

(19) World Intellectual Property Organization  
International Bureau



(43) International Publication Date  
15 December 2011 (15.12.2011)

(10) International Publication Number  
**WO 2011/154014 A1**

(51) International Patent Classification:  
A61K 9/16 (2006.01)

(21) International Application Number:  
PCT/DK2011/050209

(22) International Filing Date:  
10 June 2011 (10.06.2011)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:  
PA 2010 00517 11 June 2010 (11.06.2010) DK

(71) Applicant (for all designated States except US): **GEA PROCESS ENGINEERING A/S** [DK/DK]; Gladsaxevej 305, Box 45, DK-2860 Søborg (DK).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **SCHWARTZBACH, Henrik** [DK/DK]; Bavnevolden 21, DK-2760 Måløv (DK). **BIRKMIRE, Andrew P.** [US/US]; 109 17th Street, SE Washington, District of Columbia 20003 (US).

(74) Agents: **RASMUSSEN, Torben Ravn** et al.; Awapatent A/S, Rigensgade 11, DK-1316 København K (DK).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ,

CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

**Declarations under Rule 4.17:**

— as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))

**Published:**

— with international search report (Art. 21(3))

— before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))



**WO 2011/154014 A1**

(54) Title: CONTROLLED HUMIDITY DRYING

(57) Abstract: The invention relates to a process for preparation of spray dried particles, comprising the steps of spraying in a chamber a liquid feed comprising one or more solvents, and supplying a drying gas to the chamber with one or more solvent vapours having a dew point selected to provide a desired property to the spray dried particles.

## CONTROLLED HUMIDITY DRYING

The present invention relates to a process for preparation of spray dried particles, wherein the humidity is controlled during the process.  
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During the process of spray drying a liquid feedstock is atomized into a spray of droplets, which are contacted with hot air in a drying chamber. Evaporation of moisture from the droplets and formation of the desired product as dry particles proceed under controlled temperature and airflow conditions. A powder of the product is continuously discharged from the drying chamber and/or recovered from the exhaust gases using a cyclone or a bag filter. Generally, the entire spray drying process only endures for a few seconds.  
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In a conventional drying process a source of heat and a low relative humidity for solvents in the drying gas is all that is required for producing a product. The presence of vapours in the drying gas in a spray dryer or fluid bed dryer is inevitable. In a spray dryer the vapour pressure in the drying gas results from a combination of the vapour pressure in the inlet gas and that of the evaporated solvent(s) from the product. In a dryer that operates with absolute dry inlet drying gas (e.g. nitrogen) the vapour content and composition is given by the solvent evaporated from the product.  
15  
20

The inlet drying gas humidity is typically kept as low as economically feasible to obtain a high drying capacity. Drying plants using air as drying gas are frequently equipped with dehumidifiers to control the inlet drying gas humidity. However, few have explored the possibilities of generating special product characteristics by increasing the solvent vapors in the drying gas above the optimal level from the perspective of drying economy.  
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To obtain a certain morphology US 7,469,488 discloses spray dried particles having specified aerodynamic characteristics. The particles are produced by atomizing a liquid feed in a drying gas having a controlled humidity. By controlling the humidity of the inlet drying gas to a certain dew point between -39°C and 8°C particles with a specified de-  
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terminated tap density or aerodynamic diameter is produced.

In view of the above, the object of the present invention is to provide a spray drying process, wherein a detailed vapor control is made possible, thereby generating product characteristics different from product characteristics produced using the most economic method.

To meet this object a process is provided for the preparation of spray dried particles, said process comprising the steps of spraying in a chamber a liquid feed comprising one or more solvents and suspended and/or dissolved component(s), and supplying a drying gas to the chamber, said drying gas comprising one or more solvent vapours, each having a certain dew point, thereby producing spray dried particles; wherein the dew point is selected to provide a desired property of the spray dried particles.

The drying gas may comprise any amount of solvent vapours up to an amount corresponding to 100% relative humidity. Typically, the amount of humidity in the inlet drying gas(es) is above the level corresponding to 10% relative humidity if calculated at the temperatures and pressures at the outlet of the drying chamber, such as above 20%.

In this text the word solvent is used for any volatile component in the product or drying gas supplied to the drying chamber, whether the solvent is organic, non-organic or water. Similar the term vapour refers to this phase for any solvent. The same applies for the term humidity and relative humidity. The word gas is used for all components that appear in their gaseous form, e.g. nitrogen, carbon dioxide, air etc. throughout the process.

For stability reasons the maximum water content in most products from spray drying have to be limited, typically to below 2-5% w/w. For common organic solvents like ethanol the maximum level is usually lower (typically <0.5% w/w), e.g. due to health reasons. For problematic solvents like methylenchloride the maximum level is much lower (typically <0.05% w/w). Sometimes there is also a minimum requirement for the content of solvent (often water), e.g. to maintain the correct crystalline state or functionality. The required residual solvent levels are frequently achieved through a post drying stage.

By increasing the drying temperature, the end point of drying can be driven closer towards zero content of residual solvent in the product and/or the drying time can be reduced. This can also be achieved by lowering the vapour pressure in the drying gas. The last option of lowering the vapour pressure in the drying gas is especially used whenever there is an upper limit to the drying temperature (e.g. due to temperature related product deterioration) preventing the residual solvent goal to be reached simply by increasing the drying temperature.

The morphology as well as the chemical composition of the final product will depend on the drying gas temperature, the rate of drying as well as the ratio between the different solvents, if more than one is present.

For some properties of particles to be obtained there may be a minimum residual solvent requirement of one of the solvents. If this amount is not present the process may not lead to the desired result. Likewise, if the presence of one solvent facilitates better evaporation of another solvent, applying more drying power may not lead to optimum results, both with regard to drying time as well as final residual solvent content in the product. The present invention suggests a method for obtaining the desired characteristics of the dried particles.

If the presence of one solvent facilitates better drying of another solvent, drying at low temperature may encourage drying off one more problematic solvent (e.g. an organic solvent) at the expense of the drying of a less problematic one (e.g. water). Drying at low temperature at the outlet of the drying chamber, e.g. below 40 °C or more preferred below 20 °C, will result in high relative humidities in the drying gas due to evaporation of liquid. The same will happen when drying at elevated pressure. In any event, some sort of post drying after spray drying may be considered due to the short residence time in the spray dryer.

A high drying gas temperature may have negative effects on spray dried powders, e.g. the density of the powder, by promoting the formation of unwanted hollow particles. Increasing the drying gas humidity has the opposite effect on the drying rate of the particles and will allow the particles to shrink more during drying. In this way, more fa-

vourable properties of the particles are achieved as expressed by common parameters within the art such as tap density, volume median geometric diameter (VMGD), and mass median aerodynamic diameter (MMAD).

5           Through control of the one or more solvent vapours it is made possible to accurately control the particle temperature, the particle drying rate and the particle drying end point, so that desired properties of the final product can be achieved.

10           The vapour phase composition of the drying gas can be controlled by selective removal of vapours from the drying gas prior to its entering the dryer and/or by addition of vapours to the drying gas prior to its entering the dryer or even in the dryer itself. The effects can be general if vapours are added to the drying gas prior to entering the dryer or localized if vapours with or without gas are added inside the dryer.

15           Further, to effect a desired vapour phase composition of the drying gas, the content of one or more solvents in the liquid feed may be adjusted.

20           The selected dew point may conveniently be adjusted prior to the addition of an optional auxiliary gas. The auxiliary gas may be added in some types of close-cycled system to compensate for the escape of gas and evaporation of volatile compounds. By the addition of the auxiliary gas the predetermined dew point may be decreased slightly, however, usually not severely.

25           In one embodiment of the invention, the drying gas being supplied to the drying chamber comprises one or more solvent vapours being provided with a predetermined dew point before an optional auxiliary gas is added. In some designs two or more solvent vapours are used, said two or more solvent vapours being provided with a common dew point prior to the optional addition of the auxiliary gas.

30           Advantageously, the common dew point is provided by processing the drying gas in a condenser. The condensing may take place in one or more stages.

          According to a preferred embodiment, the condenser is preceded by, combined with or replaced by a scrubber capable of adjusting the concentration of one or more solvent vapours. The scrubbing may

happen in one or more stages at controlled temperature conditions. The scrubber may be a dry scrubber or a wet scrubber, the latter optionally operating in a condensing scrubber mode.

In one embodiment of the invention, the dew point of the solvent vapour is 20°C or more, preferably 30 °C or more. In another embodiment the dew point of the solvent vapour is 40°C or more, preferably 50 °C or more. Operating at a high relative humidity makes it possible to extensively affect the processing of particles. In preferred aspect water is used as the solvent vapour to form the above mentioned relative humidities.

According to a specific embodiment, the drying is delayed by increasing the solvent vapour content to allow chosen properties of the particles to be developed. By controlling the content of one or more of the volatile components in the inlet drying gas the rate of evaporation of said volatile component can be reduced, whereby evaporation of other volatile components in the feed may be facilitated. Further, the liquid temperature can be raised during the evaporation, whereby liquid phase reactions can be accelerated and potentially be completed before the liquid is evaporated. Additionally and as previously suggested particle morphology can be influenced. For example, the powder and particle density can be affected as well as the ratio between crystalline and amorphous material in the final product.

In one embodiment, of the one or more solvents one is water.

According to a specific embodiment, a second solvent, which is miscible with water, is also present.

In a specific embodiment, the solvent, which is miscible with water, is an alcohol, such as methanol, ethanol, propanol, isopropanol, t-butanol, and n-butanol, most preferred ethanol. Further water miscible solvents include acetone, diethylether, ethyl acetate, acetonitrile and methylethylketone.

According to an alternative embodiment, none of the solvent vapours are aqueous.

Preferably, one or more of said non-aqueous solvents is selected among perfluorocarbons, dichloromethane, chloroform, ether,

ethyl acetate, methyl-tert-butyl ether, hexane, heptane, n-dodecane, m-xylene, isopentene isooctane, tetrahydrofuran, dimethyl sulfoxide, dimethylformamide, toluene, glacial acetic acid, and acetonitrile.

According to a specific embodiment, the drying gas being supplied to the chamber comprises two or more solvent vapours having different dew points.

In this case, preferably a dew point is selected to promote the evaporation of a solvent component from the particles being formed or to suppress the evaporation of a solvent component from the particles being formed. Alternatively, or in addition a dew point of a solvent vapour is selected to suppress the evaporation of a solvent component from the particles being formed.

According to one embodiment, the liquid feed, which is introduced into the drying chamber, comprises a solution or suspension of biomolecules, such as proteins, monoclonal antibodies, vaccines, synthetic peptides or oligonucleotides, in an organic solvent such as acetonitrile or acetone, and furthermore water in an amount of 1-10% (vol/vol), preferably 3% (vol/vol), is added to the liquid feed. The proteins may be industrial enzymes like

In the following, a preferred embodiment of the invention will be illustrated by reference to the non-limiting figure.

Figure 1 shows an embodiment of a plant for carrying out the process according to the invention.

Referring now to the figure, the main features of the illustrated plant are referenced by numbers as follows: 1 is feed for feeding to the chamber 2 of a spray dryer; 3 is a cyclone for recovering a main powder fraction 4 from the product stream leaving the spray dryer; 5 is a bag filter for recovering fines 6 from the exhaust gases received from the cyclone; 7 and 15 are high efficiency particulate air (HEPA) filters for removing a substantial part of residual airborne particles; 8 is a condenser; 9 is discharged condensate of solvent; 10 is a scrubber, 14 is a heaters; 11 is an inlet and/or discharge for auxiliary gas; 13 is a fan; 16 is a pipe for addition of solvent and/or solvent vapour to the stream of drying gas prior to its entrance into the chamber of the spray dryer; 17

is a pipe for addition of solvent and/or solvent vapour/gas to a specific location within the spray dryer; 18 is a pipe for supplying additional drying gas.

An overall description of a preferred embodiment of the process according to the invention will now be given.

A feed stream 1 to be processed is received in the drying chamber 2 of a closed cycle spray dryer using an inert drying gas. Upon separation of the main powder fraction 4 and the fraction of fines 6 in the cyclone 3 and the bag filter 5, respectively, the stream of drying gas is passed through the HEPA filter 7 such as to arrive at the condenser 8, from which condensed solvent 9 may be removed. After passing through the condenser 8 the gas stream is treated in the scrubber 10, wherein its content of solvents is adjusted by selective removal or addition of gas stream components. In the alternative the scrubber 10 may be positioned prior or the condenser 8.

In the present embodiment a first solvent originates from the feed material, while a second solvent is added as a co-solvent to promote evaporation of the first solvent. Thus, the scrubber is operated such as to selectively trap vapour of the first solvent. The pressure in the cyclic drying system is maintained by additional supply of the auxiliary gas at the inlet 11 as required. With the aid of pipe 16 additional quantities of the second solvent is added to the stream of drying gas prior to its entrance into the chamber of the spray dryer, aiming for a pre-established optimum dew point, at which the net effect of the second solvent as an aid-solvent to promote the evaporation of the first solvent is most pronounced.

Alternatively, the steps of condensing and scrubbing might have been interchanged by making use of a wet scrubber operating in a condensing scrubber mode, or the scrubber 12 might have been interposed in an alternative position between the HEPA filter 7 and the condenser 8. Moreover, if operating the plant in a non-cyclic mode, drying gas would have been supplied to the plant at an immediately upstream position relative to the condenser 8 and possibly the scrubber 12 in said alternative position, whereas gas exhaust from the plant would take place at a



position just downstream the HEPA filter 7.

In another operation, the drying system might have been run with a feed and drying gas presenting a single predominant solvent. The dew point of the solvent vapour is managed by condensation and/or scrubbing and/or addition of further solvent in order to attain optimum properties of the resultant particles, e.g. with regard to density, morphology and residual solvent content. The addition of further solvent might happen through the pipe 17, so that the solvent vapour is released directly into the spraying chamber, possibly to a confined area around the spray nozzle with a view to enhanced suppression of drying in this zone. The choice of an appropriate dew point and solvent is informed by preceding drying trials, e.g. drying kinetics simulation with the computerized drying model DRYNETICS™ (GEA Niro) assisted by the DRYING KINETICS ANALYZER™ (GEA Niro), where a droplet of the feed in question is suspended in an ultrasonic field and dried under well-defined conditions.

According to a further aspect of the present invention, the process for the preparation of spray dried particles comprises the steps of:

- a. spraying in a chamber a liquid feed comprising a solvent mixture and suspended and/or dissolved component(s),
  - b. supplying a drying gas to the chamber
  - c. allowing the sprayed liquid feed to interact with the drying gas,
  - d. collecting the at least partly dried particles, and
  - e. discarding or recycling the spent drying gas,
- wherein the solvent mixture comprises a main solvent and a co-solvent.

Embodiments, wherein a second solvent is added as a co-solvent to promote evaporation of a first solvent have important application in the processing of biomolecules, e.g. for biopharmaceutical applications. For instance, when spray drying a feed of proteins in acetone with a small amount of water, it is possible to preferentially remove the more volatile organic solvents by varying the amount of water in the

feed and processing at low temperature, e.g. with an outlet temperature in the range of -10 to 40 °C. For other products it may be possible to operate in the range of -10 to 80°C, especially when the biomolecules is less sensitive. A key point in this situation is that polar organic solvents can bind to the same hydrophilic sites on the protein as the polar water molecules, and once they are bound they cannot be removed. To avoid this, adding water as a co-solvent to the feed allows the organic solvents to be driven off faster as they are more volatile, while the water molecules protect the hydrophilic sites from having an organic solvent molecule bind to them. Thus, the residual contents of water and organic solvent in the powders may be tuned by varying both the relative amount of water in the feed suspension and the outlet temperature of the spray drying process.

Within the biomolecule area, the process may e.g. be relevant for solutions of recombinant proteins, monoclonal antibodies, vaccines, synthetic peptides and oligonucleotides in organic solvents such as acetonitrile or acetone which are both polar solvents and miscible with water, which is an important point in this context. Conventional spray drying of these temperature-sensitive macromolecules typically results in 2 or 3% residual solvent in the powders, until a sufficiently high outlet temperature of 70°C or higher is reached, at which temperature the molecules are typically denatured. This means that the acceptable limit for residual organic solvent cannot be met using conventional spray drying, because the organic solvents bind to the hydrophilic sites on the molecule, and increasing heat does not drive off additional solvent.

A great deal of linear peptide synthesis, for example, is either carried out in organic solvents or may include a final rinsing step with an organic solvent cocktail, which may then be lyophilized. In the lyophilization process, it is possible to reduce the organic solvent to a sufficiently low level using vacuum, but in conventional spray drying the same low level cannot be achieved as this is normally performed near atmospheric pressure. Accordingly, where conventional spray drying is failing as the organic solvents bind to the macromolecules, and higher temperatures denature the macromolecules, operating according to a specific

embodiment of the invention by adding a co-solvent, such as water to the feed and instead spray drying at a relatively low temperature results in much lower and acceptable residual organic solvent levels, and residual water levels in the range of 1-4%.

5           This technique is relevant to the synthetic peptide industry but also when it comes to traditional biotech proteins and emerging oligonucleotides and siRNA molecules, which are very large macromolecules with various hydrophilic/hydrophobic domains. As these are typically very unstable in the liquid organic solvent mixture, the solution can rapidly be spray dried by adding tunable small amounts of water which will  
10           attach to the hydrophilic domains allowing the spray drying process to preferentially drive off the more volatile polar organic solvents at temperatures low enough that the macromolecule is not denatured.

          The invention may be applied on microorganisms, which is selected from the group comprising bacteria, virus, yeast, fungus and algae to obtain dried particles including these microorganisms.  
15

          The present invention is also useful in the formulation of a solid dispersion comprising a hydrophilic polymer and a bioactive compound having low aqueous solubility and dissolution rate. The solid dispersion improves the solubility and dissolution rate of the bioactive compound  
20           having low aqueous solubility and dissolution rate, such as BCS Class II or Class IV drug compounds. BCS (Biopharmaceutics Classification System) is a guide for predicting the intestinal drug absorption provided by the U.S. Food and Drug Administration. BCS restricts the prediction using the parameters solubility (high/low) and intestinal permeability  
25           (high/low). BCS Class II compounds have high permeability and low solubility, whereas BCS Class IV compounds have low permeability and low solubility.

          In a certain aspect of the invention the bioactive compound is dissolved or suspended in a liquid feed together with a hydrophilic polymer, which includes polymers well known in pharmaceutical compositions e.g. a polymer selected among the group consisting of hydroxypropyl methylcellulose (HPMC), hydroxypropylmethylcellulose acetate succinate (HPMCAS), polyvinylpyrrolidone (PVP), and vinylpyrrolidone-  
30

vinyl acetate copolymers. The spray dried dispersion formulation may also contain surfactants (e.g. poloxamer or polyethylene glycol) and flow aiding agents (e.g. fumed silica). The solvent of the liquid feed may be an organic solvent containing a minor amount of water, such as 1-10%  
5 (vol/vol) water.

The spray dried particles resulting from any of the processes disclosed herein may be post-processed, including post-drying, post-cooling, post-crystallising, and any combination thereof. The post-drying may be performed in a fluid bed.

10 The particles produced according to the process described above may be useful within various industries including the pharmaceutical, food, diary, and chemical industry.

#### Examples

##### 15 Polymerisation of para-formaldehyde

In the process of spray congealing/drying of para-formaldehyde a final polymerization takes place after the atomization of the feed into droplets. Here, it is very important to control the temperature of the droplets before they dry out to allow for the final polymerization to take  
20 place. If the air humidity is too low, it turns out that the molecular chain length becomes inadequate. Conversely, by controlling the inlet and outlet humidity of the process air so that the relative humidity of the outlet air is around 50% a fully satisfactory polymerization is attained.

##### 25 Co-solvent-aided drying

The presence of certain second solvents is observed to promote the drying of certain first solvents. Accordingly, the residual level of the first solvent in the dried product is lower if a suitable second solvent is present during otherwise identical drying conditions. However, prema-  
30 ture drying off of the solvent meant to aid the drying may prevent the desired result. If the vapour composition in the drying gas is optimized (most frequently impossible in traditional dehumidifiers and condensers) to retain a specific level of second aid-solvent(s) in the product, while at the same time good conditions are provided for the evaporation of the

more persistent first solvent(s), optimum results are achieved.

Bovine serum albumine or salmon calcitonin in a solution of acetone or acetonitrile together with water in an amount of 3 % (vol/vol) is fed into a drying chamber. Due to this procedure, a sufficiently low  
5 level of organic solvent in the final product can be attained while still operating at a modest temperature, which is harmless to the protein in question. In addition, a fully acceptable residual water content in the range of 1-4% is also accomplished.

## P A T E N T   C L A I M S

1. A process for the preparation of spray dried particles, comprising the steps of:
  - a. spraying in a chamber a liquid feed comprising one or more solvents and suspended and/or dissolved component(s),
  - b. supplying a drying gas to the chamber, said drying gas comprising one or more solvent vapours having a certain dew point,
  - c. allowing the sprayed liquid feed to interact with the drying gas,
  - d. collecting at least partly dried particles, and
  - e. discarding or recycling spend drying gas,wherein the dew point(s) of the one or more solvent vapours is selected to provide a desired property of the spray dried particles.
2. The process according to claim 1, wherein the drying gas being supplied to the drying chamber comprises one or more solvent vapours being provided with a predetermined dew point before an optional auxiliary gas (11) is added.
3. The process according to claim 1 or 2, wherein the drying gas being supplied to the drying chamber comprises two or more solvent vapours being provided with a predetermined common dew point before an optional auxiliary gas is added.
4. The process according to claim 3, wherein the common dew point is provided by processing the drying gas in a condenser.
5. The process according to claim 4, wherein the condenser is combined with or replaced by a scrubber capable of adjusting the concentration of one or more solvent vapours.
6. The process according to any one of the preceding claims, wherein the dew point of the solvent vapour is 20 °C or more, preferably 30°C or more.
7. The process according to any one of the preceding claims, wherein the dew point of the solvent vapour is 40 °C or more, preferably 50°C or more.
8. The process according to any one of the preceding claims, wherein the drying rate is reduced by increasing the solvent vapour con-

tent to allow chosen properties of the particles to be developed.

9. The process according to any one of the preceding claims, wherein one of the solvents is water.

10. The process according to any one of the preceding claims,  
5 wherein a second solvent is miscible with water.

11. The process according to claim 10, wherein the solvent miscible with water is selected from the group consisting of an alcohol, such as methanol, ethanol, propanol, isopropanol, t-butanol, and n-butanol; acetone; diethylether; ethyl acetate; acetonitrile; and methylethylketon.

10 12. The process according to any one of the preceding claims, wherein a second solvent is immiscible with water.

13. The process according to any one of claims 1 to 8, wherein none of the solvent vapours are aqueous.

14. The process according to claim 13, wherein one or more of  
15 the non-aqueous solvents is selected from the group consisting of per-fluorocarbons, dichloromethane, chloroform, ether, ethyl acetate, methyl-tert-butyl ether, hexane, heptane, n-dodecane, m-xylene, isopentene isooctane, tetrahydrofuran, dimethyl sulfoxide, dimethylformamide, toluene, glacial acetic acid, and acetonitrile.

20 15. The process according to any one of claims 1 to 14, wherein the drying gas being supplied to the chamber comprises two or more solvent vapours having different predetermined dew points.

25 16. The process according to claim 15, wherein a dew point is selected to promote the evaporation of a solvent component from the particles being formed.

17. The process according to claim 15, wherein a dew point is selected to suppress the evaporation of a solvent component from the particles being formed.

30 18. The process according to any of claims 1 to 17, wherein the liquid feed comprises a bioactive compound having a low aqueous solubility and dissolution rate, and a hydrophilic polymer.

19. The process according to claim 18, wherein the liquid feed contains a mixture of organic solvent and 1-10 %(vol/vol) of water.

20. The process according to claims 18 or 19, wherein the bio-

active compound is selected among the group consisting of BCS Class II and Class IV drug compounds.

21. The process according to claim 18, wherein the hydrophilic polymer is selected among the group consisting of  
5 hydroxypropylmethylcelluloses and polyvinylpyrrolidones.

22. The process according to any of the claims 1 to 21, wherein the liquid feed comprises a solution of biomolecules in an organic solvent, and wherein water in an amount of 1-10% (vol/vol) is furthermore added to the liquid feed.

10 23. The process according to claim 22, wherein the biomolecule is selected among the group consisting of proteins, monoclonal antibodies, vaccines, peptides and oligonucleotides.

24. The process according to any of the claims 18 to 23, wherein the organic solvent is acetonitrile, ethanol, or acetone.

15 25. The process according to any of the claims 18 to 24, wherein the amount of water is 1.5 to 5 %(vol/vol).

26. A process for the preparation of spray dried particles, comprising the steps of:

20 a. spraying in a chamber a liquid feed comprising a solvent mixture and suspended and/or dissolved component(s),  
b. supplying a drying gas to the chamber  
c. allowing the sprayed liquid feed to interact with the drying gas,

25 d. collecting the at least partly dried particles, and  
e. discarding or recycling the spend drying gas,  
wherein the solvent mixture comprises a main solvent and a co-solvent.

27. The process according to claim 26, wherein the co-solvent is water.

30 28. The process according to claim 26 or 27, wherein the co-solvent is present in an amount of 0.5-30% (vol/vol).

29. The process according to claim 28, wherein the co-solvent is present in an amount of 1-10% (vol/vol).

30. The process according to any of the claims 26 to 29,



wherein the amount of water is 1.5 to 5 %(vol/vol).

31. The process according to any of the claims 26 to 30, wherein the main solvent is more volatile than the co-solvent.

32. The process according to any of the claims 26 to 31, where-  
5 in the main solvent is acetonitrile, ethanol, or acetone.

33. The process according to any of the claims 26 to 32, wherein the temperature of the spent drying gas is in the range of -10°C to 80°C.

34. The process according to any of the claims 26 to 33,  
10 wherein the temperature of the spent drying gas is in the range of -10°C to 40°C.

35. The process according to any of the claims 26 to 34, wherein the spray dried particles include a bioactive compound having a low aqueous solubility and dissolution rate, and a hydrophilic polymer.

15 36. The process according to any of the claims 26 to 35, wherein the spray dried particles include a biomolecule selected among the group consisting of proteins, peptides, mono- or polyclonal antibodies, nucleotides, microorganisms, and biopharmaceutical macromolecules in general.

20 37. The process according to claim 36, wherein microorganism is selected from the group comprising bacteria, virus, yeast, fungus and algae.

38. The process according to claim 36, wherein the biomolecule comprises a protein selected from the group comprising enzymes and  
25 hormones.

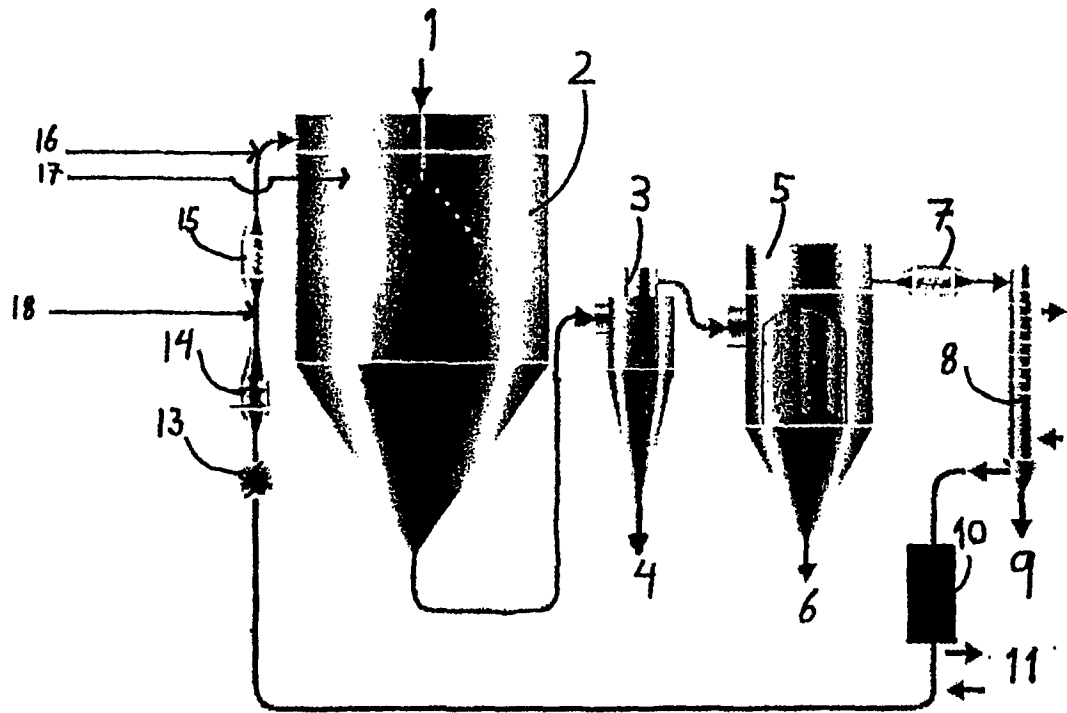
39. The process according to claim 36, wherein the biomolecule is a nucleotide selected from the group consisting of synthetic oligonucleotides and siRNA molecules.

40. The process according to any of the claims 1 to 39, wherein  
30 the residual water level of the spray dried particles is in the range of 1-4%.

41. The process according to any of the claims 1 to 40, wherein the spray dried particles are post-dried.

42. The process according to claim 41, wherein the post-drying

is performed in a fluid bed.



# INTERNATIONAL SEARCH REPORT

International application No  
PCT/DK2011/050209

<b>A. CLASSIFICATION OF SUBJECT MATTER</b> INV. A61K9/16 ADD.				
According to International Patent Classification (IPC) or to both national classification and IPC				
<b>B. FIELDS SEARCHED</b>				
Minimum documentation searched (classification system followed by classification symbols) A61K				
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched				
Electronic data base consulted during the international search (name of data base and, where practical, search terms used) EPO-Internal, CHEM ABS Data, EMBASE, WPI Data, BIOSIS, FSTA				
<b>C. DOCUMENTS CONSIDERED TO BE RELEVANT</b>				
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.		
X  Y	WO 2005/011636 A2 (PFIZER PROD INC [US]; BEYERINCK RONALD ARTHUR [US]; DOBRY DANIEL ELMON) 10 February 2005 (2005-02-10) page 31, line 10 - page 32, line 35 page 7, line 18 - line 26 page 16, line 14 - line 16 page 19, line 19 - line 22 examples -----	1,2,5,6, 8,10,11, 16-18,24 1-25		
X  Y	WO 02/085326 A2 (ADVANCED INHALATION RES INC [US]; PENN STATE RES FOUND [US]) 31 October 2002 (2002-10-31) page 12, line 10 - page 14, line 2 claims 1-28 ----- -/--	1,8-13, 16,17, 19,22-25 1-25		
<table style="width: 100%; border: none;"> <tr> <td style="width: 50%; border: none;"> <input checked="" type="checkbox"/> Further documents are listed in the continuation of Box C.                 </td> <td style="width: 50%; border: none;"> <input checked="" type="checkbox"/> See patent family annex.                 </td> </tr> </table>			<input checked="" type="checkbox"/> Further documents are listed in the continuation of Box C.	<input checked="" type="checkbox"/> See patent family annex.
<input checked="" type="checkbox"/> Further documents are listed in the continuation of Box C.	<input checked="" type="checkbox"/> See patent family annex.			
* Special categories of cited documents :				
<table style="width: 100%; border: none;"> <tr> <td style="width: 50%; border: none; vertical-align: top;">                 "A" document defining the general state of the art which is not considered to be of particular relevance                  "E" earlier document but published on or after the international filing date                  "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)                  "O" document referring to an oral disclosure, use, exhibition or other means                  "P" document published prior to the international filing date but later than the priority date claimed             </td> <td style="width: 50%; border: none; vertical-align: top;">                 "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention                  "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone                  "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.                  "&amp;" document member of the same patent family             </td> </tr> </table>			"A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art. "&" document member of the same patent family
"A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art. "&" document member of the same patent family			
Date of the actual completion of the international search  <p style="text-align: center; font-size: 1.2em;">27 September 2011</p>		Date of mailing of the international search report  <p style="text-align: center; font-size: 1.2em;">06/10/2011</p>		
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016		Authorized officer  <p style="text-align: center; font-size: 1.2em;">Schüle, Stefanie</p>		

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/DK2011/050209

## Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1.  Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
  
2.  Claims Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
  
3.  Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1.  As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2.  As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.
3.  As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
  
4.  No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

### Remark on Protest

- The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- No protest accompanied the payment of additional search fees.

## INTERNATIONAL SEARCH REPORT

International application No

PCT/DK2011/050209

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	VEHRING ET AL: "Particle formation in spray drying", JOURNAL OF AEROSOL SCIENCE, PERGAMON, vol. 38, no. 7, 1 July 2007 (2007-07-01), pages 728-746, XP022167042, ISSN: 0021-8502, DOI: 10.1016/J.JAEROSCI.2007.04.005 the whole document	1-25
X	EP 2 172 190 A1 (LICONSA S A LAB [ES]) 7 April 2010 (2010-04-07)	26,27, 31-35,40
Y	examples	25-42
X	US 2003/163931 A1 (BEYERINCK RONALD A [US] ET AL) 4 September 2003 (2003-09-04)	26-29, 31-35,40
Y	example 3	25-42
X	US 5 985 248 A (GORDON MARC S [US] ET AL) 16 November 1999 (1999-11-16)	26-28, 31-36,40
Y	claims 1-13 examples table 2	25-42
X	WO 03/079993 A2 (ADVANCED INHALATION RES INC [US]; JACKSON BLAIR [US]; JOHNSTON LLOYD []) 2 October 2003 (2003-10-02)	26,27, 31-36, 38,40
Y	examples	25-42
X	US 2007/172430 A1 (BRITO LUIS [US] ET AL) 26 July 2007 (2007-07-26)	26-28, 31-36, 39,40
Y	examples	25-42
Y	MAA YF ET AL: "Effect of spray drying and subsequent processing conditions on residual moisture content and physical/biochemical stability of protein inhalation powders", PHARMACEUTICAL RESEARCH, KLUWER ACADEMIC PUBLISHERS, NEW YORK, NY, US, vol. 15, no. 5, 1 May 1998 (1998-05-01), pages 768-775, XP002114088, ISSN: 0724-8741, DOI: 10.1023/A:1011983322594 the whole document	41,42

## INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/DK2011/050209

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Information on patent family members

International application No

PCT/DK2011/050209

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
----- US 2007172430	A1	26-07-2007 US 2011077284 A1	31-03-2011 -----



**FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210**

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

## 1. claims: 1-25

A process for the preparation of spray dried particles, comprising the steps of:

- a) spraying in a chamber a liquid feed comprising one or more solvents and suspended and/or dissolved component(s),
- b) supplying a drying gas to the chamber, said drying gas comprising one or more solvent vapours having a certain dew point,
- c) allowing the sprayed liquid feed to interact with the drying gas,
- d) collecting at least partly dried particles, and
- e) discarding or recycling spend drying gas,

wherein the dew point(s) of the one or more solvent vapours is selected to provide a desired property of the spray dried particles.

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## 2. claims: 26-42

A process for the preparation of spray dried particles, comprising the steps of:

- a) spraying in a chamber a liquid feed comprising a solvent mixture and suspended and/or dissolved component(s),
- b) supplying a drying gas to the chamber
- c) allowing the sprayed liquid feed to interact with the drying gas,
- d) collecting the at least partly dried particles, and
- e) discarding or recycling the spend drying gas, wherein the solvent mixture comprises a main solvent and a cosolvent.

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