inlet A to outlet B, the pressure decreases due to pressure drop. Between the inlet A and outlet B, the pressure of the spray solution 55 decreases to a value that is less than the vapor pressure of the solvent in the spray solution, leading to the formation of vapor bubbles of the solvent (a process known as cavitation). By the time the spray solution 55 reaches outlet B of the central tube 51, it is a fluid 56 comprising droplets of spray solution and vapor-phase solvent. In one embodiment, the central tube 51 is coated with a non-stick coating. In another embodiment, the outer tube 53 is coated with a non-stick coating. In still another embodiment, the central tube 51 and the outer tube 53 are coated with a non-stick coating. Non-stick coatings include, for example, polytetrafluoroethylene (PTFE) or other suitable non-stick coatings.

The sweep gas 52 exiting through the outer tube outlet 58 is in fluid communication with the fluid 56 exiting through the central tube 51. The sweep gas 52 decreases the likelihood that solid material will form at the exit from the central tube 51 or the outer tube 53.

Active Agents

The process of the present invention is used to form a composition comprising an active agent. By "active agent" is meant a drug, medicament, pharmaceutical, therapeutic agent, nutraceutical, agrochemical, fertilizer, pesticide, herbicide, nutrient, or other compound that may be desired to be formulated with a matrix material. The active agent may be a "small molecule," generally having a molecular weight of 2000 Daltons or less. The active agent may also be a "biological active." Biological actives include proteins, antibodies, antibody fragments, peptides, oligoneucleotides, vaccines, and various derivatives of such materials. In one embodiment, the active agent is a small molecule. In another

embodiment, the active agent is a biological active. In still another embodiment, the active agent is a mixture of a small molecule and a biological active. In yet another embodiment, the compositions made by certain of the disclosed processes comprise two or more active agents.

The active agent may be highly water soluble, sparingly water soluble, or poorly water soluble. In one embodiment, the active agent is "poorly water soluble," meaning that the active agent has a solubility in water (over the pH range of 6.5 to 7.5 at 25°C) of less than 5 mg/mL. The active agent may have an even lower aqueous solubility, such as less than about 1 mg/mL, less than about 0.1 mg/mL, and even less than about 0.01 mg/mL.

Matrix Materials

The disclosed processes are used to form compositions comprising a matrix material. Matrix materials suitable for use in the compositions formed by the disclosed methods should be inert, in the sense that they do not chemically react with the active agent in an adverse manner. The matrix material can be neutral or ionizable. In one embodiment, the composition includes two or more matrix materials.

Exemplary matrix materials include polysaccharides. Polysaccharides can be underivatized, such as cellulose, starch, dextran, pullulan, dextrin, maltodextrin, glycogen, inulin, fructan, mannan, chitin, polydextrose, fleximer (a ring-opened form of dextran), and oligosaccharides. Often, derivatives and substituted versions of the polysaccharides are preferred. Examples of such polysaccharide derivatives include ester- and ether-linked derivatives. Included in this class are cellulose ethers, cellulose esters, and cellulose derivatives that have both ester and ether substituents. Specific examples include cellulose acetate, ethyl cellulose, hydroxypropyl methyl cellulose and hydroxyethyl cellulose. Starch derivatives include starch acetate and carboxymethyl starch. Also included are synthetic matrix materials, such as polyacrylates and polymethacrylates, vinyl matrix materials, polyethylenes, polyoxyethylenes, polypropylenes, polyamides, polyesters, polycarbonates, and derivatives and substituted versions thereof; copolymers of various types, including random and block copolymers; other matrix materials such

as lactose, trehalose, sucrose, fructose, maltose, dextrose, xylitol, sorbitol, glycine, amino acids, citric acid, phospholipids, bile salts; and mixtures thereof.

In one embodiment, the matrix material is amphiphilic, meaning that the matrix material has hydrophobic and hydrophilic portions. In another embodiment, the matrix material is ionizable.

In yet another embodiment, the matrix material comprises a polymer. Appropriate matrix polymers include polyvinylpyrrolidone, vinyl acetate/vinylpyrrolidone copolymers, vinyl alcohol, vinyl acetate/vinyl alcohol copolymers, hydroxyethyl cellulose, hydroxypropyl methylcellulose, hydroxypropyl methylcellulose phthalate, carboxymethyl cellulose, carboxymethyl ethylcellulose, hydroxypropyl methylcellulose acetate succinate, cellulose acetate phthalate and cellulose acetate trimellitate. In still another embodiment, the matrix material comprises an ionizable cellulosic polymer. In yet another embodiment, the matrix material comprises an amphiphilic, ionizable polymer.

In one embodiment, the matrix material is biodegradable, meaning that the matrix material will degrade over time. By "degrade" is meant that in a use environment, the matrix material is broken down into smaller species that can be absorbed, metabolized, or otherwise eliminated or removed from the environment of use. This degradation can occur through enzymatic, hydrolytic, oxidative, or other reaction, as is well known in the art, or by degrading the matrix material into aqueous soluble species that can readily be removed from the environment of use.

Compositions

In one embodiment, the composition made by the disclosed processes is in the form of a solid amorphous dispersion of the active agent and the matrix material.

In another embodiment, the particles comprise a solid amorphous dispersion of the active agent and matrix material consisting essentially of amorphous active agent molecularly dispersed throughout the matrix material. In this embodiment, the solid dispersion may be considered a "solid solution" of active agent and matrix material. The term "solid solution" includes both thermodynamically stable solid solutions in which the active agent is completely dissolved in the matrix material, as well as homogeneous materials consisting of amorphous active agent molecularly

dispersed throughout the matrix material in amounts greater than the solubility of the active agent in the matrix material. A dispersion is considered a "solid solution" when it displays a single glass-transition temperature when analyzed by differential scanning calorimetry (DSC). In one embodiment, the particles have at least one Tg due to the amorphous character of the matrix material. In another embodiment, at least 90 wt% of the active agent in the particles is amorphous. In yet another embodiment, the active agent is amorphous and molecularly dispersed in a portion of one or more of the matrix materials, while the remaining portion of the matrix materials is present as a separate phase. This separate phase matrix material may be amorphous, crystalline, or a mixture of both amorphous and crystalline.

In another embodiment the particles comprise the active agent in crystalline form, which is homogeneously or substantially homogeneously distributed in the matrix material. In still another embodiment, the particles comprise the active agent in amorphous or non-crystalline form, which is homogeneously distributed in the matrix material matrix. In yet another embodiment, the particles comprise a mixture of active agent in crystalline and amorphous forms homogeneously distributed in the matrix material.

In still another embodiment, the particles comprise a mixture of active-agent-rich domains and matrix material-rich domains. The active agent in the domains may be amorphous, crystalline, or a mixture of amorphous and crystalline.

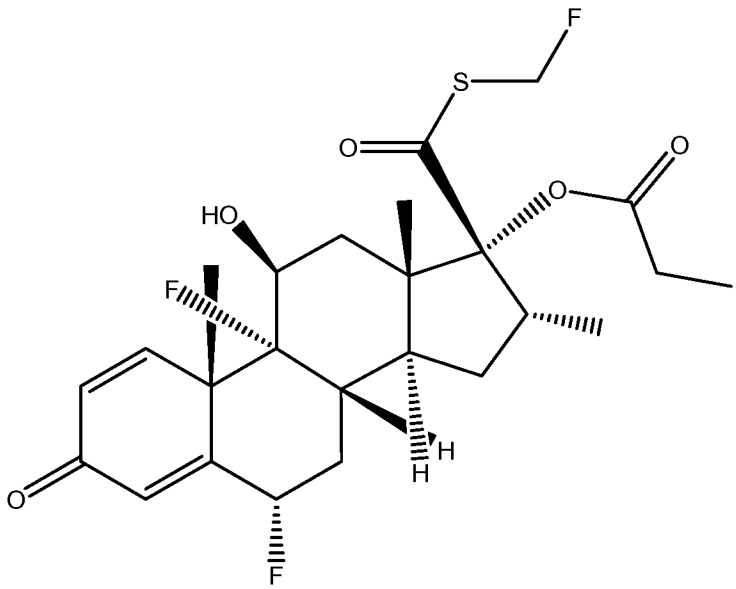
In yet another embodiment, the compositions comprise a third component in addition to the active agent and the matrix material. This third component may be any compound or mixture of compounds that facilitates the intended use of the disclosed compositions. Exemplary third components include, but are not limited to, matrix materials, surface active agents, wetting agents, diluents, fillers, bulking agents, disintegrants, flavors, fragrances, buffering agents, and/or other components known in the art.

Without further elaboration, it is believed that one of ordinary skill in the art can, using the foregoing description, utilize the present invention to its fullest extent. Therefore, the following specific embodiments are to be construed as merely illustrative and not restrictive of the scope of the invention. Those of ordinary skill

in the art will understand that variations of the conditions and processes of the following examples can be used.

Examples

Active Agent 1 was S-(fluoromethyl) 6α,9-difluoro-11β,17-dihydroxy-16α-methyl-3-oxoandrosta-1,4-diene-17β-carbothioate, 17-propionate, also known as fluticasone propionate, having the structure:



Active Agent 1 has a solubility of 0.4 μg/mL in pH 7.4 buffer, and a Log P value of 3.7. The Tg of amorphous Active Agent 1 was determined by DSC to be 84°C. The room temperature (20°C to 30°C) solubility of Active Agent 1 in methanol is 0.3 wt%.

Example 1

A spray-dried dispersion was made using an apparatus similar to that shown in FIG. 1. A feed suspension was prepared by mixing 3 gm of Active Agent 1 and 9 gm of the MG grade of hydroxypropyl methylcellulose acetate succinate (HPMCAS-MG, AQOAT-MG available from Shin Etsu, Tokyo, Japan) with 88 gm of a methanol solvent. The HPMCAS-MG dissolved in the solvent, while the active agent remained in suspension. The feed suspension was maintained at ambient temperature, 20°C to 30°C, with stirring in a pressure pot to prevent settling of the

particles of Active Agent 1. The total solids content of the feed suspension was 12 wt%.

The feed suspension in the pressure pot was pressurized to 245 psig and directed at a rate of 26 gm/min to a tube-in-shell heat exchanger. Heating fluid at 160°C was circulated in a countercurrent manner through the heat exchanger. The spray solution exiting the heat exchanger was at a temperature, T_2, of 120°C, and all of the active agent and matrix material were dissolved in the spray solution. The average residence time of the spray solution in the heat exchanger was less than 60 seconds. The total time the spray solution was at a temperature of 120°C was less than 80 seconds. Thus, the elapsed time from the time the spray solution exited the heat exchanger to the time it exited the pressure nozzle was 20 seconds. The temperature of the nozzle was 120°C.

The spray solution was delivered to the spray-drying chamber where it was atomized using a Schlick 2.0 pressure nozzle (Düsen-Schlick GmbH of Untersiemau, Germany). The spray solution was atomized into droplets within the spray-drying chamber, while simultaneously mixing the droplets with a nitrogen drying gas which was introduced to the drying chamber at a temperature of 140°C and at a flow rate of 520 gm/min, resulting in the formation of solid particles.

The solid particles, along with the evaporated solvent and the drying gas, were directed to a cyclone separator, where the solid particles were collected. The particles were subsequently dried in a vacuum chamber at 0.15 atm for 2 to 3 hours to remove residual methanol from the particles.

The resulting particles had 25 wt% Active Agent 1 in HPMCAS-MG.

Control 1

As a control, a 25 wt% Active Agent 1 in HPMCAS-MG composition was made using a conventional ambient-temperature spray-drying process. For Control 1, a feed solution was formed by dissolving 0.45 gm of Active Agent 1 and 1.35 gm of HPMCAS-MG in 179.7 gm methanol. Both the active agent and the matrix material completely dissolved in the methanol at ambient temperature. The total solids content of this solution was 1.0 wt%.

This solution was spray dried using the same apparatus as described for Example 1, except that the heat exchanger was bypassed, such that the spray solution was not heated prior to atomization. All other operating variables were nominally the same as described in Example 1.

Control 2

As a second control, a feed suspension similar to that formed for Example 1 was prepared and then spray dried without heating the spray solution. The feed suspension consisted of 2.25 gm of Active Agent 1, 6.75 gm of HPMCAS-MG, and 66 gm of methanol, resulting in a feed suspension containing 12 wt% solids. Because the feed was a suspension rather than a solution, a two-fluid nozzle was used (manufactured by Spray Systems, Wheaton, Illinois) to avoid clogging.

The feed suspension was spray dried using the same apparatus as described for Example 1, except that the heat exchanger was bypassed, such that the spray solution was not heated prior to atomization, and a two-fluid nozzle was used for atomization of the feed. All other operating variables were nominally the same as described in Example 1.

Analysis of Compositions from Examples 1, Control 1, and Control 2

Samples of the compositions of Example 1, Control 1, and Control 2 were analyzed by powder X-ray diffraction using an AXS D8 Advance PXRD measuring device (Bruker, Inc. of Madison, Wisconsin). Samples (approximately 100 mg) were packed in Lucite sample cups fitted with Si(511) plates as the bottom of the cup to give no background signal. Samples were spun in the φ plane at a rate of 30 rpm to minimize crystal orientation effects. The x-ray source (KCu_{α}, $\lambda = 1.54$ Å) was operated at a voltage of 45 kV and a current of 40 mA. Data for each sample were collected over a period of 27 minutes in continuous detector scan mode at a scan speed of 1.8 seconds/step and a step size of 0.04°/step. Diffractograms were collected over the 2θ range of 4° to 40°.

FIG. 3 shows the results of this analysis. The composition of Example 1, made using a concentrated feed suspension and a heat exchanger to increase the feed

temperature according to the disclosed processes, showed an amorphous halo, indicating the active agent in the composition was amorphous. Likewise, the composition of Control 1, made using a conventional spray-drying process using a dilute spray solution of active agent and matrix material dissolved in a solvent at ambient temperature, also showed only an amorphous halo. However, the composition of Control 2, made using a concentrated feed suspension but not heated, showed a large number of well-defined peaks, indicating the presence of crystalline active agent in the composition.

This analysis shows that the compositions of Example 1 and Control 1 had similar properties. However, because the spray solution for Example 1 contained 12 wt% solids, while the spray solution for Control 1 only contained 1 wt% solids, certain embodiments of the disclosed processes (Example 1) had a throughput that was 12-fold greater than that of the conventional spray-drying process.

Example 2

A spray-dried dispersion is made using an apparatus similar to that shown in FIG. 1 using the procedures outlined in Example 1, except that the flash nozzle of FIG.2 is used. The resulting particles consist of 25 wt% Active Agent 1 in HPMCAS.

An embodiment of the disclosed spray-drying processes comprises delivering a spray solution comprising an active agent and a matrix material in an organic solvent to a spray-drying apparatus, atomizing said spray solution into droplets within said spray-drying apparatus via a nozzle to remove at least a portion of the organic solvent from said droplets to form a plurality of particles, wherein said spray solution is delivered to said nozzle at a temperature T_3, and collecting said particles, wherein said particles comprise said active agent and said matrix material, and wherein said spray solution is formed by forming a feed suspension comprising said active agent, said matrix material and said organic solvent, wherein said feed suspension is at a temperature T_1, and directing said feed suspension to a heat exchanger, thereby increasing the temperature of said feed suspension to a temperature T_2, wherein temperature T_2 is greater than temperature T_1, and said spray solution is at a pressure that is greater than the vapor pressure of said solvent

at temperature T_2, such that said active agent and said matrix material are soluble in said solvent at temperature T_2. In one embodiment, said temperature T_2 is greater than the ambient-pressure boiling point of said solvent.

In either of the above embodiments, said active agent and said matrix material may be soluble in said solvent at temperature T_3. In any or all of the above embodiments, said spray solution may be atomized using a flash nozzle.

In any or all of the above embodiments, said temperature T_2 may be at least 100°C. In any or all of the above embodiments, said spray solution may be at temperature T_2 for less than 10 minutes. Alternatively, said spray solution may be at temperature T_2 for less than 5 minutes.

In any or all of the above embodiments, said organic solvent is selected from methanol, ethanol, n-propanol, isopropanol, butanol acetone, methyl ethyl ketone, methyl isobutyl ketone, ethyl acetate, propyl acetate, tetrahydrofuran, acetonitrile, methylene chloride, toluene, 1,1,1-trichloroethane, and mixtures thereof. In certain embodiments, said organic solvent is selected from the group consisting of methanol, ethanol, n-propanol, isopropanol, butanol acetone, methyl ethyl ketone, methyl isobutyl ketone, ethyl acetate, propyl acetate, tetrahydrofuran, acetonitrile, methylene chloride, toluene, 1,1,1-trichloroethane, and mixtures thereof. In any or all of the above embodiments, said organic solvent may contain less than 50 wt% water.

In any or all of the above embodiments, said particles may have a mass median aerodynamic diameter ranging from 0.5 μm to 10 μm. In any or all of the above embodiments, said particles may have an average diameter of greater than 10 μm.

In any or all of the above embodiments, said matrix material may comprise a polymer. In some embodiments, said particles comprise a solid amorphous dispersion of said active agent in said polymer.

Also disclosed are embodiments of products made by any or all of the above processes. In some embodiments, the product comprises a solid amorphous dispersion of said active agent and said polymer.

An embodiment of a process for producing a composition comprises forming a feed suspension comprising an active agent, a matrix material and an organic

solvent, wherein said feed suspension is at a temperature T_1, forming a spray solution by directing said feed suspension to a heat exchanger, thereby increasing the temperature of said feed suspension to a temperature T_2, wherein temperature T_2 is greater than temperature T_1, said spray solution is at a pressure that is greater than the vapor pressure of said solvent at temperature T_2, and said active agent and said matrix material are soluble in said solvent at temperature T_2, directing said spray solution to a spray-drying apparatus, said spray-drying apparatus comprising a drying chamber, a nozzle for atomizing said spray solution into droplets, and a source of heated drying gas for removing at least a portion of said organic solvent from said droplets, atomizing said spray solution into droplets in said drying chamber by said nozzle, wherein the spray solution is delivered to said nozzle at a temperature T_3, contacting said droplets with said heated drying gas to remove at least a portion of said organic solvent from said droplets to form a plurality of particles comprising said active agent and said matrix material, and collecting said particles. In some embodiments, said temperature T_2 is greater than the ambient-pressure boiling point of said solvent.

In either of the above embodiments, said active agent and said matrix material may be soluble in said solvent at temperature T_3. Alternatively, said active agent or said matrix material may not be soluble in said solvent at temperature T_3.

The terms and expressions which have been employed in the foregoing specification are used therein as terms of description and not of limitation, and there is no intention in the use of such terms and expressions of excluding equivalents of the features shown and described or portions thereof, it being recognized that the scope of the invention is defined and limited only by the claims which follow.

What is claimed is:

1. A spray-drying process, comprising:

(a) delivering a spray solution comprising an active agent and a matrix material in an organic solvent to a spray-drying apparatus;

(b) atomizing said spray solution into droplets within said spray-drying apparatus via a nozzle to remove at least a portion of the organic solvent from said droplets to form a plurality of particles, wherein said spray solution is delivered to said nozzle at a temperature T_3; and

(c) collecting said particles, wherein said particles comprise said active agent and said matrix material; and

wherein said spray solution is formed by

forming a feed suspension comprising said active agent, said matrix material and said organic solvent, wherein said feed suspension is at a temperature T_1; and

directing said feed suspension to a heat exchanger, thereby increasing the temperature of said feed suspension to a temperature T_2, wherein

(i) temperature T_2 is greater than temperature T_1; and

(ii) said spray solution is at a pressure that is greater than the vapor pressure of said solvent at temperature T_2;

such that said active agent and said matrix material are soluble in said solvent at temperature T_2.

2. The process of claim 1 wherein said temperature T_2 is greater than the ambient-pressure boiling point of said solvent.

3. The process of claim 1 or 2 wherein said active agent and said matrix material are soluble in said solvent at temperature T_3.

4. The process of any one of claims 1-3 wherein said spray solution is atomized using a flash nozzle.

5. The process of any one of claims 1-4 wherein said temperature T_2 is at least 100°C.

6. The process of any one of claims 1-5 wherein said spray solution is at temperature T_2 for less than 10 minutes.

7. The process of any one of claims 1-6 wherein said spray solution is at temperature T_2 for less than 5 minutes.

8. The process of any one of claims 1-7 wherein said organic solvent is selected from methanol, ethanol, n-propanol, isopropanol, butanol acetone, methyl ethyl ketone, methyl isobutyl ketone, ethyl acetate, propyl acetate, tetrahydrofuran, acetonitrile, methylene chloride, toluene, 1,1,1-trichloroethane, and mixtures thereof.

9. The process of any one of claims 1-8 wherein said organic solvent contains less than 50 wt% water.

10. The process of any one of claims 1-9 wherein said particles have a mass median aerodynamic diameter ranging from 0.5 μm to 10 μm.

11. The process of any one of claims 1-9 wherein said particles have an average diameter of greater than 10 μm.

12. The process of any one of claims 1-11 wherein said matrix material comprises a polymer.

13. The process of claim 12 wherein said particles comprise a solid amorphous dispersion of said active agent in said polymer.

14. The product of any one of claims 1-13.

15. The product of claim 12 wherein said product comprises a solid amorphous dispersion of said active agent and said polymer.

16. A process for producing a composition comprising:

(a) forming a feed suspension comprising an active agent, a matrix material and an organic solvent, wherein said feed suspension is at a temperature T_1;

(b) forming a spray solution by directing said feed suspension to a heat exchanger, thereby increasing the temperature of said feed suspension to a temperature T_2, wherein,

(i) temperature T_2 is greater than temperature T_1;

(ii) said spray solution is at a pressure that is greater than the vapor pressure of said solvent at temperature T_2; and

(iii) said active agent and said matrix material are soluble in said solvent at temperature T_2;

(c) directing said spray solution to a spray-drying apparatus, said spray-drying apparatus comprising:

(i) a drying chamber;

(ii) a nozzle for atomizing said spray solution into droplets; and

(iii) a source of heated drying gas for removing at least a portion of said organic solvent from said droplets;

(d) atomizing said spray solution into droplets in said drying chamber by said nozzle, wherein the spray solution is delivered to said nozzle at a temperature T_3;

(e) contacting said droplets with said heated drying gas to remove at least a portion of said organic solvent from said droplets to form a plurality of particles comprising said active agent and said matrix material; and

(f) collecting said particles.

17. The process of claim 16 wherein said temperature T_2 is greater than the ambient-pressure boiling point of said solvent.

18. The process of claim 16 or 17 wherein said active agent and said matrix material are soluble in said solvent at temperature T_3.

19. The process of claim 16 or 17 wherein said active agent or said matrix material are not soluble in said solvent at temperature T_3.

FIG. 1

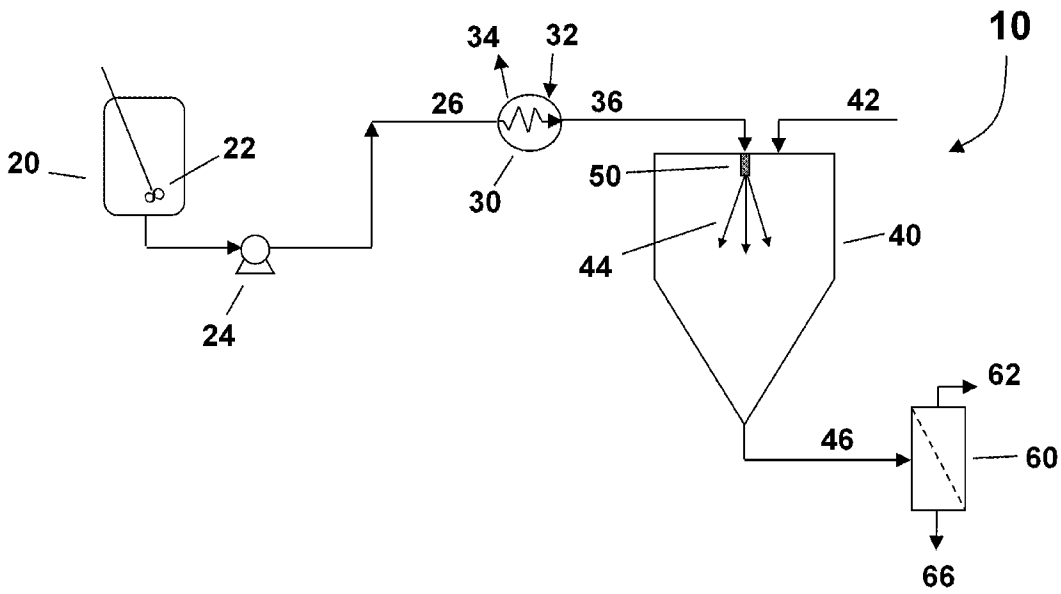

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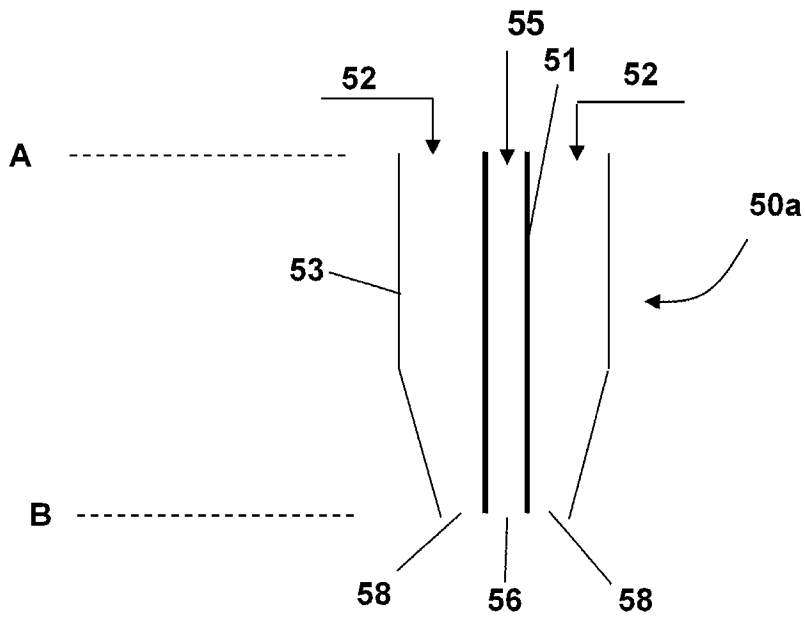
FIG. 2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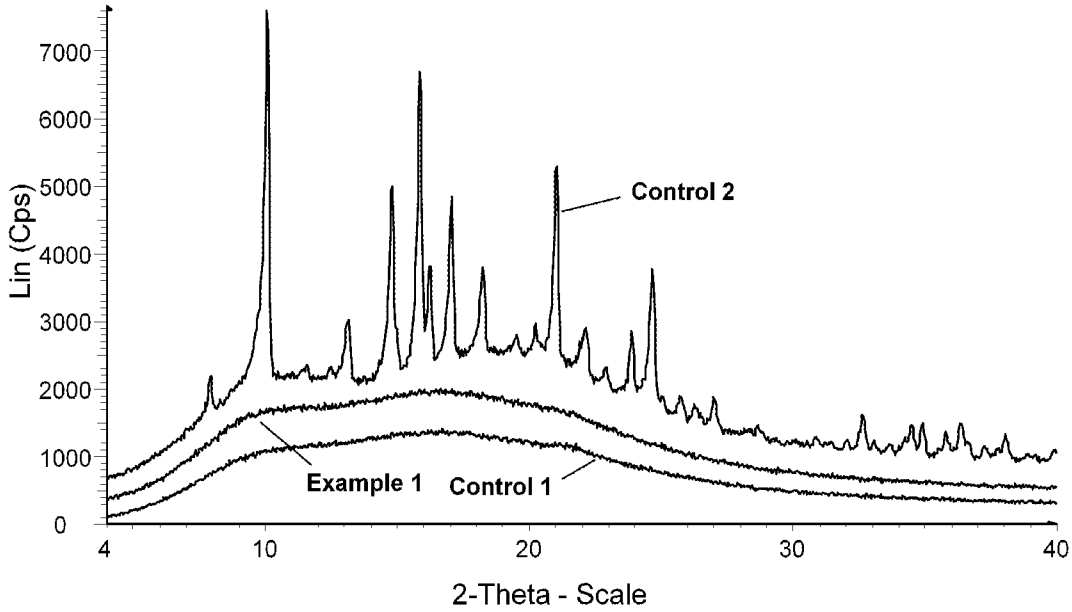
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Example 1
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