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1,4 O-linked Saccharose Derivatives for Stabilising Antibodies or Antibody Derivatives

Field of the Invention

The invention concerns the application of novel oligosaccharides / oligosaccharide mixtures for the production and stabilisation of pharmaceutical compositions, chiefly powders, that contain antibodies or antibody derivatives as pharmaceutical active substance. The production of powders is preferably accomplished through spray drying or freeze drying. The present invention particularly concerns corresponding antibody-containing powders as well as processes for their production.

Background

Active substances/preparations of active substances formulated in aqueous solutions are to some extent subject to instabilities that may lead to reduced efficacy or bioactivity and elevated toxicity or incompatibilities. This applies to both conventional pharmaceuticals and peptide- or protein-containing active substances. The stability of pharmaceutical active substances can be positively affected through modification of the structure (internal) or through the addition of suitable adjuvants (external).

A conventional process for external stabilisation of pharmaceutical active substances is the application of suitable adjuvants. Adjuvants that stabilise active substances can be broadly classified into: sugars and polyols, amino acids, amines, salts, polymers, and surfactants.

Sugars and polyols are often used as nonspecific stabilisers. Their stabilising effect on biological active substances is chiefly ascribed to "preferential exclusion" (Xie and Timasheff, 1997, Biophysical Chemistry 64(1-3), 25-43; Xie and Timasheff, 1997, Protein Science, 6(1), 211-221; Timasheff, 1998, Advances in Protein Chemistry, 51, 355-432). During the selection of sugars, reducing sugars are mostly avoided for biological active substances. Saccharose and trehalose as non-reducing sugars are preferably used. Other examples of suitable adjuvants are glucose, sorbitol, glycerol (Bector and Mehta, 1992, Journal of Pharmacy and Pharmacology, 44 (7), 600-3; Ti-

masheff, 1993, Annual Review of Biophysics and Biomolecular Structure, 22, 67-97; Chang et al., 1993, Pharmaceutical Research, 10(10), 1478-83), and Mannitol (Hermann et al., 1996, Pharmaceutical Biotechnology, 9 (Formulation, Characterisation, and Stability of Protein Drugs) 303-328; Chang et al., 1996, Pharmaceutical Research, 13(5), 756-761). Also known is the stabilising effect that a wide variety of polymers have on pharmaceutical active substances, chiefly proteins, such as e.g. antibodies. Human serum albumin (HAS) frequently used in the past, while in fact featuring very good stabilising and aggregation-inhibiting properties, has in the meantime been found unsuitable because of its potential contamination with blood-borne pathogens. Among previously known polymers, hydroxypropyl-β-cyclodextrin (HP-β-CD) is especially suitable, since it can also be used parenterally in a completely safe way. Further examples are higher-molecular dextrans (18 to 82 kD), PVP, heparin, type A and B gelatines, and hydroxyethyl starch (HES), heparin, dextran sulphate, polyphosphoric acid, poly-L-glutamic acid, poly-L-lysine.

Alongside sugars and polyols, amino acids can also be used in a stabilising role or in combination with other adjuvants. Amino acids are chiefly used in the stabilisation of proteins. For example, addition of histidine, glycine, sodium aspartate (Na-Asp), glutamate, and lysine hydrochloride (Lys-HCl) inhibits the aggregation of rhKGF in 10 mM sodium phosphate buffer (pH 7.0) together with 5% mannitol (Zhang et al., 1995, Biochemistry, 34 (27), 8631-41). Combination of amino acids and propylene glycol, for example, improves the structural stability of rhCNTF (Dix et al., 1995, Pharmaceutical Research (Supplement), 12, S97). Lysine and arginine enhance the thermal stability of IL-1R (Tm enhancement), whereas glycine and alanine have a destabilising effect (Remmele et al., 1998, Pharmaceutical Research, 15(2), 200-208).

The stability of pharmaceutical active substances can be moreover enhanced through various drying processes. Drying, however, also mostly proceeds in the presence of adjuvants intended to maintain the stability of active substances and to improve the properties of the dry powder. A decisive factor affecting stabilisation through drying is immobilisation of the active substance in an amorphous matrix. The amorphous state confers high viscosity with low molecular mobility and low reactivity. Advantageous adjuvants must therefore be able to form an amorphous matrix having the high-

est possible glass transition temperature wherein the active substance is embedded. Selection of adjuvants therefore particularly depends on their stabilisation capabilities. Other factors, such as the pharmaceutical acceptability of the adjuvant, its influence on particle formation, dispersibility, and fluidity, also play an important role, particularly in respect of spray drying processes.

Spray drying constitutes an especially suitable process for enhancement of the chemical and physical stability of peptide-/protein-containing pharmaceutical active substances (Maa et al., 1998, Pharmaceutical Research, 15(5). 768-775). Spray drying is being increasingly used particularly in the field of pulmonary therapy (US 5,626,874; US 5,972,388; Broadhead et al., 1994, J. Pharm. Pharmacol., 46(6), 458-467), since application in an inhaler in the meantime represents a viable alternative in the treatment of systemic diseases (WO 99/07340). A prerequisite is that the mean particle size of powders should be in the 1-10 μm range, preferably in the 1-7.5 μm range, so that the particles can penetrate into deeper lung segments and thus into the bloodstream. For example, DE-A-179 22 07 describes the production of corresponding spray drying particles. In the meantime, numerous processes for the production of corresponding powders have been described (WO 95/31479; WO 96/09814; WO 96/32096; WO 96/32149; WO 97/41833; WO 97/44013; WO 98/16205; WO 98/31346; WO 99/66903; WO 00/10541; WO 01/13893; Maa et al., 1998, ibid; Vidgrén et al., 1987, Int. J. Pharmaceutics, 35, 139-144; Niven et al., 1994, Pharmaceutical Research, 11(8), 1101-1109).

Also suitable as adjuvants are sugars and their alcohols (e.g. trehalose, lactose, saccharose, or mannitol) as well as various polymers (Maa et al., 1997, Pharm. Development and Technology, 2(3), 213-223; Maa et al., 1998, ibid, Adler, 1998, Dissertation University of Erlangen; Constantino et al., 1998, J. Pharm. Sci, 87(11), 1406-1411). The adjuvants chiefly used, however, have various disadvantages. For example, addition of trehalose and mannitol impairs the fluidity of spray drying formulations (C. Bosquillon et al., 2001, Journal of Controlled Release, 70(3), 329-339). At a content of more than 20 weight percent, mannitol additionally tends to recrystallise (Constantino et al., 1998, ibid), with stabilising effects dramatically decreasing. Lactose, a frequently used adjuvant, while improving the fluidity of spray drying formula-

tions (C. Bosquillon et al., 2001, ibid), raises problems particularly during the formulation of peptide-/protein-containing active substances, since lactose, because of its reducing property, may engage in destabilising Maillard reactions with peptides/proteins.

During spray drying of antibodies without addition of stabilisers, dehydration, heat, and shearing regularly lead to unfolding of the native secondary structure and thus to dramatic loss of bioactivity. Previously inward facing hydrophobic fractions of the antibody then revert to facing outwards. This progressively occurs on the hydrophobic interfaces between the water droplets generated during spray drying and ambient air. Antibodies in the aqueous phase moreover accumulate to form dimers or higher-order aggregates. Such aggregation is often irreversible. The high temperature at which the proteins are sprayed further represents a critical parameter. The high energy consumption may lead to destabilisation of the peptide bonds and to denaturation of the antibody. Aggregation of spray-dried antibodies further occurs during storage of powders. The residual water content of the powder then exerts a particularly adverse effect. Protein aggregates are characterised by reduced or absent biological activity and reinforced antigenicity.

Multiple sugars described as Coupling Sugars (oligosaccharides) with their principal components of maltosyl sucrose and glucosyl sucrose as well as lactosucrose are used in the food industry. They are used as fillers and dispersants, alongside sweeteners such as aspartame, as moderately sweet components in chewing gums, for stabilisation of trehalose syrups against crystallizing out, or as so-called NDOs (non-digestible oligosaccharides). Also known is improvement and stabilisation of the sweetening quality of aspargyl peptides or the sweet-sour relationship in ballast- and sweetener-containing beverages (US 2003/0059511, EP 1 223 175, DE 199 53 727). Further known from US 5,489,577 and EP 0630 651 is the application of oligosaccharides for stabilisation of suspensions produced from therapeutic proteins and fat or oil bases. It is stated that, without premixing with the oligosaccharides during blending and kneading with the hydrophobic, semi-solid masses, the proteins would lose their activity. The stabilisation potential over storage, in hydrophilic mixtures or in powders, is not mentioned in any way.

A task of the invention was to propose new adjuvants for the production of pharmaceutical preparations. The corresponding preparations were to be distinguished, inter alia, by good long-term stability.

A further task of the present invention was to provide new adjuvants for the production of dried pharmaceutical preparations. The corresponding powdered pharmaceutical preparations were to be distinguished by good long-term stability and, if possible, by inhalability.

A further task of the present invention was to provide novel adjuvants for the production of peptide/protein-containing pharmaceutical formulations, particularly those generated by spray drying. The corresponding peptide/protein-containing pharmaceutical preparations were to be distinguished by good long-term stability and, if possible, by inhalability.

A further task of the present invention was to provide novel adjuvants for the formulation of therapeutic antibodies or antibody derivatives, particularly those generated by spray drying. The corresponding antibody-containing pharmaceutical preparations were again to be distinguished by good long-term stability and, if possible, by inhalability.

A further task of the present invention was to provide corresponding pharmaceutical preparations for application in an inhaler, whether in the form of a dry powder, propellant-containing metered-dose aerosol, or propellant-free inhalation solution.

The tasks underlying the invention are resolved by the following statements as well as by the objects/processes represented in the patent claims.

Summary of the Invention

According to a first aspect, there is provided a composition containing at least one antibody or one functional antibody derivative thereof and one or more 1,4 O-linked saccharose derivatives selected from the compounds: 1,4 O-linked D-Gal-saccharose (lactosucrose), 1,4 O-linked D-Glu-

saccharose (glucosyl sucrose), or 1,4 O-linked Glu-Glu-saccharose (maltosyl sucrose). Preferred combinations are those that contain glucosyl and maltosyl sucrose.

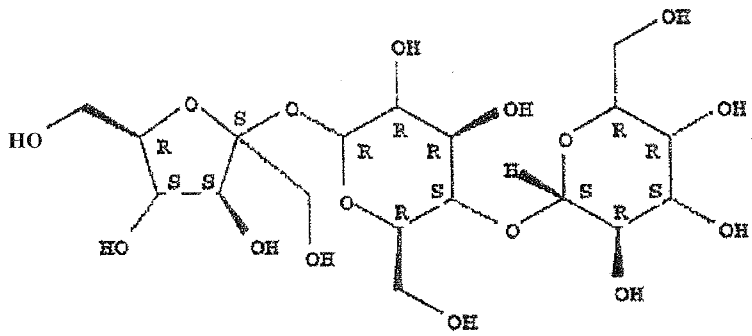
According to a second aspect, there is provided a powder as disclosed above, characterised in that the particles in the powder have an MMD between 1 and 10 µm.

According to a third aspect, there is provided a process for production of a powder as disclosed above, characterised in that a) an antibody or functional antibody derivative is dissolved / suspended in an aqueous solution / suspension; b) one or more 1, 4 O-linked saccharose derivatives selected from the combinations lactosucrose, glucosyl sucrose, or maltosyl sucrose or a sugar mixture containing at least one of these 1, 4 O-linked saccharose derivatives is / are dissolved / suspended in an aqueous solution / suspension; c) where an antibody or functional antibody derivative and 1, 4 O-linked saccharose derivative or the sugar mixture containing at least 1, 4 O-linked saccharose derivative are dissolved / suspended in different solutions / suspensions, these are mixed; d) the solution / suspension containing the antibody or functional antibody derivative and the 1, 4 O-linked saccharose derivative(s) are dried.

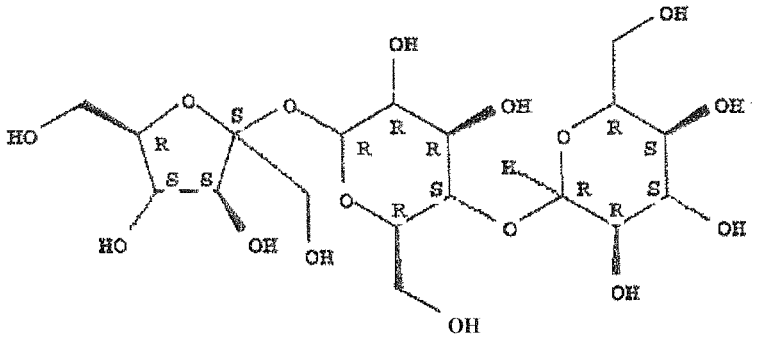
According to a fourth aspect, there is provided a powder as disclosed above for use as of a medicinal drug.

According to a fifth aspect, there is provided a spray-dried powder as disclosed above for use as a medicinal inhalant.

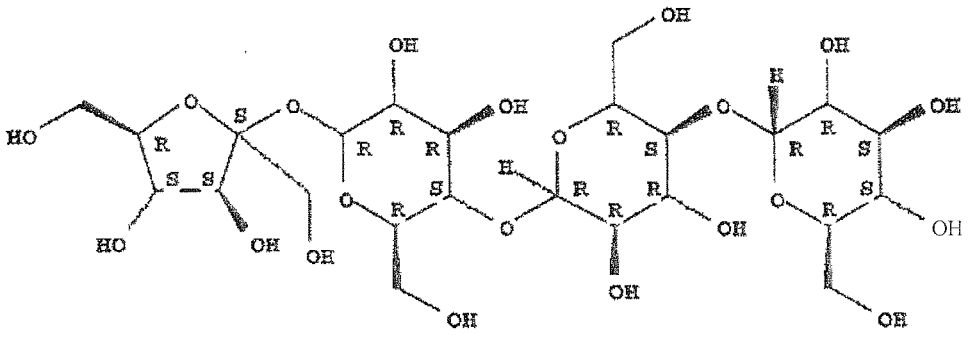
The term lactosucrose further means molecules with the following structural formula:



Glucosyl sucrose in the sense of the present disclosure is further understood to mean molecules with the following structural formula:



The term maltosyl sucrose further means molecules with the following structural formula:



According to a further embodiment of the disclosure, the corresponding compositions contain, alongside the antibody or antibody derivative and the 1,4 O-linked saccharose derivative, additionally one or more mono-, di- and/or polysaccharides, whereby the additional application of mono- and/or di-saccharides is preferred. Compositions produced from a combination of glucosyl and maltosyl sucrose in combination with one antibody or one antibody derivative have also proven to accord with the disclosure, again preferably in combination with mono-, di- and/or polysaccharides.

Compositions particularly according with the disclosure are thus those with a fraction of **(a)** 25 to 99.99% (w/w), preferably 80 to 90% (w/w), of at least one 1,4 O-linked saccharose derivative or of a sugar mixture containing at least one 1,4 O-linked saccharose derivative (in relation to the dry weight of the composition) and **(b)** one antibody or one antibody derivative, preferably at a concentration between 0.01 and 75% (w/w), again in relation to the dry weight of the composition, whereby the sum of the weight percentages of sugar/sugar mixture and antibody or antibody derivative amounts to max 100% (w/w).

The compositions may be aqueous compositions, solid or semi-solid compositions. Particularly preferred are solid compositions, preferably powdered compositions. It was surprisingly found that corresponding powdered antibody-containing compositions i) form an amorphous structure, ii) have a glass transition temperature greater than 40°C, and iii) have a low tendency to recrystallise. This particularly applies to spray-dried powders.

The compositions according to the disclosure, particularly powdered compositions, alongside at least one 1,4 O-linked saccharose derivative or one sugar mixture containing at least one 1,4 O-linked saccharose derivative, may contain further adjuvants, such as e.g. amino acids, peptides, proteins, and other sugars. Particularly advantageous are compositions which, alongside at least one 1,4 O-linked saccharose derivative or one sugar mixture containing at least one 1,4 O-linked saccharose derivative and one antibody or antibody derivative, contain at least one amino acid, one peptide, preferably a di-peptide or tri-peptide, and/or one salt. According to a preferred embodiment, the present disclosure preferably concerns powdered compositions, such as

e.g. spray-dried powders which, in relation to their dry weight, contain **(a)** between 25 and 90% (w/w) of at least one 1,4 O-linked saccharose derivative or one sugar mixture containing at least one 1,4 O-linked saccharose derivative, **(b)** between 1 and 39.99% (w/w) of at least one amino acid and/or at least one peptide as a further adjuvant, and **(c)** at least 0.01% (w/w) of one antibody or antibody derivative. The further adjuvant preferably refers to the amino acid isoleucine or to a peptide, preferably to a di- or tri-peptide, with at least one isoleucine group. According to a specific embodiment, the present disclosure concerns compositions, such as e.g. spray-dried powders which, in relation to their dry weight, contain **(a)** around 60 to 80% (w/w) of at least one 1,4 O-linked saccharose derivative or one sugar mixture containing at least one 1,4 O-linked saccharose derivative, **(b)** around 10 to 19.99% (w/w) of at least one amino acid, preferably isoleucine, and **(c)** around 0.01 to 30% (w/w) of one antibody or antibody derivative. According to a further alternative embodiment, the present disclosure concerns compositions, preferably powdered compositions, such as e.g. spray-dried powders, which, in relation to their dry weight, contain **(a)** around 60 to 80% (w/w) of at least one 1,4 O-linked saccharose derivative or one sugar mixture containing at least one 1,4 O-linked saccharose derivative, **(b)** around 1 to 19.99% (w/w) of a peptide, preferably an isoleucine-containing peptide, particularly preferably an isoleucine-containing di- or tri-peptide, more preferably tri-isoleucine, and **(c)** around 0.01 to 39% (w/w) of one antibody or antibody derivative. After being mixed with isoleucine or isoleucine-containing tri-peptides, particularly powders with a corresponding composition show very good fluidity. Corresponding spray-dried powders further have a very high fraction of inhalable particles. Corresponding powders further have very good process and storage stability.

According to a further embodiment, the present disclosure concerns corresponding powdered compositions, preferably spray-dried powders, which contain **a)** one or more 1,4 O-linked saccharose derivative(s) in the combinations described above or one sugar mixture containing at least one 1,4 O-linked saccharose derivative and **b)** at least one antibody or one antibody derivative, whereby the powder has a glass transition temperature greater than 40°C, preferably greater than 45°C, more preferably greater than 50°C, still more preferably greater than 55°C, and particularly preferably greater than 60°C. The corresponding powders according to the disclosure normally have a maximum glass transition temperature of around 96 to 110°C. In individual

cases, however, the value may be even higher. The fraction of added adjuvant, particularly the fraction of 1,4 O-linked saccharose derivative or the fraction of derivative mixture in the powder, is primarily responsible for the corresponding glass transition temperature.

According to a further embodiment, the present disclosure concerns pharmaceutical compositions containing antibodies or antibody derivatives for applications in an inhaler, which contain one of the powdered compositions according to the disclosure described here and consist thereof. Preferred in this context are pharmaceutical compositions which contain the powders according to the disclosure as propellant-containing metered-dose aerosols or propellant-free inhalation solutions. The powders according to the disclosure used for production of the pharmaceutical compositions, preferably powders produced by spray drying, are distinguished according to a further embodiment by a high fraction of inhalable particles with a mean aerodynamic particle diameter (mass mean aerodynamic diameter, MMAD) smaller than 10 μm, preferably 0.5-7.5 μm, more preferably 0.5-5.5 μm, particularly preferably 0.5-5.0 μm.

The disclosure further proposes processes for production of the corresponding compositions according to the disclosure, preferably powdered compositions, such as e.g. production of spray-dried powders, characterised in that an aqueous composition which contains a) one or more 1,4 O-linked saccharose derivative(s) or one sugar mixture containing at least one 1,4 O-linked saccharose derivative and b) at least one antibody or one antibody derivative is produced, and, in the case of a powdered composition, the latter is dried under suitable conditions, e.g. sprayed.

Description of the Figures

All percentage data specified in the descriptions relate to concentrations of solids in solutions (w/w). All legends in the drawings described below relate to the percentage (w/w) composition of powders achieved by spray drying and freeze drying with ensuing pulverisation. The legends further specify the total solids concentrations of solutions (total solids = TS) in percent (w/w). In the legend of Figure 8, Coupling Sugar is abbreviated to CS. In the legends of Figures 18, 19, 20, and 21, tri-isoleucine is abbreviated to Ile3. Figures 15, 16, 17, 18, 19, 20, and 21 further specify the atomisation

rate (AAF = atomising air flow) set during the spray drying process on the Büchi B-290. The figure 40 then corresponds to a real volume flow of ~ 0.67 m^3/h, 50 to a real volume flow of ~ 1.05 m^3/h, and 60 to a real volume flow of ~ 1.74 m^3/h. In all other drawings, the atomisation rate of 40 corresponded to a real volume flow of ~ 0.67 m^3/h respectively.

Figure 1 shows the aggregate content after freeze drying, pulverisation, one week's open storage at 75% relative humidity and 40°C (forced storage stability), and reconstitution. Aqueous solutions with a) 4.5% LS55P fraction and 0.5% IgG fraction, b) 4.5% Coupling Sugar fraction and 0.5% IgG fraction, c) 5.0% IgG fraction, and d) 4.5% mannitol fraction and 0.5% IgG fraction were freeze-dried. Both the LS55P- and Coupling Sugar-containing powders are distinguished by a low aggregate fraction.

Figure 2 shows the aggregate content after freeze drying, pulverisation, equilibration, and four weeks' dry storage at 40°C (equilibrated storage stability), and reconstitution. Aqueous solutions with a) 4.5% LS55P fraction and 0.5% IgG fraction, b) 4.5% Coupling Sugar fraction and 0.5% IgG fraction, c) 5.0% IgG fraction, and d) 4.5% mannitol fraction and 0.5% IgG fraction were freeze-dried. Both the LS55P- and Coupling Sugar-containing powders are distinguished by a low aggregate fraction.

Figure 3 shows the aggregate content after freeze drying, pulverisation, vacuum drying, four weeks' dry storage at 40°C (vacuum-dried storage stability), and reconstitution. Aqueous solutions with a) 4.5% LS55P fraction and 0.5% IgG fraction, b) 4.5% Coupling Sugar fraction and 0.5% IgG fraction, c) 5.0% IgG fraction, and d) 4.5% mannitol fraction and 0.5% IgG fraction were freeze-dried. Both the LS55P- and Coupling Sugar-containing powders are distinguished by a low aggregate fraction.

Figure 4 shows the aggregate content after spray drying, one week's open storage at 75% relative humidity and 40°C (forced storage stability), and reconstitution. Aqueous solutions with a) 9% LS55P fraction and 1% IgG fraction, b) 9% Coupling Sugar fraction and 1% IgG fraction, c) 9% Coupling Sugar S fraction and 1% IgG fraction, d) 9% trehalose fraction and 1% IgG fraction, and e) 10% IgG fraction were spray-

dried. Both the LS55P- as well as the Coupling Sugar- and Coupling Sugar S-containing powders are distinguished by a low aggregate fraction.

Figure 5 shows the aggregate content after spray drying, one week's open storage at 75% relative humidity and 40°C (forced storage stability), and reconstitution. Aqueous solutions with a) 8% LS55P fraction, 1% isoleucine fraction, and 1% IgG fraction, b) 8% Coupling Sugar fraction, 1% isoleucine fraction, and 1% IgG fraction, c) 8% Coupling Sugar S fraction, 1% isoleucine fraction, and 1% IgG fraction, d) 8% trehalose fraction, 1% isoleucine fraction, and 1% IgG fraction, and e) 10% IgG fraction were spray-dried. Both the LS55P- as well as the Coupling Sugar- and Coupling Sugar S-containing powders are distinguished by a low aggregate fraction.

Figure 6 shows the aggregate content after spray drying, one week's open storage at 75% relative humidity and 40°C (forced storage stability), and reconstitution. Aqueous solutions with a) 3% LS55P fraction, 6% citrulline fraction, and 1% IgG fraction, b) 3% Coupling Sugar fraction, 6% citrulline fraction, and 1% IgG fraction, c) 3% Coupling Sugar S fraction, 16% citrulline fraction, and 1% IgG fraction, d) 3% trehalose fraction, 6% citrulline fraction, and 1% IgG fraction, and e) 10% IgG fraction were spray-dried. Both the LS55P- as well as the Coupling Sugar- and Coupling Sugar S-containing powders are distinguished by a low aggregate fraction.

Figure 7 shows the aggregate content after spray drying, one week's open storage at 75% relative humidity and 40°C (forced storage stability), and reconstitution. Aqueous solutions with a) 9.9% LS55P fraction and 0.1% IgG fraction, b) 9% LS55P fraction and 1% IgG fraction, c) 6% LS55P fraction and 4% IgG fraction, d) 4% LS55P fraction and 6% IgG fraction, e) 2.5% LS55P fraction and 7.5% IgG fraction, f) 9% LS55P fraction and 1% IgG fraction, g) 0.5% LS55P fraction and 9.5% IgG fraction, and h) 10% IgG fraction were spray-dried. The LS55P-containing powders are distinguished by a low aggregate fraction.

Figure 8 shows the aggregate content after spray drying, one week's open storage at 75% relative humidity and 40°C (forced storage stability), and reconstitution. Aqueous solutions with a) 9.9% Coupling Sugar fraction and 0.1% IgG fraction, b) 9% Coupling Sugar fraction and 1% IgG fraction, c) 6% Coupling Sugar fraction and 4%

IgG fraction, d) 4% Coupling Sugar fraction and 6% IgG fraction, e) 2.5% Coupling Sugar fraction and 7.5% IgG fraction, f) 1% Coupling Sugar fraction and 9% IgG fraction, and g) 10% IgG fraction were spray-dried. The LS55P-containing powders are distinguished by a low aggregate fraction.

Figure 9 shows the aggregate content after spray drying, one week's open storage at 75% relative humidity and 40°C (forced storage stability), and reconstitution. Aqueous solutions with a) 3.00% LS55P fraction and 0.33% IgG fraction, b) 2.9166% LS55P fraction, 0.0833% tri-isoleucine fraction, and 0.33% IgG fraction, c) 2.833% LS55P fraction, 0.166% tri-isoleucine fraction, and 0.33% IgG fraction, and d) 2.66% LS55P fraction, 0.33% tri-isoleucine fraction, and 0.33% IgG fraction were spray-dried. The LS55P-containing powders are distinguished by a low aggregate fraction. Protein aggregation is further significantly reduced by an increase in the tri-isoleucine fraction from 0% to 10% in relation to the total solids content of the LS55P-containing powders.

Figure 10 shows the aggregate content after spray drying, one week's open storage at 75% relative humidity and 40°C (forced storage stability), and reconstitution. Aqueous solutions with a) 3.00% LS90P fraction and 0.33% IgG fraction, b) 2.9166% LS90P fraction, 0.0833% tri-isoleucine fraction, and 0.33% IgG fraction, c) 2.833% LS90P fraction, 0.166% tri-isoleucine fraction, and 0.33% IgG fraction, and d) 2.66% LS90P fraction, 0.33% tri-isoleucine fraction, and 0.33% IgG fraction were spray-dried. The LS90P-containing powders are distinguished by a low aggregate fraction.

Figure 11 shows the aggregate content after spray drying, one week's open storage at 75% relative humidity and 40°C (forced storage stability), and reconstitution. Aqueous solutions with a) 2.66% LS90P fraction, 0.33% tri-isoleucine fraction, and 0.33% IgG fraction, b) 2.66% LS55P fraction, 0.33% tri-isoleucine fraction, and 0.33% IgG fraction, c) 2.66% saccharose fraction, 0.33% tri-isoleucine fraction, and 0.33% IgG fraction, d) 2.00% saccharose fraction, 0.66% lactose fraction, 0.33% tri-isoleucine fraction, and 0.33% IgG fraction, e) 2.66% raffinose fraction, 0.33% tri-isoleucine fraction, and 0.33% IgG fraction, f) 2.66% hydroxyethyl starch (HES) fraction, 0.33% tri-isoleucine fraction, and 0.33% IgG fraction, and g) 2.66% trehalose fraction, 0.33% tri-isoleucine fraction, and 0.33% IgG fraction were spray-dried. The LS90P-

and LS55P-containing powders are distinguished by a low aggregate fraction, particularly in comparison with raffinose and hydroxyethyl starch (HES) specified as state-of-the-art.

Figure 12 shows the aggregate content after spray drying, vacuum drying, four weeks' dry storage at 40°C (vacuum-dried storage stability), and reconstitution. Aqueous solutions with a) 9% Coupling Sugar fraction and 1% IgG fraction, b) 8% Coupling Sugar fraction, 1% (w/w) isoleucine fraction, and 1% IgG fraction, c) 3% Coupling Sugar fraction, 6% citrulline fraction, and 1% IgG fraction, and d) 10% IgG fraction were spray-dried. The Coupling Sugar-containing powders are distinguished by a low aggregate fraction.

Figure 13 shows the aggregate content after spray drying, vacuum drying, four weeks' dry storage at 40°C (vacuum-dried storage stability), and reconstitution. Aqueous solutions with a) 9.9% LS55P fraction and 0.1% IgG fraction, b) 9% LS55P fraction and 1% IgG fraction, c) 2.5% LS55P fraction and 7.5% IgG fraction, d) 1% LS55P fraction and 9% IgG fraction, e) 10% IgG fraction, f) 8% LS55P fraction, 1% isoleucine fraction, and 1% IgG fraction, and g) 3% LS55P fraction, 6% citrulline fraction, and 1% IgG fraction were spray-dried. The LS55P-containing powders are distinguished by a low aggregate fraction.

Figure 14a+b shows the aggregate content after spray drying, vacuum drying, one or three months' dry storage at 2-8°C, 25°C, and 40°C (1 or 3 months' stability), and reconstitution. Aqueous solutions with a) 3.00% LS90P fraction and 0.33% IgG fraction, b) 2.66% LS55P fraction, 0.33% isoleucine fraction, and 0.33% IgG fraction, c) 2.66% LS90P fraction, 0.33% isoleucine fraction, and 0.33% IgG fraction, d) 2.66% LS55P fraction, 0.33% tri-isoleucine fraction, and 0.33% IgG fraction, e) 2.66% LS90P fraction, 0.33% tri-isoleucine fraction, and 0.33% IgG fraction, and f) 3.33% IgG fraction were spray-dried. Both the LS90P- and LS55P-containing powders are distinguished by a particularly low aggregate fraction after three months' storage.

Figure 15a+b shows the aggregate content after spray drying, vacuum drying, one or three months' dry open storage at 29% relative humidity and 43% relative humidity at 25°C respectively (1 or 3 months' open stability), and reconstitution. Aqueous solu-

tions with a) 2.9166% LS90P fraction, 0.0833% tri-isoleucine fraction, and 0.33% IgG fraction at an AAF of 40, b) 2.833% LS90P fraction, 0.166% tri-isoleucine fraction, and 0.33% IgG fraction at an AAF of 40, c) 2.66% LS90P fraction, 0.33% tri-isoleucine fraction, and 0.33% IgG fraction at an AAF of 40, d) 1.60% LS90P fraction, 0.20% tri-isoleucine fraction, and 0.33% IgG fraction at an AAF of 40, e) 2.66% LS90P fraction, 0.33% tri-isoleucine fraction, and 0.33% IgG fraction at an AAF of 50, f) 2.66% LS90P fraction, 0.33% tri-isoleucine fraction, and 0.33% IgG fraction at an AAF of 60, and g) 3.33% IgG fraction at an AAF of 40 were spray-dried. The LS90P-containing powders are distinguished by a particularly low aggregate fraction after three months' storage.

Figure 16 shows the fine particle fraction (FPF) with a cut-off diameter smaller than 5 μm for various powders. The powders were produced by spray drying of aqueous solutions which have contained LS55P and IgG1 or LS55P, isoleucine and IgG1. The solutions were produced and sprayed as described under EXAMPLES. Isoleucine-containing powder has a FPF of ~35%, whereas isoleucine-free powder only has a FPF of ~16%.

Figure 17 shows the fine particle fraction (FPF) with a cut-off diameter smaller than 5 μm for various powders. The powders were produced by spray drying of aqueous solutions which have contained LS90P and IgG1 or LS90P, isoleucine and IgG1. The solutions were produced and sprayed as described under EXAMPLES. Isoleucine-containing powder has a FPF of ~28%, whereas isoleucine-free powder only has a FPF of ~23%.

Figure 18 shows the fine particle fraction (FPF) with a cut-off diameter smaller than 5 μm for various powders. The powders were produced by spray drying of aqueous solutions which have contained LS55P and IgG1 or LS55P, tri-isoleucine and IgG1. The solutions were produced and sprayed as described under EXAMPLES. Tri-isoleucine-containing powders have a FPF of more than 50 or 58%, whereas tri-isoleucine-free powder only has a FPF of ~16%.

Figure 19 shows the mass mean aerodynamic diameter (MMAD) and mass mean diameter (MMD) of various powders. The powders were produced by spray drying of aqueous solutions which have contained LS55P and IgG1 or LS55P, tri-isoleucine and IgG1. The solutions were produced and sprayed as described under EXAMPLES. All powders have a MMAD smaller than 5 µm and a MMD smaller than 3.5 µm. The diagram shows the effect of the tri-isoleucine fraction at constant total solids concentrations and spraying parameters on the MMAD and MMD. A 10% tri-isoleucine fraction related to the total solids content of the formulation significantly reduces the MMAD.

Figure 20 shows the fine particle fraction (FPF) with a cut-off diameter smaller than 5 µm for various powders. The powders were produced by spray drying of aqueous solutions which have contained LS90P and IgG1 or LS90P, tri-isoleucine and IgG1. The solutions were produced and sprayed as described under EXAMPLES. Tri-isoleucine-containing powders have a FPF of ~40% to ~59%, whereas tri-isoleucine-free powder only has a FPF of ~24%.

Figure 21 shows the mass mean diameter (MMD) and mass mean aerodynamic diameter (MMAD) of various powders. The powders were produced by spray drying of aqueous solutions which have contained LS90P and IgG1 or LS90P, tri-isoleucine and IgG1. The solutions were produced and sprayed as described under EXAMPLES. All powders have a MMAD smaller than 6.5 µm and a MMD smaller than 5 µm. The diagram shows the effect of the tri-isoleucine fraction at constant total solids concentrations and spraying parameters on the MMAD and MMD. A 10% tri-isoleucine fraction related to the total solids content of the formulation significantly reduces the MMAD. Both a lower solids content (e.g. TS: 2%) and a higher spraying pressure (AAF of 50 or 60), however, significantly reduce the MMD.

Figure 22 shows the residual monomer content after spray drying, forced storage, and reconstitution. Aqueous solutions with a) 3.33% (w/w) lysozyme fraction, b) 0.33% (w/w) lysozyme fraction and 3.0% (w/w) LS90P fraction, c) 0.33% (w/w) lysozyme fraction, 0.33% (w/w) isoleucine fraction, and 2.66% (w/w) LS90P fraction, and d) 0.33% (w/w) lysozyme fraction, 0.33% (w/w) tri-isoleucine fraction, and 2.66%

(w/w) LS90P fraction were sprayed. The LS90P-containing powder is distinguished by a high residual monomer content.

Figure 23 shows the aggregate content after spray drying, vacuum drying, three months' dry storage at 2-8°C, 25°C, and 40°C (3 months' stability), and reconstitution. Aqueous solutions with a) 3.33% (w/w) calcitonin fraction, b) 0.166% (w/w) calcitonin fraction and 3.166% (w/w) LS90P fraction, c) 0.166% (w/w) calcitonin fraction, 0.33% (w/w) isoleucine fraction, and 2.833% (w/w) fraction, and d) 0.166% (w/w) calcitonin fraction, 0.33% (w/w) tri-isoleucine fraction, and 2.833% (w/w) fraction were sprayed. The LS90P-containing powder is distinguished by a low aggregate content.

Figure 24 shows an inhaler for application of dry powder preparations.

Detailed description of the invention

Definitions

The terms and expressions used within the scope of this invention specification have the meanings defined below. The weight and weight percentage data, unless otherwise indicated, respectively relate to the dry weight of the compositions or to the solids content of the solutions / suspensions. The general embodiments "containing" and "contains" are inclusive of the more specific embodiment "consisting of". "Singular" and "plural" are further used without limitation.

The expression "1,4 O-linked saccharose derivative or a sugar mixture containing at least one 1,4 O-linked saccharose derivative" means i) a 1,4 O-linked saccharose derivative with one of the formulae specified in this patent specification, ii) a mixture thereof, preferably a mixture of maltosyl and glucosyl sucrose, iii) a mixture of at least one 1,4 O-linked saccharose derivative with one of the formulae specified above and further sugars, preferably a mixture of lactosucrose, lactose, and saccharose or of glucosyl and/or maltosyl sucrose, saccharose, fructose, and glucose, iv) a mixture of at least 55% (w/w) lactosucrose, max 25% (w/w) lactose, and max 10% (w/w) saccharose, v) a mixture of at least 88% (w/w) lactosucrose, max 10% (w/w) lactose and saccharose, vi) a mixture of respectively 25% (w/w) glucosyl and/or maltosyl sucrose, between 48 and 56% (w/w) saccharose and not more than 10% (w/w) glucose and

fructose, vii) a mixture of respectively 18% (w/w) glucosyl and maltosyl sucrose, between 11 and 15% (w/w) saccharose, and respectively between 5 and 9% (w/w) glucose, viii) a sugar mixture described as Nyuka-Oligo® LS40L (abbreviated to LS40L), Nyuka-Oligo® LS55L (abbreviated to LS55L), Nyuka-Oligo® LS55P (abbreviated to LS55P), Nyuka-Oligo® LS-90P (abbreviated to LS90P), Coupling Sugar®, or Coupling Sugar S® as made by Hayashibara Shoji Inc., Japan.

The expression "composition" means liquid, semi-solid or solid mixtures of at least two starting substances.

The term "pharmaceutically acceptable adjuvants" relates to adjuvants that can be optionally contained in the formulation within the scope of the invention. The adjuvants may e.g. have pulmonary applications without then having significantly adverse toxicological effects on subjects or subjects' lungs.

The expression "pharmaceutically acceptable salts" covers e.g. the following salts, although not limited thereto: salts of inorganic acids, such as chloride, sulphate, phosphate, diphosphate, bromide, and nitrate salts. Additionally salts of organic acids, such as malate, maleate, fumarate, tartrate, succinate, ethylsuccinate, citrate, acetate, lactate, methanesulphonate, benzoate, ascorbate, para-toluenesulphonate, palmoate, salicylate, and stearate as well as estolate, gluceptate, and lactobionate salts.

The term "pharmaceutically acceptable cations", without being limited thereto, covers e.g. lithium, sodium, potassium, calcium, aluminium, and ammonium (including substituted ammonium).

The expression "amino acid" means compounds containing at least one amino and at least one carboxyl group. Although the amino group is normally located in the α-position to the carboxyl group, any other arrangement in the molecule is conceivable. The amino acid may also contain other functional groups, such as e.g. amino, carboxamide, carboxyl, imidazole, thio, and other groups. Amino acids of natural or synthetic origin with racemic or optical (D or L form) activity, including the different stereoisomeric relationships, are used. For example, the term covers isoleucine as well

as D-isoleucine, L-isoleucine, racemic isoleucine, and the different relationships of both enantiomers.

The term "biological macromolecule" means, peptides, proteins, fats, fatty acids, or nucleic acids as well.

The term "peptide" or "polypeptide" means polymers of amino acids consisting of two to one hundred amino acid groups. The term peptide or polypeptide is used as a pseudonym and covers both homo- and heteropeptides, i.e. polymers of amino acids consisting of identical or different amino acid groups. A "di-peptide" is thus composed of two peptidically linked amino acids and a "tri-peptide" of three peptidically linked amino acids. The term "protein" used in this context means polymers of amino acids with more than 100 amino acid groups.

The term "analogues" means peptides/proteins wherein individual or more amino acids have been substituted, eliminated (e.g. fragments), added (e.g. derivatives with a C or N terminal extension), or otherwise modified from the native (wild type) sequence. Derivatisation of native proteins e.g. by sugar, polyethylene glycol, or the like is also possible. Analogues have a bioactivity of at least 10, 20, 30, or 40%, preferably of at least 50, 60, or 70%, and particularly preferably of at least 80, 90, 95, 100% or more than 100% of the bioactivity of the native, non-synthetic protein.

The expression "oligosaccharide" or "polysaccharide" means multiple sugars composed of at least three monomeric sugar molecules.

The expression "pure protein formulation" means a powder consisting of one or more antibodies or antibody derivatives and optionally a suitable buffer (typically 0 to 15% (w/w) in relation to the weight of the dry powder). The powder basically contains no other adjuvants, i.e. the content of any other adjuvants that may be included is less than 1% (w/w) in relation to the weight of the dry powder.

The term "spray-dried powder formulation" or "dry powder formulation" means powder formulations which normally contain less than around 10% (w/w) residual moisture, preferably less than 7% (w/w) residual moisture, particularly preferably less than

5% (w/w) residual moisture, and still more preferably less than 3% (w/w) residual moisture. Given constant spray, vacuum, or freeze drying conditions and identical adjuvants, the residual moisture largely depends on the type and fraction of the pharmaceutical active substance in the powder formulation.

The term "amorphous" means that the powdered formulations contain less than 10% crystalline fractions, preferably less than 7%, more preferably less than 5%, and particularly preferably less than 4, 3, 2, or 1%.

The term "inhalable" means that the powders are suitable for pulmonary application. Inhalable powders can be dispersed and inhaled with the aid of an inhaler so that the particles can reach the lungs and where necessary unfold systemic action via the alveoli. Inhalable particles e.g. have a median particle diameter (mass median diameter, MMD) between 0.4-10 μm, mostly between 0.5-5.0 μm, preferably between 1-3 μm and/or a median aerodynamic particle diameter (mass median aerodynamic diameter, MMAD) between 0.5-10 μm, preferably between 0.5-7.5 μm, more preferably between 0.5-5.5 μm, still more preferably between 1-5 μm, and particularly preferably between 1-4.5 μm.

Mass median diameter or MMD is a unit characterising the median particle size distribution, since the powders specified in the invention are generally polydisperse. The results are expressed as the diameter of the total volume distribution at 50% total throughput. The MMD values can be e.g. determined by means of laser diffractometry (cf. the chapter on EXAMPLES, Methods), although any other conventional method can also be used (such as e.g. electron microscopy, centrifugal sedimentation).

The term "median aerodynamic particle diameter" (= mass median aerodynamic diameter, MMAD) indicates the aerodynamic particle size at which 50% of powder particles normally have a smaller aerodynamic diameter. The method specified in this patent specification (cf. the chapter EXAMPLES, Methods) serves as the reference method for MMAD determination in doubtful cases.

The term "*fine particle fraction*" (FPF) describes the inhalable part of a powder consisting of particles with a particle size of ≤ 5 µm MMAD. In well dispersible powders, the FPF amounts to more than 20%, preferably more than 30%, particularly preferably more than 40%, still more preferably more than 50%, and more preferably more than 55%. The term "cut-off diameter" used in this context indicates the particles taken into account when determining the FPF. An FPF of 30% at a cut-off diameter of 5 µm (FPF_5) means that 30% of all particles in the powder have a mean aerodynamic particle diameter smaller than 5 µm.

The term "spray solution" means aqueous solutions or suspensions in which the pharmaceutical active substance is dissolved / suspended together with at least one adjuvant.

The term "time of flight" is the description used in a standard measurement method as described in more detail in the chapter on EXAMPLES. The MMAD and FPF are simultaneously determined during a time of flight measurement (cf. the chapter EXAMPLES, Methods).

A "surface-active" substance is able to reduce the surface tension of the solution wherein it is dissolved. The surface activity is e.g. measured by the tensiometer method proposed by Lecomte du Noüy (Bauer, Frömming, Führer, 6th edition).

Compositions according to the invention

The present invention concerns compositions, preferably powdered compositions such as e.g. spray-dried powders, containing **a)** one antibody or one antibody derivative as pharmaceutical active substance and **b)** one or more 1,4 O-linked saccharose derivative(s) selected from the combinations: 1,4 O-linked D-Gal-saccharose (lactosucrose), 1,4 O-linked D-Glu-saccharose (glucosyl sucrose), or 1,4 O-linked Glu-Glu-saccharose (maltosyl sucrose).

According to a further embodiment of the invention, the corresponding compositions contain, alongside the antibody or antibody derivative and the 1,4 O-linked saccharose derivative, additionally one or more mono-, di- and/or polysaccharides, whereby

the additional application of mono- and/or di-saccharides is preferred particularly during powder production. The invention also consequently embraces compositions, preferably powdered compositions, such as e.g. spray-dried powders with lactosucrose, lactose, and saccharose, whereby the fraction of lactosucrose in relation to the total sugar fraction of the composition amounts to ≥ 40% (w/w), preferably ≥ 55% (w/w), and also ≥ 88% (w/w). According to a preferred embodiment, the compositions according to the invention, alongside one antibody or antibody derivative as pharmaceutical active substance, contain a sugar mixture specified as Nyuka-Oligo® LS55P (abbreviated to LS55P) of Hayashibara Shoji Inc., Japan which contains at least 55% lactosucrose, max 25% (w/w) lactose, and max 10% (w/w) saccharose. According to a further preferred embodiment, the compositions according to the invention, alongside the pharmaceutical active substance, contain a sugar mixture specified as Nyuka-Oligo® LS90P (abbreviated to LS90P) of Hayashibara Shoji Inc., Japan which contains at least 88% lactosucrose and max 10% (w/w) lactose and saccharose.

Compositions, preferably powdered compositions such as e.g. spray-dried powders consisting of a combination of an antibody and antibody derivative with glucosyl and maltosyl sucrose, have moreover proven to accord with the invention, again preferably in combination with other mono-, di- and/or polysaccharides. The invention also consequently covers corresponding compositions, preferably powdered compositions, which, alongside the antibody or antibody derivative, contain a mixture of glucosyl and maltosyl sucrose, saccharose, glucose, and/or fructose, whereby the fraction of glucosyl and maltosyl sucrose in relation to the total sugar fraction of the composition preferably amounts to 25% (w/w) or more. According to a further preferred embodiment, the respective fraction of glucosyl and maltosyl sucrose amounts to at least 18% (w/w) of the total sugar fraction of the composition. According to a preferred embodiment, the compositions according to the invention, preferably the powdered compositions, alongside the antibody or antibody derivative as pharmaceutical active substance, contain a sugar mixture described as Coupling Sugar® of Hayashibara Shoji Inc., Japan which respectively contains at least 18% (w/w) glucosyl and maltosyl sucrose, between 11 and 15% (w/w) saccharose, and respectively between 5 and 9% (w/w) glucose and fructose. The present invention further concerns compositions, preferably powdered compositions, which, alongside the antibody or antibody derivative as pharmaceutical active substance, contain a sugar mixture described as Cou-

pling Sugar S® of Hayashibara Shoji Inc., Japan which contains at least 25% (w/w) glucosyl and maltosyl sucrose, between 48 and 56% (w/w) saccharose, and not more than 10% (w/w) glucose and fructose.

Compositions, preferably powdered compositions such as e.g. spray-dried powders, which have proven to be particularly advantageous are those whose fraction of 1,4 O-linked saccharose derivative or of a sugar mixture containing at least one 1,4 O-linked saccharose derivative in relation to the dry weight of the composition amounts to between 25 and 99.99% (w/w), preferably between 40 and 99% (w/w), more preferably between 60 and 99% (w/w), and still more preferably between 60 and 90% (w/w), for example 25, 25.1, 25.2, 25.3, ... 25.7, 25.8, 25.9, etc; 26, 27, 28, 29 30, etc; 31, 32, 33, ... 38, 39, 40, etc; 41, 42, 43, ... 48, 49, 50, etc; 51, 52, 53, ... 58, 59, 60, etc; 61, 62, 63, ... 68, 69, 70, etc; 71, 72, 73, ... 78, 79, 80, etc; 81, 82, 83, ... 88, 89, 90, etc; 91, 92, 93, ... 98, etc; 99, 99.1, 99.2, 99.3, ... 99.8, 99.9, etc; 99.91, 99.92, 99.93, ... 99.98, 99.99% (w/w). In conjunction with application of LS55P or also LS90P, a fraction of 60-90% (w/w) has proven to be particularly advantageous. Where the composition refers to a powdered composition, such as e.g. a spray-dried powder, the fraction of 1,4 O-linked saccharose derivative or of sugar mixture containing at least one 1,4 O-linked saccharose derivative should be selected so that the powdered composition is at least partially amorphous, preferably completely amorphous. The fraction of 1,4 O-linked saccharose derivative or of sugar mixture containing at least one 1,4 O-linked saccharose derivative may also be reduced below 60% (w/w). Powders are then preferably mixed with other stabilising adjuvants in suitable quantity. Examples of other stabilising adjuvants are given elsewhere in this patent specification.

The fraction of antibody or antibody derivative in relation to the dry weight of the composition according to the invention generally amounts to between 0.01 and 75% (w/w), preferably between 0.01 and 50% (w/w), more preferably between 0.33 and 50% (w/w), still more preferably between 0.33 and 40% (w/w). According to a further preferred embodiment, the fraction of antibody or antibody derivative in relation to the solids content of the composition according to the invention amounts to between 0.33 and 35% (w/w), preferably between 0.33 and 30% (w/w). For example, the fraction thus amounts to: 0.01, 0.02, 0.03, ... 0.08, 0.09, etc; 0.1, 0.2, 0.3, ... 0.8, 0.9, etc; 1, 2, 3, ... 8, 9, 10, etc; 21, 22, 23, ... 28, 29, 30, etc; 31, 32, 33, ... 38, 39, 40, etc; 41,

42, 43, ... 48, 49, 50, etc; 51, 52, 53, ... 58, 59, 60, etc; 61, 62, 63, ... 68, 69, 70, etc; 71, 72, 73, 74, 74.1, 74.2, 74.3, ... 74.8, 74.9, etc; 74.91, 74.92, 74.93, ... 74.98, 74.99, 75% (w/w).

Compositions according with the invention are thus compositions, preferably powdered compositions such as e.g. spray-dried powders, with a ratio of 1,4 O-linked saccharose derivative or sugar mixture containing at least one 1,4 O-linked saccharose derivative to the pharmaceutical active substance (antibody or antibody derivative) of e.g. 25/75, 26/74, 27/73, 28/72, 29/71, 30/70, 31/69, 32/68, 33/67, 34/66, 35/65, 36/64, 37/63, 38/62, 39/61, 40/60, 41/59, 42/58, 43/57, 44/56, 45/55, 46/54, 47/53, 48/52, 49/51, 50/50, 51/49, 52/48, 53/47, 54/46, 55/45, 56/44, 57/43, 58/42, 59/41, 60/40, 61/39, 62/38, 63/37, 64/36, 65/35, 66/34, 67/33, 68/32, 69/31, 70/30, 71/29, 72/28, 73/27, 74/26, 75/25, 76/24, 77/23, 78/22, 79/21, 80/20, 81/19, 82/18, 83/17, 84/16, 85/15, 86/14, 87/13, 88/12, 89/11, 90/10, 91/9, 92/8, 93/7, 94/6, 95/5, 96/4, 97/3, 98/2, 99/1, 99.1/0.9, 99.2/0.8, 99.3/0.7, 99.4/0.6, 99.5/0.5, 99.6/0.4, 99.66/0.33, 99.7/0.3, 99.8/0.2, 99.9/0.1, 99.99/0.01 (w/w). Where the corresponding composition contains one or more additional adjuvants, either a) the fraction of the 1,4 O-linked saccharose derivative or of the sugar mixture containing at least one 1,4 O-linked saccharose derivative, b) the fraction of antibody or antibody derivative, or c) both fractions are correspondingly reduced, whereby the fraction of the 1,4 O-linked saccharose derivative or of the sugar mixture containing at least one 1,4 O-linked saccharose derivative in relation to the dry weight of the composition according to the invention preferably has one of the values between 60 and 90% (w/w).

Pharmaceutical active substances in the sense of the invention are antibodies or antibody derivatives. Examples thereof, alongside other monoclonal, polyclonal, multispecific, and single-chain antibodies, are fragments thereof, such as e.g. Fab, Fab', $F(ab')_2$, Fc, and Fc' fragments, light (L) and heavy (H) antibody chains and their constant, variable, or hypervariable regions as well as Fd and Fv fragments and fusion proteins containing at least an antibody fraction or at least a fragment of a double- or single-chain antibody (Chamov et al., 1999, Antibody Fusion Proteins, Wiley-Liss Inc.). The antibodies may be of human or non-human origin. The following classes known in humans fall under the latter: IgA, IgD, IgE, IgG, and IgM with their various subclasses, such as e.g. IgA1, IgA2, IgG1, IgG2, IgG3, and IgG4. Humanized and

chimeral antibodies also arise in this context. Of special therapeutic importance and thus forming the subject of the present invention are compositions, preferably powdered compositions such as e.g. spray-dried powders, which contain antibodies against e.g. various surface antigens, such as CD4, CD20, or CD44, or various cytokinins, such as e.g. IL2, IL4, or IL5. Other examples are antibodies against specific antibody classes (e.g. anti-IgE antibodies) or against viral proteins (e.g. anti-RSV, anti-CMV antibodies, etc).

Fragment antigen-binding or Fab fragments consist of the variable regions of both chains that are held together by the adjacent constant regions. Other antibody fragments are $F(ab')_2$ fragments that can be produced by proteolytic digestion with pepsin. Gene cloning can also be used to produce shortened antibody fragments that only consist of the variable region of the heavy (VH) and light (VL) chain. The latter are described as Fv fragments (fragment variable = fragment of the variable part). Such antibody fragments are also described as single-chain Fv (scFv) fragments. Examples of scFv fragments are known and previously described (see e.g. Huston et al., 1988, Proc. Natl. Acad. Sci. USA, 16, 5879ff).

In previous years, various strategies have been developed to produce multimeric scFv derivatives, such as e.g. dia-, tria- and pentabodies. The skilled man describes a bivalent homodimeric scFv derivative as a "diabody". Shortening of the peptide linker in the scFv molecule to 5-10 amino acids results in the formation of homodimers through the superimposition of VH/VL chains. The diabodies can be additionally stabilised through introduced disulphide bridges. Examples of diabodies have been documented in the literature e.g. by Perisic et al., 1994 (Structure, 2, 1217ff). The skilled man describes a bivalent homodimeric scFv derivative as a "minibody". It consists of a fusion protein that contains the CH3 region of an antibody, preferably IgG, particularly preferably IgG1, as the dimerising region. The latter connects the scFv fragments via a hinge region, also of IgG, and a linker region. Both examples of such minibodies have been described by Hu et al., 1996, Cancer Research, 56, 3055ff. The skilled man describes a trivalent homodimeric scFv derivative as a "triabody" (Kortt et al., 1997, Protein Engineering, 10, 423ff). The direct fusion of VH-VL without application of a linker sequence leads to the formation of trimers.

The fragments described by the skilled man as mini-antibodies that have a bi-, tri- or tetravalent structure are also derivatives of scFv fragments. Multimerising is then accomplished via di-, tri-, or tetrameric "coiled coil" structures (Pack P. et al., 1993, Biotechnology, 11 1271ff, Lovejoy B. et al., 1993, Science, 259, 1288ff, Pack P. et al., 1995, J. Mol. Biol. 246, 28ff).

An especially preferred embodiment of the invention concerns a protein of the antibody class, more specifically type 1 antibody G. The latter is a humanized monoclonal antibody with 95% human and 5% murine antibodies. The antibody has a molecular weight of around 148 kilodaltons (kDa), consisting of two light and two heavy chains and altogether four disulphide bridges.

According to a further embodiment, the present invention concerns compositions, preferably powdered compositions such as e.g. spray-dried powders, characterised in that the dry weight of the corresponding composition contains at least 50% (w/w), preferably between 50 and 99.99% (w/w), particularly preferably between 60 and 90% (w/w) sugar, and up to 40% (w/w) of an antibody or antibody derivative as pharmaceutical active substance, whereby the fraction of lactosucrose, maltosyl sucrose, and/or glucosyl sucrose amounts to at least 20% (w/w) in relation to the dry weight of the composition according to the invention, and the sum of the weight percentages amounts to max 100% (w/w). An skilled man is able to produce corresponding compositions, preferably powdered compositions such as e.g. spray-dried powders as well. An skilled man thus knows that, in relation to the total solids content of the composition according to the invention, he can mix in max 10% (w/w) of an antibody or antibody derivative, if the fraction of 1,4 O-linked saccharose derivative or a sugar mixture containing at least one 1,4 O-linked saccharose derivative should be 90% (w/w).

The compositions according to the invention, particularly powdered compositions such as e.g. spray-dried powders, can moreover contain other adjuvants, such as e.g. amino acids, peptides, non-biological or biological polymers, and/or one or more sugars. Other known state-of-the-art adjuvants are e.g. lipids, fatty acids, fatty acid esters, steroids (e.g. cholesterol), or chelating agents (e.g. EDTA), and diverse cations (see above). Particularly preferred for the production of powdered compositions such as

e.g. spray-dried powders are adjuvants with a high glass transition temperature, e.g. greater than 40°C, preferably greater than 45°C, more preferably greater than 50°C, or preferably greater than 55°C. A listing of suitable adjuvants is given e.g. in Kippe (eds.) "*Handbook of Pharmaceutical Excipients*" 3rd edition, 2000.

Suitable protein-containing adjuvants are e.g. albumin (of human or recombinant origin), gelatine, casein, haemoglobin, and the like. The sugars are preferably a mono-, di-, oligo- or polysaccharide or a combination thereof. Examples of monosaccharides are fructose, maltose, galactose, glucose, D-mannose, sorbose, and the like. Suitable disaccharides in the sense of the invention are e.g. lactose, saccharose, trehalose, cellobiose, and the like. Particularly raffinose, melecitose, dextrin, starch, and the like may be suitably used as multiple sugars, or oligo- and polysaccharides. Among sugar alcohols, mannitol, xylitol, maltitol, galactitol, arabinitol, adonitol, lactitol, sorbitol (glucitol), pyranosylsorbitol, inositol, myoinositol, and the like may be considered as suitable adjuvants. Suitable amino acids include e.g. alanine, glycine, arginine, histidine, glutamate, asparagine, cysteine, lucine, lysine, isoleucine, valine, tryptophan, methionine, phenylalanine, tyrosine, citrulline, L-aspartyl-L-phenylalanine-methyl ester (= aspartame), trimethylammonium acetate (= betaine), and the like. Amino acids that act as a buffer (e.g. glycine or histidine) and/or as a dispersing agent are preferably used. The latter groups particularly include primarily hydrophobic amino acids such as e.g. lucine, valine, isoleucine, tryptophan, alanine, methionine, phenylalanine, tyrosine, histidine, or proline.

Within the scope of the present invention, particularly the application of amino acids, preferably isoleucine or citrulline and particularly preferably isoleucine, has proven advantageous alongside the 1,4 O-linked saccharose derivative or a sugar mixture containing at least one 1,4 O-linked saccharose derivative, preferably at a concentration of 1 to 19.99% (w/w), particularly preferably at a concentration of 5 to 19.99% (w/w), particularly preferably at a concentration of 10 to 19.99% (w/w), and still more preferably at a concentration of 12 to 19.99% (w/w). The fraction, however, can also be increased to values up to 40% (w/w), provided the fraction of the 1,4 O-linked saccharose derivative or a sugar mixture containing at least one 1,4 O-linked saccharose derivative or the fraction or the antibody or antibody derivative is correspondingly reduced, while the solids fraction of the powder cannot exceed 100% (w/w).

It is also particularly advantageous to use as other adjuvants di-, tri-, oligo-, or polypeptides that contain one or more of these primarily hydrophobic amino acid groups. Particularly preferred are peptides with up to 20 amino acids, more preferred are those with up to 15 amino acids, yet more preferred are those with up to 12 amino acids, yet more preferred are those with up to 11 amino acids, yet more preferred are those with up to 10 amino acids, yet more preferred are those with up to 9 amino acids, yet more preferred are those with up to 8 amino acids, yet more preferred are those with up to 7 amino acids, and yet more preferred are those with up to 7, 6. 5, 4, or 3 amino acids. The peptides used for stabilisation then do not simultaneously correspond to the pharmaceutical active substance.

Suitable examples of tri-peptides include e.g. one or more of the following tri-peptides: Leu-Leu-Gly, Leu-Leu-Ala, Leu-Leu-Val, Leu-Leu-Leu, Leu-Leu-Met, Leu-Leu-Pro, Leu-Leu-Phe, Leu-Leu-Trp, Leu-Leu-Ser, Leu-Leu-Thr, Leu-Leu-Cys, Leu-Leu-Tyr, Leu-Leu-Asp, Leu-Leu-Glu, Leu-Leu-Lys, Leu-Leu-Arg, Leu-Leu-His, Leu-Gly-Leu, Leu-Ala-Leu, Leu-Val-Leu, Leu-Met-Leu, Leu-Pro-Leu, Leu-Phe-Leu, Leu-Trp-Leu, Leu-Ser-Leu, Leu-Thr-Leu, Leu-Cys-Leu, Leu-Try-Leu, Leu-Asp-Leu, Leu-Glu-Leu, Leu-Lys-Leu, Leu-Arg-Leu, and Leu-His-Leu. Application of tri-peptides with the general formulae Ile-X-X; X-Ile-X; X-X-Ile has proven particularly advantageous, where X may be any one of the following amino acids: alanine, glycine, arginine, histidine, glutamic acid, glutamine, asparagine, asparaginic acid, cysteine, lucine, lysine, isoleucine (Ile), valine, tryptophan, methionine, phenylalanine, proline, serine, threonine, tyrosine, L-aspartyl-L-phenylalanine-methyl ester (= aspartame), trimethylammonium acetate. Particularly preferred are corresponding tri-peptides with the formula $(Ile)_2$-X, such as e.g. Ile-Ile-X, Ile-X-Ile, or X-Ile-Ile, where X may again be any one of the amino acids specified above. For example, the following peptides are included here: Ile-Ile-Gly, Ile-Ile-Ala, Ile-Ile-Val, Ile-Ile-Ile, Ile-Ile-Met, Ile-Ile-Pro, Ile-Ile-Phe, Ile-Ile-Trp, Ile-Ile-Ser, Ile-Ile-Thr, Ile-Ile-Cys, Ile-Ile-Tyr, Ile-Ile-Asp, Ile-Ile-Glu, Ile-Ile-Lys, Ile-Ile-Arg, Ile-Ile-His, Ile-Gly-Ile, Ile-Ala-Ile, Ile-Val-Ile, Ile-Met-Ile, Ile-Pro-Ile, Ile-Phe-Ile, Ile-Trp-Ile, Ile-Ser-Ile, Ile-Thr-Ile, Ile-Cys-Ile, Ile-Try-Ile, Ile-Asp-Ile, Ile-Glu-Ile, Ile-Lys-Ile, Ile-Arg-Ile, Ile-His-Ile. It is particularly advantageous to use Ile-Ile-Ile.

Suitable polymers e.g. include those specified above as adjuvants, polyvinyl pyrrolidone, derivatised celluloses, such as e.g. hydroxymethyl, hydroxyethyl, or hydroxypropyl ethylcellulose, polymeric sugars, such as e.g. ficoll, starches, such as e.g. hydroxyethyl or hydroxypropyl starch, dextrins, such as e.g. cyclodextrin (2-hydroxypropyl-β-cyclodextrin, sulphobutylether-β-cyclodextrin), polyethylene glycols, and/or pectins.

The salts are, for example, inorganic salts such as chloride, sulphate, phosphate, diphosphate, hydrobromide, and/or nitrate salts. The powders according to the invention may further contain organic salts such as e.g. malate, maleate, fumarate, tartrate, succinate, ethylsuccinate, citrate, acetate, lactate, methanesulphonate, benzoate, ascorbate, para-toluenesulphonate, palmoate, salicylate, stearate, estolate, gluceptate, and lactobionate salts. Corresponding salts may simultaneously contain pharmaceutically acceptable cations such as e.g. sodium, potassium, calcium, aluminium, lithium, or ammonium. Application of corresponding cations during stabilisation of antibodies or antibody derivatives has proven particularly suitable.

The present invention thus also concerns compositions, preferably powdered compositions such as e.g. spray-dried powders, which, alongside the 1,4 O-linked saccharose derivative or a sugar mixture containing at least one 1,4 O-linked saccharose derivative and one antibody or one antibody derivative as pharmaceutical active substance, contain one or more pharmaceutically compatible adjuvants and/or one or more salts. The adjuvants may be e.g. the amino acids, peptides and their salts, sugars, polyols, salts of organic acids, and/or polymers specified above.

According to a further embodiment, the present invention concerns compositions, preferably powdered compositions such as e.g. spray-dried powders, which, alongside the 1,4 O-linked saccharose derivative or a sugar mixture containing at least one 1,4 O-linked saccharose derivative and one antibody or one antibody derivative as pharmaceutical active substance, contain one or more amino acid(s), preferably one amino acid, as a further adjuvant. In this context, the present invention also concerns compositions, preferably powdered compositions such as e.g. spray-dried powders, which, in relation to their dry weight, contain **a)** at least 25% (w/w), preferably between 50 and

90% (w/w), particularly preferably between 60 and 90% (w/w) of one 1,4 O-linked saccharose derivative or one sugar mixture containing at least one 1,4 O-linked saccharose derivative, **b)** between 1 and 19.99% (w/w) amino acids, and **c)** between 0.01 and 74% (w/w) antibodies or antibody derivatives as pharmaceutical active substance, whereby the sum of the weight fractions gives 100% (w/w). According to a preferred embodiment, the fraction of the 1,4 O-linked saccharose derivative or a sugar mixture containing at least one 1,4 O-linked saccharose derivative is at least 60% (w/w), preferably between 70 and 90% (w/w) in relation to the dry weight of the corresponding composition. In a corresponding formulation, the fraction of amino acids preferably amounts to between 1 and 19.99% (w/w) and the fraction of the antibody or antibody derivative to between 0.01 and 39% (w/w).

The present invention according to a further embodiment also consequently concerns compositions, preferably powdered compositions such as e.g. spray-dried powders, which e.g. contain 80% (w/w) of a 1,4 O-linked saccharose derivative or a sugar mixture containing at least one 1,4 O-linked saccharose derivative / 19% (w/w) amino acid / 1% (w/w) antibody or antibody derivative (80/19/1); or, for example, (80/18/2); (80/17/3); (80/16/4); (80/15/5); (80/14/6); (80/13/7); (80/12/8); (80/11/9); (80/10/10); (70/20/10); (70/19/11); (70/18/12); (70/17/13); (70/16/14); (70/15/15); (70/14/16); (70/13/17); (70/12/18); (70/11/19); (70/10/20); (60/20/20); (60/19/21); (60/18/22); (60/17/23); (60/16/24); (60/15/25); (60/14/26); (60/13/27); (60/12/28); or (60/11/29) or consist thereof. Provided the fraction of antibody or antibody derivative at a constant amino acid fraction is reduced from 20% (w/w) to 0.01% (w/w), e.g. to 9.99, ... 9.9, 9.8, 9.7, ... 9.3, 9.2, 9.1, ... 9, 8, 7, 6, 5, 4, 3, 2, 1, ... 0.9, 0.8, 0.7, ... 0.66, ... 0.6, 0.5, 0.4, 0.3, 0.2, 0.1, 0.09, 0.08, 0.07, 0.06, 0.05, 0.04, 0.03, 0.02, 0.01% (w/w), the fraction of the 1,4 O-linked saccharose derivative or a sugar mixture containing at least one 1,4 O-linked saccharose derivative can be accordingly increased e.g. to 80.01, ... 80.1, 80.2, 80.3, ... 80.8, 80.9, ... 81, 82, 83, 84, 85, 86, 87, 88, 89, ... 89.1, 89.2, 89.3, ...89.33, ... 89.4, 89.5, 89.6, 89.7, 89.8, 89.9, ... 89.91, 89.92, 89.93, ... 89.97, 89.98, 89.99% (w/w), so that the sum of the weight fractions of the individual components of the composition in relation to their dry weight gives 100% (w/w). Through the addition of other adjuvants or salts, the fraction of the 1,4 O-linked saccharose derivative or a sugar mixture containing at least one 1,4 O-linked saccharose derivative amino acids/peptides, and/or antibody or antibody derivative can be corre-

spondingly adjusted/reduced, so that the weight fractions of the individual components in total give 100% (w/w).

Where the added amino acid is isoleucine, then, according to a further embodiment, compositions, preferably powdered compositions such as e.g. spray-dried powders, with **a)** a fraction of 1,4 O-linked saccharose derivative or a sugar mixture containing at least one 1,4 O-linked saccharose derivative of at least 25% (w/w), preferably from 50 to 90% (w/w), particularly preferably from 60 to 90% (w/w), **b)** an isoleucine fraction of 1 to 19.99% (w/w), and **c)** a fraction of at least 0.01% (w/w), preferably 0.01 to max 74% (w/w) of an antibody or antibody derivative as pharmaceutical active substance, preferably a peptide/protein, accord with the invention. The isoleucine fraction preferably amounts to 5 to 19.99% (w/w), more preferably to 10 to 19.99% (w/w), of the total solids fraction of the composition according to the invention. Here again, the sum of the weight percentages of the individual components gives max 100% (w/w). Compositions, preferably powdered compositions such as e.g. spray-dried powders, with the following composition also accord with the invention: 80% (w/w) 1,4 O-linked saccharose derivative or a sugar mixture containing at least one 1,4 O-linked saccharose derivative / 10% (w/w) amino acid or peptide / 10% (w/w) antibody or antibody derivative (80/10/10); (79/11/10); (78/12/10); (77/13/10); (76/14/10); (75/15/10); (74/16/10); (73/17/10); (72/18/10); (71/19/10); (70/20/10), whereby the fraction of antibody or antibody derivative can also be reduced from 10 to 0.01% (w/w), e.g. to 9.99, ... 9.9, 9.8, 9.7, ... 9.3, 9.2, 9.1, ... 9, 8, 7, 6, 5, 4, 3, 2, 1, ... 0.9, 0.8, 0.7, ... 0.66, ... 0.6, 0.5, 0.4, 0.3, 0.2, 0.1, 0.09, 0.08, 0.07, 0.06, 0.05, 0.04, 0.03, 0.02, 0.01% (w/w), and the fraction of the 1,4 O-linked saccharose derivative or a sugar mixture containing at least one 1,4 O-linked saccharose derivative can be accordingly increased e.g. to 80.01, ... 80.1, 80.2, 80.3, ... 80.8, 80.9, ... 81, 82, 83, 84, 85, 86, 87, 88, 89, ... 89.1, 89.2, 89.3, ...89.33, ... 89.4, 89.5, 89.6, 89.7, 89.8, 89.9, ... 89.91, 89.92, 89.93, ... 89.97, 89.98, 89.99% (w/w), so that the sum of the weight fractions of the individual components of the composition in relation to the dry weight of the corresponding composition gives max 100% (w/w). Compositions, preferably powdered compositions such as e.g. spray-dried powders, with the following composition thus also accord with the invention: 80% (w/w) 1,4 O-linked saccharose derivative or a sugar mixture containing at least one 1,4 O-linked saccharose derivative / 19% (w/w) isoleucine / 1% (w/w) antibody or antibody derivative (80/19/1);

(80/18/2); (80/17/3); (80/16/4); (80/15/5); (80/14/6); (80/13/7); (80/12/8); (80/11/9); (80/10/10); (70/19/11); (70/18/12); (70/17/13); (70/16/14); (70/15/15); (70/14/16); (70/13/17); (70/12/18); (70/11/19); (70/10/20); (60/19/21); (60/18/22); (60/17/23); (60/16/24); (60/15/25); (60/14/26); (60/13/27); (60/12/28); (60/11/29); (60/10/30). Where other adjuvants or salts are added, the fraction of 1,4 O-linked saccharose derivative or a sugar mixture containing at least one 1,4 O-linked saccharose derivative, isoleucine, and/or antibody or antibody derivative should be correspondingly adjusted, so that the weight fractions of the individual components in total give 100% (w/w).

A further embodiment of the present invention concerns the application of at least one 1,4 O-linked saccharose derivative or a sugar mixture containing at least one 1,4 O-linked saccharose derivative and a peptide, preferably a di- or tri-peptide, for stabilisation of compositions, preferably powdered compositions such as e.g. spray-dried powders containing an antibody or antibody derivative as pharmaceutical active substance, preferably in the form of a peptide, protein, or mixture thereof. The present patent specification e.g. specifies a number of tri-peptides which, together with the 1,4 O-linked saccharose derivative or a sugar mixture containing at least one 1,4 O-linked saccharose derivative, can be used for production of the compositions according to the invention, preferably powdered compositions such as e.g. spray-dried powders. According to a special embodiment, the peptides, preferably di- or tri-peptides, are those that contain at least one isoleucine group, preferably two isoleucine groups, or, according to a particularly advantageous embodiment, tri-peptides that consist of three isoleucines.

In this context, compositions, preferably powdered compositions such as e.g. spray-dried powders, are deemed to accord with the invention with **a)** a fraction of at least one 1,4 O-linked saccharose derivative or a sugar mixture containing at least one 1,4 O-linked saccharose derivative of at least 25% (w/w), preferably from 60 to 99% (w/w), particularly preferably from 60 to 90% (w/w), **b)** a fraction of 1 to 19.99% (w/w) of a peptide, preferably a di- or tri-peptide, particularly preferably an isoleucine-containing peptide, and **c)** 0.01 to max 74% (w/w) of an antibody or antibody derivative. Here again, the sum of individual solids may not exceed 100% (w/w). Compositions, preferably powdered compositions such as e.g. spray-dried powders,

with the following composition further accord with the invention: 89% (w/w) of at least one 1,4 O-linked saccharose derivative or a sugar mixture containing at least one 1,4 O-linked saccharose derivative / 1% (w/w) peptide, preferably a di- or tri-peptide, particularly preferably an isoleucine-containing tri-peptide, still more preferably tri-isoleucine / 10% (w/w) antibody or antibody derivative (89/1/10); (88/2/10); (87/3/10); (86/4/10); (85/5/10); (84/6/10); (83/7/10); (82/8/10); (81/9/10); (80/10/10); (79/11/10); (78/12/10); (77/13/10); (76/14/10); (75/15/10); (74/16/10); (73/17/10); (72/18/10); or (71/19/10), while the fraction of antibody or antibody derivative can also be reduced from 10 to 0.01% (w/w), e.g. to 9.99, ... 9.9, 9.8, 9.7, ... 9.3, 9.2, 9.1, ... 9, 8, 7, 6, 5, 4, 3, 2, 1, ... 0.9, 0.8, 0.7, ... 0.66, ... 0.6, 0.5, 0.4, 0.3, 0.2, 0.1, 0.09, 0.08, 0.07, 0.06, 0.05, 0.04, 0.03, 0.02, 0.01% (w/w), and the fraction of the 1,4 O-linked saccharose derivative or a sugar mixture containing at least one 1,4 O-linked saccharose derivative can be accordingly increased e.g. to 80.01, ... 80.1, 80.2, 80.3, ... 80.8, 80.9, ... 81, 82, 83, 84, 85, 86, 87, 88, 89, ... 89.1, 89.2, 89.3, ...89.33, ... 89.4, 89.5, 89.6, 89.7, 89.8, 89.9, ... 89.91, 89.92, 89.93, ... 89.97, 89.98, 89.99% (w/w), so that the sum of the weight fractions of the individual components of the composition in relation to the dry weight of the composition gives max 100% (w/w). Compositions, preferably powdered compositions such as e.g. spray-dried powders, with the following composition further accord with the invention: 80% (w/w) of at least one 1,4 O-linked saccharose derivative or a sugar mixture containing at least one 1,4 O-linked saccharose derivative / 19% (w/w) peptide, preferably a di- or tri-peptide, particularly preferably an isoleucine-containing peptide, still more preferably tri-isoleucine / 1% (w/w) antibody or antibody derivative (80/19/1); (80/18/2); (80/17/3); (80/16/4); (80/15/5); (80/14/6); (80/13/7); (80/12/8); (80/11/9); (80/10/10); (70/19/11); (70/18/12); (70/17/13); (70/16/14); (70/15/15); (70/14/16); (70/13/17); (70/12/18); (70/11/19); (70/10/20); (60/19/21); (60/18/22); (60/17/23); (60/16/24); (60/15/25); (60/14/26); (60/13/27); (60/12/28); (60/11/29); (60/10/30), whereby the amount of peptide (di, tri-, isoleucine containing peptide, tri or di-peptide or tri-isoleucine) can also be reduced from 10 to 1% (w/w), e.g. to 9.99, ... 9.9, 9.8, 9.7, ... 9.3, 9.2, 9.1, ... 9, 8, 7, 6, 5, 4, 3, 2, 1.9, 1.8, 1.7, ... 1.66, ... 1.6, 1.5, 1.4, 1.3, 1.2, 1.1, 1% (w/w), and the amount of antibody or antibody derivative can be accordingly increased e.g. to 30.1, 30.2, 30.3, ... 30.8, 30.9, 31, 32, 33, 34, 35, 36, 37, 38, 38.1, 38.2, 38.3, ...38.33, ... 38.4, 38.5, 38.6, 38.7, 38.8, 38.9, ... 39% (w/w), so that the sum of the weight fractions of the individual components of the composition in rela-

tion to the dry weight of the composition gives max 100% (w/w). If the fraction of peptide (di-, tri-, isoleucine-containing peptide, tri- or di-peptide, or tri-isoleucine) is reduced from 10 to 1% (w/w), as represented here, the fraction of the 1,4 O-linked saccharose derivative or a sugar mixture containing at least one 1,4 O-linked saccharose derivative in the powder can also be increased. For example, at a constant active substance fraction of antibody or antibody derivative of 10% (w/w), corresponding compositions with a fraction of 1,4 O-linked saccharose derivative or a sugar mixture containing at least one 1,4 O-linked saccharose derivative of 80.1, 80.2, 80.3, ... 80.8, 80.9, 81, 82, 83, 84, 85, 86, 87, 88, 88.1, 88.2, 88.3, ...88.33, ... 88.4, 88.5, 88.6, 88.7, 88.8, 88.9, or 89% (w/w) can be produced.

Compositions that have proven to be particularly preferred are compositions, preferably powdered compositions such as e.g. spray-dried powders, with **a)** a fraction of at least one 1,4 O-linked saccharose derivative or a sugar mixture containing at least one 1,4 O-linked saccharose derivative of 60 to 80% (w/w), **b)** a fraction of 10 to 19.99% (w/w) of a peptide, preferably a di- or tri-peptide, particularly preferably an isoleucine-containing peptide, more preferably a tri-peptide, preferably of tri-isoleucine, and **c)** 0.01 to max 30% (w/w) of an antibody or antibody derivative. Here again, the sum of individual solids may not exceed 100% (w/w).

According to a further embodiment that accords with the invention, the compositions, preferably powdered compositions such as e.g. spray-dried powders, may additionally contain surface-active substances, such as Tween 20, 40, 60, 80, Brij 35, Pluronic F 88, and Pluronic F 127. The latter substances are preferably used at a concentration of 0.01-0.1% (w/w). Particularly preferred are compositions, preferably powdered compositions such as e.g. spray-dried powders, which contain, as adjuvant, at least one 1,4 O-linked saccharose derivative or a sugar mixture containing at least one 1,4 O-linked saccharose derivative and additionally Tween 20, preferably at a concentration of 0.01-0.1% (w/w) as surface-active substances.

According to a further embodiment, the particles in the powdered compositions according to the invention have a MMD between 1 and 10 μm, preferably between 1 and 5 μm.

According to a further embodiment, the present invention concerns compositions, preferably powdered compositions such as e.g. spray-dried powders, that contain **a)** at least one 1,4 O-linked saccharose derivative or a sugar mixture containing at least one 1,4 O-linked saccharose derivative and **b)** one antibody or one antibody derivative, whereby the powdered composition is characterised by a glass transition temperature greater than 40°C. The corresponding powders according to the invention normally have a maximum glass transition temperature of around 96 to 110°C. In individual cases, however, the value may be even higher.

The present invention further concerns pharmaceutical compositions that contain at least one of the compositions described here.

Production of the compositions according to the invention

The compositions according to the invention are liquid, semi-solid, or solid compositions that contain **a)** at least one 1,4 O-linked saccharose derivative or a sugar mixture containing at least one 1,4 O-linked saccharose derivative and **b)** one antibody or one antibody derivative. Particularly preferred are solid powdered compositions, such as e.g. those generated by freeze drying or spray drying of an aqueous solution or suspension. Aqueous solutions or suspensions can be obtained through mixing or suspension of corresponding components (such as e.g. a 1,4 O-linked saccharose derivative and an antibody) in a suitable solvent. The respective substances can also be added as dry substances to a solvent and dissolved or suspended therein. Semi-solid preparations are also suitable. Semi-solid preparations consist of a simple or composite base wherein, according to the invention, **a)** a 1,4 O-linked saccharose derivative or a sugar mixture containing at least one 1,4 O-linked saccharose derivative and **b)** antibodies or antibody derivatives are dissolved or dispersed. The 1,4 O-linked saccharose derivative or a sugar mixture containing at least one 1,4 O-linked saccharose derivative and antibodies or antibody derivatives can be added to the base individually or, as described above, within a powder produced by a suitable process described above. The preparations may further contain suitable adjuvants such as preservatives, antioxidants, stabilisers, emulsifiers, thickeners, and penetration accelerators, or other suitable adjuvants. Suitable semi-solid bases are, without being limited thereto, hydrophobic ointments, water-absorbing ointments, hydrophilic ointments, lipophilic

creams, hydrophilic creams, lipophilic gels, hydrophilic gels, pastes, and enrobing pastes.

Particularly preferred are solid powdered compositions generated e.g. through drying of previously aqueous solutions or suspensions. Known drying processes include, inter alia, freeze drying, spray drying, vacuum drying, infrared drying, or microwave drying. A general description of appropriate processes is given e.g. in the publication by Willmann (Dissertation, 2000, Dr. Hut Verlag, Munich, Germany – ISBN 3-89963-027-0), the contents of which are hereby incorporated by reference. Powdered compositions consisting of **a)** at least one 1,4 O-linked saccharose derivative or a sugar mixture containing at least one 1,4 O-linked saccharose derivative and **b)** one antibody or antibody derivative which have been produced by spray drying or freeze drying have proven to be particularly stable.

Production of dried powders according to the invention

The present invention also provides processes for the production of a dried powder described in more detail above, preferably a spray-dried powder. The spray drying process is e.g. characterised in that a solution / suspension to be sprayed that contains **a)** an antibody or antibody derivative as pharmaceutical active substance and **b)** at least one 1,4 O-linked saccharose derivative or a sugar mixture containing at least one 1,4 O-linked saccharose derivative is sprayed below a temperature of 200/120°C (inlet/outlet temperature), preferably at a temperature below 186/96°C, preferably between 186/96°C and 60/40°C, e.g. at 180-150/95-80°C. The process according to the invention is described in more detail on the basis of a number of examples in the EXAMPLES section.

The powders according to the invention can be basically produced by dissolving the antibody or antibody derivative in an aqueous solution depending on the solubility conditions of the antibody or antibody derivative. Buffered solutions with a pH of 3-11, preferably 3.5-9, are mostly used. During the production of inhalable powders, an aqueous solution with a pH of 4-7.8 is particularly advantageous. To guarantee adequate solubility, the pH value of the solution should be below the pH value of the antibody / antibody derivative. The aqueous solution may optionally contain additional water-soluble organic solvents, such as e.g. acetone, alcohols, or the like. Particularly

suitable are lower alcohols, such as e.g. methanol, ethanol or propanol (n- or iso-propanol). Such mixed solvent systems normally contain between 10-20% (v/v) of a water-soluble organic solvent. The solids fraction in the solution to be dried generally amounts to between 0.01-20% (w/w), preferably between 0.05-10% (w/w), particularly preferably between 0.1-5% (w/w). Within the scope of the present invention, spray-dried powders were produced on the basis of an aqueous solution with a solids fraction of 10% (w/w), 3.33% (w/w), or 2.00% (w/w) as well as freeze-dried powders on the basis of an aqueous solution with a solids fraction of 10% (w/w).

The adjuvant or a mixture of suitable adjuvants, as e.g. specified above, is normally dissolved in a second container in purest water or a suitable buffer solution with a pH value of 3 to 11, preferably 3.5 to 9, and particularly preferably 4.0 to 7.8, and mixed in a second step with the active substance solution that contains the antibody or antibody derivative. The solution / suspension is then adjusted to the required solids content with purest water or a suitable buffer solution with a pH value of 3 to 11, preferably 3.5 to 9, and particularly preferably 4.0 to 7.8.

The present invention consequently relates to a process for the production of a powder, characterised in that

a) an antibody or antibody derivative is dissolved in an aqueous solution / suspension;
b) one or more 1,4 O-linked saccharose derivatives selected from the compounds lactosucrose, glucosyl sucrose, or maltosyl sucrose or a sugar mixture containing at least one of these 1,4 O-linked saccharose derivatives is / are dissolved / suspended in an aqueous solution / suspension;
c) where an antibody or antibody derivative and 1,4 O-linked saccharose derivatives or the sugar mixture containing at least one 1,4 O-linked saccharose derivative are dissolved / suspended in different solutions / suspensions, these are mixed;
d) the solution / suspension containing one or more 1,4 O-linked saccharose derivative(s) and the antibody or antibody derivative is dried.

Where the drying process is spray drying, the drying under point d) is carried out by spraying the corresponding solution / suspension below a temperature of 200/120°C (inlet/outlet temperature), preferably between 60/40°C and 186/96°C.

The 1,4 O-linked saccharose derivative may also form part of a sugar mixture containing at least one 1,4 O-linked saccharose derivative. Examples of correspondingly suitable sugar mixtures are e.g. described in more detail in "Definitions". The sugar mixtures, alongside the 1,4 O-linked saccharose derivative, may then additionally contain one or more mono-, di- and/or polysaccharides, whereby the additional application of mono- and/or di-saccharides is preferred, particularly during powder production. Within the scope of the invention, sugar mixtures may thus e.g. be used with lactosucrose, lactose, and saccharose, whereby the fraction of lactosucrose in relation to the total sugar fraction of the composition amounts to ≥ 40% (w/w), preferably ≥ 55% (w/w), and also ≥ 88% (w/w). The sugar mixture is preferably a sugar mixture specified as Nyuka-Oligo® LS55P (abbreviated to LS55P) of Hayashibara Shoji Inc, Japan which contains at least 55% lactosucrose, max 25% (w/w) lactose, and max 10% (w/w) saccharose. According to a further preferred embodiment, the sugar mixture is preferably a sugar mixture specified as Nyuka-Oligo® LS90P (abbreviated to LS90P) of Hayashibara Shoji Inc, Japan which contains at least 88% lactosucrose and max 10% (w/w) lactose and saccharose. Sugar mixtures consisting of a combination of glucosyl and maltosyl sucrose, again preferably in combination with other mono-, di- and/or polysaccharides, may further be used. Sugar molecules that are suitable in the sense of the present invention are consequently those that consist of glucosyl and maltosyl sucrose, saccharose, glucose, and/or fructose, whereby the fraction of glucosyl and maltosyl sucrose in relation to the total sugar fraction of the composition preferably amounts to 25% (w/w) or more. According to a further preferred embodiment, the respective fraction of glucosyl and maltosyl sucrose amounts to at least 18% (w/w) of the total sugar fraction. According to another preferred embodiment, the sugar mixture used is a Coupling Sugar® of Hayashibara Shoji Inc, Japan which respectively contains at least 18% (w/w) glucosyl and maltosyl sucrose, between 11 and 15% (w/w) saccharose, and respectively between 5 and 9% (w/w) glucose and fructose. Also suitable in the sense of the present invention is a sugar mixture described as Coupling Sugar S® of Hayashibara Shoji Inc, Japan which contains at least 25%

(w/w) glucosyl and/or maltosyl sucrose, between 48 and 56% (w/w) saccharose, and not more than 10% (w/w) glucose and fructose.

The adjuvant content of the 1,4 O-linked saccharose derivative or a sugar mixture containing at least one 1,4 O-linked saccharose derivative in the solution / suspension to be dried amounts to between 25% and 99.99% (w/w), preferably between 60% and 99% (w/w), and particularly preferably between 60% and 90% (w/w), in relation to the solids content of the solution or suspension to be dried. The active substance concentration of antibody or antibody derivative normally amounts to between 0.01 and 75% (w/w), preferably between 0.01 and 40% (w/w), particularly preferably between 0.01 and 30% (w/w), in relation to the solids content of the solution or suspension to be dried. On the basis of the powder compositions according to the invention described above, the skilled man is able to produce solutions / suspensions to be dried which, after drying, particularly after spraying, yield the corresponding powder compositions.

The present invention also consequently relates to processes for the production of a dried powder, as described above, characterised in that the solids content of the solution / suspension to be dried contains between 25 and 99.99% (w/w), preferably between 60 and 99% (w/w), of at least one 1,4 O-linked saccharose derivative or a sugar mixture containing at least one 1,4 O-linked saccharose derivative. According to a further preferred embodiment, the present invention relates to a corresponding process, characterised in that the solids fraction of the solution / suspension to be dried contains between 0.01 and 75% (w/w), preferably between 0.01 and 30% (w/w), particularly preferably between 0.33 and 30% (w/w), of antibodies or antibody derivatives as pharmaceutical active substance.

According to a further embodiment, a solution / suspension to be dried with a solids content of **a)** at least 25% (w/w), e.g. between 25 and 99.99% (w/w), of at least one 1,4 O-linked saccharose derivative or a sugar mixture containing at least one 1,4 O-linked saccharose derivative and **b)** at least 0.01% (w/w), preferably 0.01 to 75% (w/w), of an antibody or antibody derivative as pharmaceutical active substance is produced and dried, preferably sprayed, whereby the sum of the weight percentages amounts to max 100% (w/w). According to a preferred embodiment, a solution / sus-

pension to be dried with a solids content **a)** of at least one 1,4 O-linked saccharose derivative or a sugar mixture containing at least one 1,4 O-linked saccharose derivative of at least 60% (w/w), preferably between 60 and 90% (w/w), and **b)** 0.01 and 40% (w/w) of an antibody or antibody derivative is produced and dried, preferably sprayed, whereby the sum of the weight percentages of the solution or suspension amounts to max 100% (w/w) in relation to the solids content of the spray solution / spray suspension.

Depending on the powders according to the invention as described above, the solution / suspension to be dried according to a further embodiment additionally contains one or more pharmaceutically compatible adjuvants and/or one or more salts. The adjuvants are chiefly amino acids, peptides or their salts, sugars, polyols, salts of organic acids, and/or polymers.

The solution / suspension to be dried, alongside **a)** one antibody or antibody derivative as pharmaceutical active substance and **b)** at least one 1,4 O-linked saccharose derivative or a sugar mixture containing at least one 1,4 O-linked saccharose derivative, preferably contains **c)** one or more amino acids and/or peptides or proteins as other adjuvants. The present invention also consequently relates to a process for the production of dried, preferably spray-dried, powders, characterised in that the solution / suspension to be dried contains, in relation to its solids content, **a)** at least 25% (w/w), preferably at least 60 to 90% (w/w), of at least one 1,4 O-linked saccharose derivative or a sugar mixture containing at least one 1,4 O-linked saccharose derivative, **b)** between 1 and 19.99% (w/w) of at least one amino acid and/or at least one peptide, and **c)** between 0.01 and 74% (w/w) of antibodies or antibody derivatives. Examples of suitable adjuvants, including pharmaceutically compatible salts, peptides, and amino acids, are given under "Powders according to the invention" in this patent specification. Anyone skilled in the art will be able to produce corresponding powders and to adjust the weight fractions in such a way that the sum of the solid fractions amounts to max 100% (w/w). Where the fraction (in relation to the total solids content) of antibody or antibody derivative amounts e.g. to 10% (w/w) and the fraction of at least one 1,4 O-linked saccharose derivative or a sugar mixture containing at least one 1,4 O-linked saccharose derivative amounts to 80% (w/w), the skilled

man knows that he can add max 10% (w/w) of amino acids to the solution / suspension to be dried.

According to a further preferred embodiment, the solution / suspension to be dried, alongside at least one 1,4 O-linked saccharose derivative or a sugar mixture containing at least one 1,4 O-linked saccharose derivative, additionally contains isoleucine as a further adjuvant. Solutions / suspensions deemed advantageous are those whose solids fraction contains **a)** at least 25% (w/w), preferably at least 60 to 90% (w/w), of at least one 1,4 O-linked saccharose derivative or a sugar mixture containing at least one 1,4 O-linked saccharose derivative, **b)** between 1 and 19.99% (w/w) of isoleucine, and **c)** at least 0.01% (w/w) of an antibody or antibody derivative as pharmaceutical active substance. The fraction of antibody or antibody derivative is then preferably 0.01 to max 74% (w/w), whereby the sum of the solid fractions amounts to max 100% (w/w). Anyone skilled in the art will be able to produce corresponding powders, preferably by spray drying, and to adjust the weight fractions in such a way that the sum of the solid fractions amounts to max 100% (w/w). Where the fraction (in relation to the total solids content) of antibody or antibody derivative amounts e.g. to 10% (w/w) and the fraction of at least one 1,4 O-linked saccharose derivative or a sugar mixture containing at least one 1,4 O-linked saccharose derivative amounts to 80% (w/w), the skilled man knows that he can add max 10% (w/w) of isoleucine to the solution / suspension to be dried.

According to a further embodiment, the solution / suspension to be dried, alongside at least one 1,4 O-linked saccharose derivative or a sugar mixture containing at least one 1,4 O-linked saccharose derivative, contains one or more tri-peptides, particularly preferably tri-isoleucine. Solutions / suspensions deemed advantageous are those whose solids fraction contains **a)** at least 25% (w/w), preferably 60 to 98.99% (w/w), particularly preferably 60 to 90% (w/w), of at least one 1,4 O-linked saccharose derivative or a sugar mixture containing at least one 1,4 O-linked saccharose derivative, **b)** between 1 and 19.99% (w/w) of a peptide, preferably a di- or tri-peptide, particularly preferably an isoleucine-containing peptide, more preferably tri-isoleucine, and **c)** at least 0.01% (w/w) of an antibody or antibody derivative as pharmaceutical active substance, whereby the sum of the solid fractions amounts to max 100% (w/w). The fraction of the antibody or antibody derivative then preferably amounts to 0.01 to max

74% (w/w). Anyone skilled in the art will be able to produce corresponding powders and to adjust the weight fractions in such a way that the sum of the solid fractions amounts to max 100% (w/w). Where the fraction (in relation to the total solids content) of antibody or antibody derivative amounts e.g. to 10% (w/w) and the fraction of at least one 1,4 O-linked saccharose derivative or a sugar mixture containing at least one 1,4 O-linked saccharose derivative amounts to 80% (w/w), the skilled man knows that he can add max 10% (w/w) of a peptide, preferably a di- or tri-peptide, particularly preferably an isoleucine-containing peptide, more preferably tri-isoleucine, to the solution or suspension to be dried, preferably sprayed.

As already noted, it is advantageous to produce and spray solutions to be dried, preferably sprayed, with a pH value of 3 to 11, preferably 3.5 to 9, and particularly preferably 4.0 to 7.8. Suitable buffer systems are known to the skilled man. The use of inorganic or organic salts as buffer system normally proves to be particularly advantageous.

The optimum adjuvant and protein content for each antibody or antibody derivative is typically determined experimentally. Preferred formulations of the invention may also contain a further adjuvant in order to improve powder properties such as dispersibility and fluidity with retention of superior aggregate suppression.

Spray drying

Spray drying is carried out in conventional spray dryers, such as e.g. in facilities manufactured by Niro A/S (Soeborg, DK), Büchi Labortechnik GmbH (Flawil, CH), or the like. The optimum conditions for spray drying respectively depend on the corresponding formulation and should be experimentally determined. Air is typically used as gas. However, other inert gases, such as nitrogen or argon, are suitable. The spray drying temperature, which means the inlet and outlet temperature, is further determined depending on the temperature sensitivity of the active substance used and in each case depending on the stabilisers used. It is usual to have an inlet temperature of 50-200°C, whereas the outlet temperature is mostly 30-150°C. Operations within the scope of the present invention were performed at an inlet temperature of around 170-185°C and an outlet temperature of 80-100°C. However, it is also possible to have an inlet temperature of up to 200°C, preferably 60-185°C, and an outlet temperature of

up to 120°C, preferably 40-105°C, depending on the stabiliser fraction. Spraying generally proceeds at a pressure of around 29-150 psi, preferably around 30- or 40-100 psi, e.g. at around 30, 40, 50, 60, 70, 80, 90, or 100 psi.

In respect of the Büchi type B-290 Spray Dryer, the liquid feed rate is normally between 0.1 and 100 ml/min, preferably between 0.1 and 30 ml/min, such as e.g. around 3 ml/min. In this context, an aspirator flow rate of 20-40 m^3/h, preferably 30-40 m^3/h, such as e.g. 38.3 m^3/h, and atomising flow rates of 0.3-2.5 m^3/h, preferably of around 0.67 m^3/h, 1.05 m^3/h, and 1.74 m^3/h, have proven to be particularly suitable.

The spray-dried antibody or antibody derivative formulations may optionally be subjected to a second gentle drying (after-drying). The purpose is to obtain a standard residual water content in formulations, preferably less than 2% (w/w), and thereby to improve both the active substance stability and powder properties, such as glass transition temperature, fluidity, and dispersibility. The conditions of the after-drying process must be selected in such a way that aggregation of the antibody or antibody derivative does not significantly increase. The spray-dried active substance formulations are preferably produced, further processed, and stored under dry conditions (at low relative air humidity). The after-drying process enables the moisture content of the powders to be reduced further, despite relatively high initial residual water contents after spray drying. Surprisingly, the adjuvants which are an object of the invention stabilise the proteins in superior manner in the preferred formulations, even under non-optimum process and storage conditions.

Freeze drying

Freeze drying of aqueous solutions can be performed according to the description given in "Lyophilisation" by Essig and Oschmann (Wissenschaftliche Verlagsgesellschaft, Stuttgart, 1993). The therapeutic active substance and an antibody or antibody derivative are normally freeze-dried as an aqueous solution or suspension. Consideration should be given to suitable concentrations and pH values. In a preferred formulation, the antibody or antibody derivative is initially dissolved in an aqueous solution with a suitable buffer system. The pH value of protein-containing solutions is generally from 3 to 11, preferably 3.5 to 9, and particularly preferably between 4.0 and 8. The pH value of the solution must be set below or above the isoelectric point of the

antibody / antibody derivative. In a second container, the adjuvant or a mixture of suitable adjuvants is dissolved in purest water or a suitable buffer solution with a pH value of 3 to 11, preferably 3.5 to 9, and particularly preferably 4.0 to 8.5, and in a second step mixed with the protein solution. Finally, the solution with purest water or a suitable buffer solution with a pH value of 3 to 11, preferably 3.5 to 9, and particularly preferably 4.0 to 8.5. is set to the required solids content. Suitable total solids contents are between 0.1 and 30% (w/w), preferably between 0.5 and 20% (w/w), and particularly preferably between 0.75 and 15.0% (w/w).

The solutions are then freeze-dried in a conventional commercial freeze dryer, such as the Christ LPC-16/NT Epsilon 2-12 D manufactured by Martin Christ Gefriertrocknungsanlagen GmbH, or the like. The product is a protein-containing powder or cake, which, before any further processing, is then reduced in size in a suitable process in order to obtain a polydisperse powder.

The temperatures in the freeze dryer are experimentally optimised and generally range between -70°C and +100°C, preferably between -50°C and +40°C. Preferred pressure parameters in the freeze dryer are a pressure of 10*e-5 to 1013 mbar. After their size reduction, the freeze-dried protein formulations may be preferably subjected to a second gentle drying (after-drying). The purpose is to retain a uniform residual water content of less than 2% (w/w) in the formulations and thereby to improve both the antibody stability and powder properties, such as glass transition temperature, fluidity and dispersibility. The conditions of the after-drying process must be selected in such a way that aggregation of the protein does not significantly increase.

Properties of the spray-dried dry powder formulations

The dry protein-powder formulations produced within the scope of this invention have a residual water content of less than 15% (w/w), usually less than 10% (w/w), and preferably less than 6% (w/w). The spray-dried protein-powder formulations also preferably have a residual water content of less than 5% (w/w), particularly preferably less than 3% (w/w), and most preferably between 0.2 and 2.0% (w/w). Formulations with a low residual moisture content generally exhibit improved stability during packing and storage. The dry protein-powder formulations according to the invention are moreover especially hygroscopic, i.e. they tend to absorb moisture from their envi-

ronment. To avoid this, such powders are usually stored in containers such as blister packs ensuring exclusion of airborne moisture. Surprisingly, it was found for selected formulations of powders according to the invention that the powders, even after one month's open storage at 43% relative air humidity, remain stable in terms of both protein stability and inhalability.

The stabilising effects of the adjuvants described here are able to protect the protein from extreme loadings during spray drying and storage. Pure protein formulations spray-dried in the absence of adjuvants form aggregates to a large extent. Process-dependent factors such as heat, shear stress, and denaturation at the air-water interfaces give rise to aggregation (up to around 6.6% aggregates) during spray drying and subsequent after-drying (up to around 5.8% aggregates). In the course of storage, the absence of the stabilising hydrate shell of proteins gives rise to massive aggregation (of around 11.8 to around 18.9% aggregates).

The preferred spray-dried formulations of the invention, in contrast to the pure protein formulations, are able both to reduce the formation of aggregates after spray drying and to keep this to a very low level even under a variety of storage conditions. Through spray drying and subsequent vacuum drying, only around 0.5 to around 1.8% aggregates form in the preferred formulations, in contrast to around 4.0% aggregates in pure protein formulations. Under particularly challenging storage conditions (40°C, 75% relative humidity) of forced storage stability, the preferred formulations show clear superiority (aggregates of around 1.0 to around 13.1%) over the pure protein formulations (around 18.2 to 18.9% aggregates) as well as over an analogous reference formulation with trehalose as adjuvant. This advantage becomes particularly evident in the comparison made with the formulation given in Example 4. The addition of tri-isoleucine in the spray solution leads to significant improvement of the aerodynamic properties of powders. Surprisingly, only the combinations that contain at least one 1,4 O-linked saccharose derivative, preferably lactosucrose and tri-isoleucine, particularly LS55P and tri-isoleucine as well as LS90P and tri-isoleucine, are able to safeguard the protein from aggregation (only 0.7 to 4.4% aggregates). Neither the raffinose (12.6% aggregates) and hydroxyethyl starch (around 18.6% aggregates) used in combination with tri-isoleucine described in WO 01/32144 nor the state-of-the-art trehalose described as a superior stabiliser are able to protect the pro-

tein from aggregation under particularly challenging conditions in combination with tri-isoleucine. Both the LS55P-tri-isoleucine formulations and the LS90P-tri-isoleucine formulations also appear clearly advantageous over a saccharose-tri-isoleucine formulation (5.6% aggregates) and a saccharose-lactose-tri-isoleucine formulation (8.8% aggregates). This is even more surprising in that LS55P, alongside saccharose, also contains up to 25% lactose. It is clearly the case that the negative effect exerted by the reducing sugar lactose on protein stability is overcompensated in LS55P by the 1,4 O-linked saccharose derivative lactosucrose. A high fraction of lactosucrose in the sugar fraction of the formulation is even more advantageous for protein stability (see LS90P formulations).

Formulations which, during relatively short-term storage under particularly destabilising conditions (one week at 40°C, 75% relative humidity), already have a significant stabilising effect on the incorporated proteins, stabilise the proteins in the long term under much milder standard storage conditions (e.g. one year dry at around 25°C).

After equilibration followed by four weeks' storage under dry conditions at 40°C (equilibrated storage stability), the powder formulations containing LS55P and Coupling Sugar are distinguished by low aggregate contents (around 1.4 to 3.2% aggregates), particularly in comparison with pure protein powders (around 11.8% aggregates).

After vacuum drying followed by four weeks' storage under dry conditions at 40°C (vacuum-dried storage stability), the powder formulations containing LS55P and Coupling Sugar are distinguished by low aggregate contents (around 1.1 to 2.1% aggregates), particularly in comparison with pure protein powders (around 13.2% aggregates).

LS55P (80%), isoleucine (10%), and IgG1 (10%) formulations with a fine particle fraction of around 35% show aggregate contents below 1.9% after vacuum drying followed by filling under nitrogen after three months' storage under dry conditions at 2 to 8°C, 25°C, and 40°C.

LS55P (80%), tri-isoleucine (10%), and IgG1 (10%) formulations with a MMAD of around 3.9 μm and a fine particle fraction of 58.3% after spray drying show aggregate contents below 1.9% after vacuum drying followed by filling under nitrogen after three months' storage under dry conditions at 2 to 8°C, and 25°C and aggregate contents below 2.6% under dry storage conditions at 40°C (3 months' stability).

After one month's open storage at around 43% relative air humidity and 25°C (1 month's open stability), the specified LS55P (80%), tri-isoleucine (10%), and IgG1 (10%) formulations further show a low aggregate content (around 1.3%) at approximately the same low MMAD (around 3.8 μm) and the same high fine particle fraction (around 59.6%).

LS90P (90%) and IgG1 (10%) formulations with a MMAD of around 3.8 μm, a MMD of around 2.8 μm, and a fine particle fraction of around 24% after spray drying show aggregate contents below 1.2 and 2.2% respectively after vacuum drying followed by filling under nitrogen after one and three months' storage under dry conditions at 2 to 8°C, 25°C, and 40°C (1 and 3 months' stability).

LS90P (80%), isoleucine (10%), and IgG1 (10%) formulations with a fine particle fraction of around 28% spray drying show aggregate contents below 0.9 and 1.1% respectively after vacuum drying followed by filling under nitrogen after one and three months' storage under dry conditions at 2 to 8°C, 25°C, and 40°C (1 and 3 months' stability).

LS90P (80%), tri-isoleucine (10%), and IgG1 (10%) formulations with a MMAD of around 4.8 μm and a fine particle fraction of around 53.2% after spray drying show aggregate contents below 1.0 and 2.3% respectively after vacuum drying followed by filling under nitrogen after one and three months' storage under dry conditions at 2 to 8°C, 25°C, and 40°C (1 and 3 months' stability).

After one and three months' open storage at around 43% relative air humidity and 25°C (open 1 and 3 months' stability), variations in the LS90P (80%), tri-isoleucine (10%), and IgG1 (10%) formulations specified above further show low aggregate con-

tents below around 0.5% and 0.8%. After spray drying, the MMAD values range between 3.9 and 3.3 μm and the FPF values between around 55.6 and 58.9%. After one month's open storage at around 43% relative air humidity and 25°C, the formulations specified above further show small MMAD values (around 4.1 to 3.5 μm) and a high fine particle fraction (around 62.3 to 67.3%).

Through variation in the spray drying conditions, powders which preferably have a median particle size (MMD) of less than 20 μm, preferably less than 10 μm, can be produced. According to a particularly preferred embodiment, these particles according to the invention have a mean particle size of less than 7.5 μm, preferably less than 5 μm. Particularly preferred are particles with a median particle size of less than 4 μm, and more preferably less than 3.5 μm. Particles with a mean particle diameter of 0.1-5 μm, preferably 0.2-4 μm, can also be produced. In a further embodiment, the corresponding particles are mixed with non-respirable particles, such as e.g. lactose, with a particle size of at least 40 μm. The fraction preferably amounts to at least 15%, more preferably to at least 20%, still more preferably to at least 30%, still more preferably to at least 40%, particularly preferably to at least 50 or 60%.

Alongside the median particle size (MMD), the inhalability largely depends on the median aerodynamic particle diameter (MMAD). The particles according to the invention preferably have a MMAD smaller than 10 μm, more preferably smaller than 7.5 μm. Particularly advantageous are powders consisting of particles with a MMAD smaller than 5.5 μm, preferably smaller than 5 μm, still more preferably smaller than 4.5 μm. The powders described in the examples can be produced with corresponding particle sizes through the combination of optimum spray drying conditions and appropriate selection and concentrations of adjuvants according to the invention. The addition of amino acids and/or tri-peptides particularly leads to improved particle performance with an increased fraction of inhalable particles with a MMAD smaller than 7.5 μm, preferably smaller than 5.5 μm. Through additions of isoleucine and tri-isoleucine being made, inhalable particles with a FPF greater than 28%, preferably greater than 40%, more preferably greater than 50%, and still more preferably greater than 55% (see EXAMPLES), can be produced.

The powders according to the invention are moreover distinguished by a glass transition temperature of at least 40°C, preferably at least 50°C, more preferably at least 55°C, still more preferably at least 60°C. Particularly preferred powders have a glass transition temperature of at least 65°C. The glass transition temperature of powders according to the invention generally amounts to 40 to 110°C. The present invention accordingly also concerns powders, preferably spray-dried powders, containing a pharmaceutical active substance and LS90P, LS55P, and Coupling Sugar or Coupling Sugar S, whereby the glass transition temperature amounts to 40°C and more, preferably to between 45 and 60°C or higher. According to a further preferred embodiment, the glass transition temperature amounts to 55°C and more, preferably to between 55 and 60°C or higher.

Application of the spray-dried powder

The powders according to the invention are suitable for the production of a medicinal drug, preferably the production of a medicinal inhalant.

Freeze-dried powders

Powders can also be alternatively produced by freeze drying with ensuing pulverisation (see examples). In the examples given in this context, pulverisation was performed in the simplest way conceivable by means of a spatula in the lyophilisation vial. The lyophilisate can also be self-evidently pulverized by suitable mills, such as an attrition mill, ball mill, rod mill, mortar mill, air-jet mill, or other suitable processes (see Bauer, Frömming, Führer, 6th edition).

Properties of the freeze-dried, pulverized dry powder formulations

The dry protein-powder formulations produced within the scope of this invention have a residual water content of less than 15% (w/w), usually less than 10% (w/w), and preferably less than 5% (w/w). The freeze-dried protein-powder formulations also preferably have a residual water content of less than 3% (w/w), particularly preferably less than 2% (w/w), and most preferably between 0.2 and 1.5% (w/w). Formulations with a low residual moisture content generally exhibit improved stability during packing and storage. The dry protein-powder formulations according to the invention are moreover especially hygroscopic, i.e. they tend to absorb moisture from their envi-

ronment. To avoid this, such powders are usually stored in containers such as blister packs ensuring exclusion of airborne moisture.

The stabilising effects of the adjuvants described here are able to protect the protein from extreme stresses during freeze drying and storage. Pure protein formulations freeze-dried in the absence of adjuvants form aggregates to a large extent. Process-dependent factors such as heat, shear stress, and denaturation at the air-water interfaces give rise to aggregation (up to around 2.1% aggregates) during freeze drying. In the course of storage, the absence of the stabilising hydrate shell of the proteins gives rise to massive aggregation (20.5% aggregates).

The preferred freeze-dried formulations of the invention, in contrast to the pure protein formulations, are able both to reduce the formation of aggregates after freeze drying and to keep this to a very low level even under different storage conditions. Under particularly challenging storage conditions (40°C, 75% relative humidity) of forced storage stability, the freeze-dried and pulverized lyophilisates show clear superiority (aggregates of around 1.2 to around 1.5%) over the pure protein formulations (around 14.5% aggregates) as well as over an analogous reference formulation with mannitol as adjuvant (around 34.0% aggregates).

Formulations which, during relatively short-term storage under particularly destabilising conditions (one week at 40°C, 75% relative humidity) already have a significant stabilising effect on the incorporated proteins, stabilise the proteins in the long term under much milder standard storage conditions (e.g. one year dry at around 25°C).

After freeze drying, pulverisation, and equilibration followed by four weeks' storage under dry conditions at 40°C (equilibrated storage stability), the powder formulations containing LS55P and Coupling Sugar are distinguished by low aggregate contents (around 2.6 and 4.6% aggregates), particularly in comparison with pure protein powders (around 15.3% aggregates) and an analogous reference formulation with mannitol as adjuvant (around 11.6% aggregates).

After freeze drying, pulverisation, and vacuum drying followed by four weeks' storage under dry conditions at 40°C (vacuum-dried storage stability), the LS55P and

Coupling Sugar containing powder formulations are distinguished by low aggregate contents (around 1.2 and 1.5% aggregates), particularly in comparison with pure protein powders (around 14.5% aggregates) and an analogous reference formulation with mannitol as adjuvant (around 6.2% aggregates).

The powders according to the invention are moreover distinguished by a glass transition temperature of at least 40°C, preferably at least 50°C, more preferably at least 55°C. The glass transition temperature of powders according to the invention generally amounts to 40 to 110°C but may exceed this value in individual cases. The present invention accordingly also concerns powders, preferably freeze-dried and pulverized powders, containing a pharmaceutical active substance and LS90P, LS55P, and Coupling Sugar or Coupling Sugar S, whereby the glass transition temperature amounts to 40°C and more, preferably to between 45 and 60°C or higher. According to a further preferred embodiment, the glass transition temperature amounts to 55°C and more, preferably to between 55 and 60°C or to 110 °C.

Application of the dried powder

The powders according to the invention are suitable for the production of a medicinal drug, preferably the production of a medicinal inhalant.

Delivery of the powders according to the invention

The spray-dried powder preparations according to the invention can be basically applied directly as dry powder via so-called dry powder inhalers or else, after reconstitution, in the form of aerosols via so-called atomizers. The inhalation powders according to the invention can then be applied by means of known state-of-the-art inhalers.

Inhalation powders according to the invention can be applied e.g. by means of inhalers that deliver an individual dose from a storage container by means of a metering chamber, as described in US 4,570,630A, or via other apparatuses, as described in DE 36 25 685 A. The inhalation powders according to the invention are preferably filled in capsules (to form so-called inhalettes) that are used in inhalers, as e.g. described in WO 94/28958.

Further examples of suitable inhalers are e.g. given in US 5,458,135, US 5,785,049, or WO 01/00263. Further suitable inhalers are known from WO 97/41031, US 3,906,950, and US 4,013,075. Further dispersion inhalers for dry powder preparations are described in EP 129 985, EP 472 598, EP 467 172, and US 5,522,385.

The inhalation powders according to the invention can be e.g. applied by means of the inhaler known by the proprietary name of Turbuhaler® (AstraZeneca LP) or else by means of inhalers as e.g. published in EP 237 507 A. Other suitable inhalers are the Rotahaler® or the Discus® (both of GlaxoSmithKline Corporation), the Spiros™ inhaler (Dura Pharmaceuticals), and the Spinhaler® (Fiscon).

An inhaler particularly preferred for application of the drug combination according to the invention in the form of inhalettes is shown in Figure 24. This inhaler (Handihaler) for the inhalation of powdered drugs in capsules is characterised by a housing 1 containing two windows 2, a deck 3, wherein air inlet openings are located and which is provided with a sieve 5 fixed in place via a sieve housing 4, an inhalation chamber 6 connected with deck 3, whereon a trigger 9 is provided having two sharpened needles 7 and able to move against a spring 8, and a mouthpiece 12 hinged via an axis 10 with housing 1, deck 3, and cap 11, and air holes 13 for adjustment of the flow resistance.

Where the inhalation powders according to the invention in respect of the preferred application specified above are filled in capsules (inhalettes), fill amounts of 1 to 30 mg per capsule are appropriate.

The inhalation powders according to the invention may further be applied as propellant-containing or propellant-free inhalation aerosols. For this purpose, the powders according to the invention are suspended in pressure-liquefiable solvents or solvent mixtures or reconstituted in an aqueous solution. Suitable suspensions or solutions are known in the art. For example, reconstitution is advantageous in physiological solutions with a pH of 3-11, preferably 4-9. Particularly advantageous is reconstitution in an aqueous solution with a pH of 5.5-7.8. The propellant-containing suspensions or solutions for reconstitution of the powders according to the invention may further contain other adjuvants in the form of stabilisers, emulsifiers, surface-active sub-

stances, or water-soluble organic solvents. Appropriate substances are known to the skilled man, being described e.g. in (Bauer, Textbook of Pharmaceutical Technology, Wissenschaft Verlagsgesellschaft GmbH, Stuttgart, 178-184; Adler, 1998, Journal of Pharmaceutical Sciences, 88(2) 199-208). Corresponding inhalation aerosols produced by suspension or reconstitution of the powders according to the invention are also the object of the present invention.

The propellants used to produce the inhalation aerosols according to the invention are also known in the art. Suitable propellants are selected from the group consisting of hydrocarbons, such as n-propane, n-butane, or isobutane, and halogenated hydrocarbons, such as preferably chlorinated and fluorinated derivatives of methane, ethane, propane, butane, cyclopropane, or cyclobutane. The propellants specified above may be used individually or in mixtures thereof. Particularly preferred propellants are halogenated alkane derivatives selected from TG11, TG12, TG134a (1,1,1,2-tetrafluoroethane), TG227 (1,1,12,3,3,3-heptafluoropropane), and mixtures thereof, whereby the propellants TG134a, TG227, and mixtures thereof are preferred.

The propellant-containing inhalation aerosols according to the invention may contain up to 5% (w/w) active substance. Aerosols according to the invention e.g. contain 0.002-5% (w/w), 0.01-3% (w/w), 0.015-2% (w/w), 0.1-2% (w/w), 0.5-2% (w/w), or 0.5-1% (w/w) of pharmaceutical active substance. Inhalation aerosols with a corresponding active substance concentration can be prepared in an appropriate quantity of solvent by targeted reconstitution of the powders according to the invention.

The propellant-containing inhalation aerosols according to the invention as specified above can also be applied by means of known state-of-the-art inhalers (MDIs = metered dose inhalers). In this context, reference may be made to the Ventolin® (Ventolin Pharmacy) or to the inhalers described in US 5,32,094 or US 5,672,581. A further aspect of the present invention accordingly concerns medicinal drugs in the form of propellant-containing aerosols as described above in conjunction with one or more inhalers suitable for delivery of these aerosols. The present invention further concerns inhalers characterised in that they contain propellant-containing aerosols according to the invention as described above.

The present invention further concerns cartridges that may be used through being equipped with a suitable valve in a suitable inhaler and which contain the propellant-containing inhalation aerosols according to the invention as specified above. Suitable cartridges and processes for filling these cartridges with the propellant-containing inhalation aerosols according to the invention are known in the art.

The powders according to the invention may further be reconstituted in propellant-free inhalation solutions or suspensions. Corresponding propellant-free inhalation solutions e.g. contain aqueous or alcoholic, preferably ethanolic, solvents, where necessary ethanolic solvents mixed with aqueous solvents. In the case of aqueous/ethanolic solvent mixtures, the relative fraction of ethanol in relation to water is not limited, although the maximum limit is preferably up to 70% (v/v), particularly up to 60% (v/v) ethanol. The residual volume percentages are water. The propellant-free inhalation solutions according to the invention may be mixed with co-solvents and/or other adjuvants as described above. For example, it is possible to use co-solvents containing hydroxyl groups or other polar groups, such as e.g. alcohols, particularly isopropyl alcohol, glycols, particularly propylene glycol, polyethylene glycol, polypropylene glycol, glycol ether, glycerol, polyoxyethylene alcohols, and polyoxyethylene fatty acids. In this context, adjuvants and additives are understood to mean any pharmacologically compatible substance which is not an active substance but which, together with the active substance(s), can be formulated in the pharmacologically suitable solvent in order to enhance the qualities of the active substance formulation. These substances preferably produce no, or in the context of the therapy being sought, no appreciable or at least no unwanted pharmacological effect. Adjuvants and additives, alongside the surface-active substances, such as e.g. soya lecithin, oleic acid, sorbitan esters, such as polysorbate, polyvinylpyrrolidone, other stabilisers, complexing agents, antioxidants, and/or preservatives which guarantee or prolong the shelf life of the finished drug formulation, include flavourings, vitamins, and/or other additives known in the art. Additives also include pharmacologically harmless salts, such as e.g. sodium chloride, as isotonic agents. Preferred adjuvants include antioxidants such as e.g. ascorbic acid, unless already used to adjust the pH value, vitamin A, vitamin E, tocopherols, and similar vitamins or provitamins occurring in the human organism. Preservatives may be used to protect the formulation from contamination by germs. Suitable preservatives known in the art particularly include cetyl pyridinium chloride,

benzalkonium chloride, or benzoic acid or benzoates, such as sodium benzoate, at the concentrations known in the art. The preservatives specified above are preferably contained at concentrations of up to 50 mg/100 ml, particularly preferably between 5 and 20 mg/100 ml. The present invention also accordingly concerns propellant-free inhalation aerosols produced by reconstitution of the powders according to the invention.

Particularly suitable for application of the propellant-free inhalation solutions according to the invention are inhalers able to atomize a small quantity of a liquid formulation in the therapeutically necessary dose within a few seconds into a suitable therapeutic aerosol for use in an inhaler. Preferred within the scope of the present invention are atomizers wherein a quantity of less than 100 µL, preferably less than 50 µL, particularly preferably between 10 and 30 µL, active substance solution can be atomized in one stroke to form an aerosol with an average particle size of less than 20 µm, preferably less than 10 µm, in such a way that the inhalable fraction of aerosol already corresponds to the therapeutically efficacious quantity.

Such a device for propellant-free delivery of a dosed quantity of a liquid drug for application in an inhaler is e.g. described in detail in international patent applications WO 91/14468 and WO 97/12687 (particularly in Figures 6a and 6b thereof).

Within the scope of the present invention, reference is expressly made to corresponding Figures 6a and 6b of WO 97/12687, including the associated parts used in the description. The atomizers (devices) described in this application are also known under the description of Respimat® (Boehringer Ingelheim Pharma). Thanks to its near-cylindrical shape and handy size of less than 9 to 15 cm in length and 2 to 4 cm in width, this device can be carried with the patient at all times. The atomizer sprays a specific volume of drug formulation under high pressures through small nozzles in such a way as to generate inhalable aerosols.

The preferred atomizer basically consists of an upper housing unit, pump housing, nozzle, blocking tensioning mechanism, spring housing, spring, and storage container, characterised by

- a pump housing fixed in place in the upper housing unit and carrying, at one end, a nozzle body with the nozzle or nozzle arrangement,
- a hollow piston with valve body,
- a power take-off flange wherein the hollow piston is fixed in place and which is located in the upper housing unit,
- a blocking tensioning mechanism located in the upper housing unit,
- a spring housing with the spring located therein, which is rotatably mounted on the upper housing unit by means of a pivot bearing,
- a lower housing unit inserted on the spring housing in the axial direction.

The hollow piston with valve body corresponds to a device published in WO 97/12687. It partially projects into the cylinder of the pump housing and has axial displaceability inside the cylinder. Within the scope of the present invention, reference is made to Figures 1-4 – particularly to Figure 3 – and to the associated parts used in the description. The hollow piston with valve body, on its high-pressure side at the time of spring tripping, exerts a pressure of 5 to 60 MPa (around 50 to 600 bar), preferably 10 to 60 MPa (around 100 to 600 bar), on the fluid, the metered active substance solution. Volumes of 10 to 50 microlitres are preferred. Particularly preferred are volumes of 10 to 20 microlitres, particularly a volume of 15 microlitres per stroke.

The valve body is preferably arranged at the end of the hollow piston, which faces the nozzle body.

The nozzle in the nozzle body is preferably microstructured, i.e. produced by microtechnology. Microstructured nozzle bodies are e.g. published in WO 94/07607, to whose contents this specification makes reference, particularly to published Figure 1 and its description. The nozzle body e.g. consists of two rigidly interconnected plates made of glass and/or silicon, whereof at least one plate incorporates one or more microstructured channels which connect the nozzle inlet side with the nozzle outlet side. Located on the nozzle outlet side is at least one circular and one non-circular opening of 2-10 μm depth and 5-15 μm width, whereby the depth preferably amounts to 4, 5 to 6.5 μm and the length to 7-9 μm. In the case of several nozzle openings, two being preferred, the jet directions of the nozzles in the nozzle body can run parallel to each

other, or else they are inclined against each other in the nozzle opening direction. In a nozzle body with at least two nozzle openings on the outlet side, the jet directions can be inclined against each other at an angle of 20-160 degrees. An angle of 60-150 degrees is preferred, particularly 80-100 degrees. The nozzle openings are preferably arranged at a distance of 10-200 μm, more preferably at a distance of 10-100 μm, and particularly preferably at a distance of 30-70 μm. Most preferable is a distance of 50 μm.

The jet directions accordingly converge near the nozzle openings.

The liquid drug preparation engages the nozzle body at an inlet pressure of up to 600 bar, preferably 200 to 300 bar, being atomized to form an inhalable aerosol via the nozzle openings. The preferred particle or droplet sizes of the aerosol range up to 20 μm, preferably 3-10 μm.

The blocking tensioning mechanism incorporates a spring, preferably a cylindrical screw-shaped pressure spring, for storage of mechanical energy. The spring acts on the take-off flange as a resilient member, whose movement is determined by the position of a blocking element. The path of the take-off flange is precisely limited by an upper and lower end stop. The spring is preferably tensioned via a power transmission gear, such as e.g. a screw thrust gear, by an external torque generated during rotation of the upper housing unit against the spring housing in the lower housing unit. In this case, the upper housing unit and take-off flange incorporate a single- or multi-threaded V gear.

The blocking element with engaging blocking surfaces is arranged around the take-off flange in a ring shape. It consists e.g. of an inherently radially elastically deformable ring made of plastic or metal. The ring is arranged in a plane vertical to the atomizer axis. After the spring is tensioned, the blocking surfaces of the blocking element slide into the path of the take-off flange and prevent relaxation of the spring. The blocking element is tripped by means of a button. The tripping button is connected or coupled with the blocking element. To trip the blocking tensioning mechanism, the tripping button is displaced parallel to the ring plane, and preferably into the atomizer, causing

the deformable ring to be deformed in the ring plane. Design details of the blocking tensioning mechanism are described in WO 97/20590.

The lower housing unit is slid in the axial direction over the spring housing and covers the bearing, spindle drive, and fluid storage container.

During operation of the atomizer, the upper housing unit is rotated against the lower housing unit, whereby the lower housing unit picks up the spring housing. The spring is then compressed and tensioned by the screw thrust gear, and the blocking mechanism automatically engages. The angle of rotation is preferably an integer fraction of 360 degrees, such as e.g. 180 degrees. Simultaneously as the spring is tensioned, the take-off unit in the upper housing unit is displaced over a preset path, and the hollow piston is retracted inside the cylinder in the pump housing, whereby a partial quantity of the fluid is drawn from the storage container into the high-pressure space ahead of the nozzle.

Several interchangeable storage containers containing fluid to be atomized can be where necessary consecutively inserted in the atomizer and used. The storage container contains the aqueous aerosol preparation according to the invention.

The atomisation process is started through the tripping button being lightly pressed. The blocking mechanism then vacates the path for the drive unit. The tensioned spring slides the piston into the cylinder of the pump housing. The fluid emerges from the atomizer nozzle in atomized form.

Further design details are published in PCT applications WO 97/12683 and WO 97/20590, the contents of which are hereby incorporated by reference.

The atomizer components are made of a functionally suitable material. The atomizer housing and – insofar as function allows – other parts as well are preferably made of plastic, e.g. produced by injection moulding. For medical purposes, physiologically safe materials are used.

Figures 6 a/b of WO 97/12687, including the associated description, to whose contents reference is again made in this context, shows a corresponding atomizer (Respimat®). This atomizer is particularly suitable for application of the propellant-free inhalation aerosols according to the invention.

Figure 6a of WO 97/12687 shows a longitudinal section through the atomizer with the spring tensioned, and Figure 6b of WO 97/12687 shows a longitudinal section through the atomizer with the spring relaxed. The upper housing unit (51) incorporates the pump housing (52), at whose end the holder (53) for the atomizer nozzle is arranged. The nozzle body (54) and a filter (55) are located in the holder. The hollow piston (57) fixed in the take-off flange (56) of the blocking tensioning mechanism to some extent projects into the cylinder of the pump housing. At its end, the hollow piston carries the valve body (58). The hollow piston is sealed by means of the seal (59). Located inside the upper housing unit is the end stop (60) whereon the take-off flange bears when the spring is relaxed. Located on the take-off flange is the end stop (61) whereon the take-off flange bears when the spring is tensioned. After the spring is tensioned, the blocking element (62) slides between the end stop (61) and a support (63) in the upper housing unit. The tripping button (64) connects with the blocking element. The upper housing unit terminates in the mouthpiece (65) and is sealed by the insertable protective cap (66). The spring housing (67) with pressure spring (68) is rotatably mounted on the upper housing unit by means of the snap lugs (69) and pivot bearing. The lower housing unit (70) is slid over the spring housing. The interchangeable storage container (71) for the fluid to be atomized (72) is located inside the spring housing. The storage container is sealed by the stopper (73), through which the hollow piston projects into the storage container and immerses in the fluid (supply of active substance solution) with its end. The spindle (74) for the mechanical counter is arranged in the spring housing casing. The drive pinion (75) is located at the end of the spindle that faces the upper housing unit. The slider (76) is seated on the spindle.

Where the formulation according to the invention is atomized by means of the technology (Respimat®) described above, the delivered weight during at least 97%, preferably at least 98%, of all inhaler actuations (strokes) should correspond to a specific quantity with a tolerance range of max 25%, preferably 20%, of this quantity. Be-

tween 5 and 30 mg formulation as specific weight, particularly preferably between 5 and 20 mg, should preferably be delivered per stroke.

The formulation according to the invention, however, may also be atomized by means of inhalers other than those described above, such as e.g. jet-stream inhalers or other stationary atomizers.

A further aspect of the present invention accordingly concerns medicinal drugs in the form of propellant-free inhalation solutions or suspensions as described above in conjunction with a device suitable for delivery of these formulations, preferably in conjunction with the Respimat®. The present invention preferably targets propellant-free inhalation solutions or suspensions containing one of the powders according to the invention in conjunction with the device known under the description of Respimat®. The present invention further concerns inhalation devices specified above, preferably the Respimat®, characterised in that it contains the propellant-free inhalation solutions or suspensions described above.

Inhalation solutions containing one of the powders according to the invention as described in this context in a unique commercially available form preferably accord with the invention.

The propellant-free inhalation solutions or suspensions according to the invention may, alongside the solutions and suspensions envisaged as described above for application in the Respimat®, may also be used as concentrates or sterile ready-to-use inhalation solutions or suspensions. Through addition of isotonic cooking salt solutions, ready-to-use formulations can be e.g. generated from concentrates. Sterile ready-to-use formulations can be applied by means of power-driven stationary or transportable atomizers that produce inhalable aerosols by means of ultrasound or compressed air according to the venturi principle or other principles.

A further aspect of the present invention accordingly concerns medicinal drugs in the form of propellant-free inhalation solutions or suspensions as described above which are used as concentrates or sterile ready-to-use formulations in conjunction with a device suitable for delivery of these solutions, characterised in that this device refers to a

power-driven stationary or transportable atomizer that produces inhalable aerosols by means of ultrasound or compressed air according to the venturi principle or other principles.

Other suitable atomizers for application of reconstituted aerosols in an inhaler are the AERx™ (Aradigm), the Ultravent ® (Mallinkrodt), and the Aconll® (Maquest Medical Products).

Embodiment examples

Materials and methods

Materials

A humanized monoclonal antibody with a molecular weight of around 148 kDa of Boehringer Ingelheim, Germany was used as IgG1. The antibody is derived from a murine antibody wherein the complementary-determining regions of the murine antibody were transferred to a human antibody framework. This produced a chimeral antibody with a 95% human and 5% murine fraction. The antibody was expressed from murine myeloma cell strains. The cells are removed with the aid of tangential flow microfiltration and the cell-free solution cleansed by various chromatographic methods. Further steps include nuclease treatment, treatment at low pH value, and nanofiltration. The antibody-containing bulk solution contained 25 mM histidine and 1.6 mM glycine as buffer and was concentrated to around 100 mg/ml by diafiltration for production of the spray drying solution. The bulk for production of the solution to be sprayed contained 0.4 to 0.8% aggregates. The finished drug can be kept for at least two years at 2-8°C. Nyuka-Oligo® LS55P, Nyuka-Oligo® LS90P, Coupling Sugar®, and Coupling Sugar S® were supplied by Hayashibara Shoji Inc, Japan. Saccharose, lactose, mannitol, raffinose, hydroxyethyl starch, and L-isoleucine were supplied by Sigma-Aldrich Chemie GmbH, Germany. Trehalose was procured from Georg Breuer GmbH, Germany. Tri-isoleucine was supplied by Iris Biotech GmbH, Germany. Egg white lysozyme (135500 U/mg) was supplied by SERVA Electrophoresis GmbH, Germany. Synthetic salmon calcitonin (calcitonin) was supplied by Biotrend Chemikalien GmbH, Germany.

Spray drying with Büchi B-290

Spray drying was performed with the aid of a type B-290 Büchi Mini Spray Dryer of Büchi Labortechnik GmbH. Spray drying of the formulations was basically performed in accordance with the description given in "Spray Drying Handbook", 5th edition, K. Masters, John Wiley and Sons, Inc., NY, NY (1991):

The sprayer dryer is built from a heating system, a filter, an aspirator, a drying system, a cyclone, temperature sensors for measurement of the inlet and outlet temperature, and a collecting vessel. A peristaltic pump is used to pump the solution to be

sprayed into a twin-substance nozzle, where compressed air is used to atomize the solution into small droplets. Drying proceeds in the spraying tower by warmed air, which is drawn through the spraying tower by the aspirator in a continuous flow process. The product is collected in the collecting vessel after passing through the cyclone. Two different cyclones were used:

- Cyclone I: Büchi cyclone (serial number 4189)
- Cyclone II: Büchi high-performance cyclone (serial number 46369)

The solids fraction of the sprayed solutions was 10% (w/v), 3.33%, and 2.00% in 50 to 600 ml. The inlet temperature was around 170 to 185°C, the liquid feed rate around 3 to 3.33 ml/min, the aspirator flow rate around 36.8 to 38.3 m^3/h, and the atomising rate (AAF = atomising air flow) around 0.67 m^3/h, 1.05 m^3/h, and 1.74 m^3/h, resulting in an outlet temperature of around 80-95°C.

Freeze drying

Freeze drying was performed with the aid of a Christ LPC-16/NT Epsilon 2-12 D freeze dryer made by Martin Christ Gefriertrocknungsanlagen GmbH. The freeze dryer consists of a drying chamber, a condenser for separation of the sublimated solvent, a pump for vacuum generation, and electrical equipment. Drying is controlled via the control surface temperature and drying chamber vacuum.

The solids fraction of the freeze drying solution was 5% (w/v). The solution was portioned in 2R vials containing 0.5 ml each and placed in the freeze dryer with threaded freeze drying stoppers. The solutions were initially frozen at –40°C x 30 minutes. This was followed by main drying at 0.11 mbar in three steps: first –40°C x 30 hours, then –30°C x 8 hours, and finally –16°C x 8 hours. The next step was after-drying, which proceeded at 20°C x 20 hours x 0.001 mbar. As a final step, the vials were automatically sealed with the freeze drying stoppers only inserted at the start. The thus obtained lyophilisates have been pulverized with a spatula inside the vials.

X-ray diffractometry (wide-angle X-ray diffractometry (WAXS))

To determine the crystallinity of the dried samples, the samples were investigated with a type XRD 3000 TT X-ray diffractometer (of Seifert, Ahrensburg, Germany) in a room regulated to a temperature of 22°C. The Cu anode X-ray tube using Cu-Kα

radiation with λ = 0.15418 mm (Ni primary filter) was operated at an anodic voltage of 40 kV and current intensity of 30 mA. After the sample plate was placed in the instrument, the sample was measured over the 5 to 40degrees range at a scanning rate of 2 θ = 0.05degrees and measurement time of 2 seconds at each angle.

The powder diffractograms were recorded with the aid of the ScanX-Rayflex version 3.07, device XRD 3000 (Scan) and the Rayflex version 2.1, 1996 (analysis) on a type SC 1000 V detector.

Size exclusion chromatography (SEC-HPLC)

a) IgG1 protein aggregates

To quantify the IgG1 protein aggregates in the reconstituted powders, a SEC-HPLC was performed. The SEC-HPLC was performed with a type HP1090 unit of Agilent. A type TSK3000SWXL column (300 x 7.8 mm) of Tosoh Biosep (Tosoh Bioscience, Stuttgart, Germany) was used for separation. As the fluid, a buffer consisting of 0.1M disodium hydrogen phosphate dihydrate and 0.1M sodium sulphate was dehydrated and adjusted with 85% ortho-phosphoric acid to pH 6.8. The amount of sample charged was 25 µl at a protein concentration of 2-10 mg/ml. Protein detection was performed at 280 nm with the aid of a diode array detector of Agilent. HP Chemstation software of Agilent was used to evaluate the chromatograms.

b) Calcitonin protein aggregates

To quantify the calcitonin protein aggregates in the reconstituted powders, a SEC-HPLC was performed. The SEC-HPLC was performed with a type HP1100 unit of Agilent. A type TSK2000SWXL column (300 x 7.8 mm) of Tosoh Biosep (Tosoh Bioscience, Stuttgart, Germany) was used for separation. As the fluid, a buffer consisting of 0.25 sodium sulphate with a pH of around 6 was used (Windisch et al., 1997). Alternatively, a dehydrated buffer consisting of 0.1M disodium hydrogen phosphate dihydrate and 0.1M sodium sulphate adjusted with 85% ortho-phosphoric acid to pH 6.8 can be used. The amount of sample charged was 20 µl at a protein concentration of 0.5-2 mg/ml. Protein detection was performed at 210 nm with the aid of a UV detector of Agilent. HP Chemstation software of Agilent was used to evaluate the chromatograms.

c) Lysozyme residual monomer content

To quantify the lysozyme residual monomer content in the reconstituted lysozyme formulations, a modified SEC-HPLC (van de Weert, 2000) was performed. A type TSK2000SWXL column (300 x 7.8 mm) of Tosoh Biosep (Tosoh Bioscience, Stuttgart, Germany) was used for separation. As the fluid, a buffer consisting of 0.1M disodium hydrogen phosphate dihydrate and 0.2M sodium chloride was adjusted with 85% ortho-phosphoric acid to pH 7.0. The amount of sample charged was 25 µl at a protein concentration of 2-10 mg/ml. Protein detection was performed at 280 nm with the aid of a diode array detector of Agilent. HP Chemstation software of Agilent was used to evaluate the chromatograms.

To evaluate the formulations, the residual soluble monomer was quantified by the following method. A calibration line was initially produced with lysozyme standard solutions with concentrations of 2.5 mg/ml, 5.0 mg/ml, and 10 mg/ml. Consideration was then given to the AUC of the monomer peaks in relation to the corresponding lysozyme concentrations in the investigated standard solutions.

The residual monomer content of the different investigated lysozyme formulations was calculated on the basis of the calibration lines. The higher the residual monomer content of a formulation, the better is the protein stability.

Particle size determination (MMD)

The mass mean diameter (MMD) or the mean particle size was determined with the aid of the Sympatech Helos unit of Sympatech GmbH, Clausthal-Zellerfeld, Germany. The measurement principle is based on laser diffraction, a helium-neon laser being used. Some 1-3 mg powder are dispersed at an air pressure of 2 bar and guided in front of a 50 mm Fourier lens by a parallel laser beam. The particle size distribution is evaluated with a Fraunhofer model. Two measurements were performed per powder.

Mass mean aerodynamic diameter (MMAD) and fine particle fraction (FPF)

Some 12-18 mg powder respectively filled in size 3 hard-gelatine capsules and introduced into the Handihaler (powder inhaler of Boehringer Ingelheim) were used for the

measurements. An adapter was used to couple the Handihaler to the USP EP throat of the instrument impactor inlet. The powder was drawn off at a rate of 39.0 l/min at a suction time of 6.15 seconds. The air throughput was controlled via an external control panel. At least three capsules were measured for each powder.

The APS 3321 unit of TSI Inc., MN, USA was simultaneously used in combination with the impactor inlet 3306 to determine the aerodynamic particle size (mass mean aerodynamic diameter, MMAD) via a time of flight determination and the fine particle fraction (FPF) via a single-stage impactor (with an effective cut-off diameter of 5.0 µm at 39 L/min). After being drawn off via the EP/USP throat or sample induction port, the powder passes to a thin capillary, where 0.2% of the powder quantity is sampled for time of flight measurement under isokinetic conditions. The time of flight measurement is performed after capillary passage through two laser beams, which, as in a light barrier, detect the flight times over a specific distance. The result is a numerical distribution that is subsequently converted into a mass distribution and then to the mass mean aerodynamic diameter (MMAD).

The residual 99.8% of the powder population that has passed by the capillary is separated via the single-stage impactor. The fraction greater than 5.0 µm separates in the impactor on an impact plate as a result of mass inertia. The fine particle fraction (FPF) follows the airflow, being finally separated in a depth filter. The fine particle fraction is gravimetrically determined. The fine particle fraction is calculated from the fraction of powder separated in the filter in relation to the total quantity of powder used, i.e. the weighed powder per capsule.

Residual water content

The residual water content of the dried products was determined by means of coulometric titration (Metrohm 737 KF coulometer with type 703 titration stand, Germany). To determine the residual water content, powder was dissolved or dispersed in methanol (Hydranal – Methanol dry, VWR / Merck Eurolab). The measured solution (Hydranal – Coulomat solution, VWR / Merck Eurolab) of the Metrohm coulometer was conditioned at the start of the measurements, i.e. the measured solution was cali-

brated to zero water content. The sample was injected into the titration cell and measured.

Stability determination

The powders or proteins contained in the powder were investigated for different stabilities after spray drying. The percentage fraction of protein aggregates was set at the measurement unit for formulation stability. Pure protein formulations, analogous trehalose formulations, analogous raffinose formulations, analogous saccharose formulations, analogous saccharose-lactose formulations, or analogous hydroxyethyl starch formulations were partially compared as references with the innovative adjuvants described in the invention. Aggregates were analyzed by validated size exclusion chromatography (SEC-HPLC) with UV detection (DAD). For this purpose, the pretreated powders were initially reconstituted in purest water (with a pH of 6 to 8).

- Forced storage stability: Selected formulations were investigated for stability after one week's open storage at around 40°C and around 75% relative air humidity (40°C, 75% RH) in open glass vials.
- Equilibrated storage stability: Selected formulations after spray drying were stored in open glass vials for one day at around 22°C and 50 to 55% relative air humidity (equilibration). The glass vials were subsequently sealed and beaded under the conditions specified above and investigated for stability after four weeks' dry storage at around 40°C.
- Vacuum-dried storage stability: Selected formulations after spray drying were stored for one day in open glass vials in a vacuum drying cabinet of Memmert, Germany at around 30°C and around 0.15 mbar (vacuum drying). The glass vials were subsequently removed from the vacuum drying cabinet, sealed, and beaded and investigated for stability after four weeks' dry storage at around 40°C.
- 3 months' stability: Selected formulations after spray drying were vacuum-dried in open glass vials (see above). The glass vials were sealed and beaded under nitrogen and stored at three different temperatures of 2-8°C, 25°C, and 40°C. The powders were investigated for stability after one month.
- Open 3 months' stability: Selected formulations after spray drying were respectively stored in open glass vials at 25°C and around 29% and/or 43% relative air humidity. The powders were investigated for stability after one and three months.

For selected formulations. the aerodynamic performance of the powder was also determined by means of time of flight measurements (see above).

Example 1

Spray drying of a 10% (w/v) IgG1 formulation

Pure IgG1 with a concentration of around 109 mg/ml formulated in a pH 6 glycine-histidine buffer (see Materials) was diluted with demineralised water (with a pH of around 7.5) to a content of 100 mg/ml and, in the absence of any other adjuvants, spray-dried as described above using cyclone I at an atomising air flow of around 0.67 m^3/h. The solution volume was 50 ml. The aggregate content was investigated as described above.

- After one week's open storage at 75% relative air humidity and 40°C (forced storage stability), the solution prepared from the reconstituted powder had around 18.9% and 18.2% aggregates respectively.
- After one day's equilibration and four weeks' dry storage at 40°C, the solution prepared from the reconstituted powder had around 11.8% aggregates.
- After one day's vacuum drying and four weeks' dry storage at 40°C, the solution prepared from the reconstituted powder had around 13.2% aggregates.

Spray drying of a 3.33% (w/v) IgG1 formulation

Pure IgG1 with a concentration of around 102.8 mg/ml formulated in a pH 6 glycine-histidine buffer (see Materials) was diluted with demineralised water (with a pH of around 7.5) to a content of 33 mg/ml and, in the absence of any other adjuvants, spray-dried as described above using cyclone I at an atomising air flow of around 0.67 m^3/h. The solution volume was 150 ml. The aggregate content was investigated as described above.

- After one week's open storage at 75% relative air humidity and 40°C (forced storage stability), the solution prepared from the reconstituted powder had around 16.3% aggregates.
- After 1 and 3 months' storage at 2-8°C (3 months' stability), the solution prepared from the reconstituted powder had around 4.5% and 4.4% aggregates respectively.

- After 1 and 3 months' storage at 25°C (3 months' stability), the solution prepared from the reconstituted powder had around 7.4% and 7.1% aggregates respectively.
- After 1 and 3 months' storage at 40°C (3 months' stability), the solution prepared from the reconstituted powder had around 13.3% and 18.1% aggregates respectively.
- After 1 and 3 months' storage at around 29% relative air humidity and 25°C, the solution prepared from the reconstituted powder had around 5.5% and 6.6% aggregates respectively.
- After 1 and 3 months' storage at around 43% relative air humidity and 25°C, the solution prepared from the reconstituted powder had around 5.6% and 7.0% aggregates respectively.

Spray drying of a 9% (w/v) trehalose
1% (w/v) IgG1 formulation

4.5 g trehalose were dissolved in around 40 ml demineralised water (with a pH of around 7.5). As the next step, around 4.6 ml pure IgG1 with a concentration of around 109 mg/ml formulated in a pH 6 glycine-histidine buffer (see Materials) were added and diluted with demineralised water (with a pH of around 7.5) to a volume of 50 ml. The solution thus obtained contained around 9% (w/v) adjuvant or matrix and 1% (w/v) protein and was spray-dried as described above using cyclone I at an atomising air flow of around 0.67 m^3/h. The aggregate content was investigated as described above.

The following aggregate contents were obtained for its storage stability:

- After one week's open storage at 75% relative air humidity and 40°C (forced storage stability), the solution prepared from the reconstituted powder had around 12.6% aggregates.

Spray drying of a 3.00% (w/v) LS90P
0.33% (w/v) IgG1 formulation

4.5 g LS90P were dissolved in around 140 ml demineralised water (with a pH of around 7.5). As the next step, around 4.864 ml pure IgG1 with a concentration of

around 102.8 mg/ml formulated in a pH 6 glycine-histidine buffer (see Materials) were added and diluted with demineralised water (with a pH of around 7.5) to a volume of 150 ml. The solution thus obtained contained around 3.00% (w/v) adjuvant or matrix and 0.33% (w/v) protein and was spray-dried as described above using cyclone I at an atomising air flow of around 0.67 m^3/h. The aggregate content was investigated as described above.

The following aggregate contents were obtained for its storage stability:

- After one week's open storage at 75% relative air humidity and 40°C (forced storage stability), the solution prepared from the reconstituted powder had around 1.0% aggregates.
- After 1 and 3 months' storage at 2-8°C (3 months' stability), the solution prepared from the reconstituted powder had around 0.6% and 0.9% aggregates respectively.
- After 1 and 3 months' storage at 25°C (3 months' stability), the solution prepared from the reconstituted powder had around 0.8% and 1.3% aggregates respectively.
- After 1 and 3 months' storage at 40°C (3 months' stability), the solution prepared from the reconstituted powder had around 1.1% and 2.2% aggregates respectively.

The MMD of the powder was determined as described above.

- The MMD of the powder after spray drying was 2.8 µm.

The MMAD and FPF of the powder were determined as described above.

- The MMAD of the powder after spray drying was 3.8 µm, and the FPF was 23.6% in relation to the powder capsule weight.

Spray drying of a 9.9% (w/v) LS55P
0.1% (w/v) IgG1 formulation

4.950 g LS55P were dissolved in around 40 ml demineralised water (with a pH of around 7.5). As the next step, around 0.518 ml pure IgG1 with a concentration of around 96.55 mg/ml formulated in a pH 6 glycine-histidine buffer (see Materials) were added and diluted with demineralised water (with a pH of around 7.5) to a volume of 50 ml. The solution thus obtained contained around 9.9% (w/v) adjuvant or matrix and 0.1% (w/v) protein and was spray-dried as described above using cyclone I at an atomising air flow of around 0.67 m^3/h. The aggregate content was investigated as described above.

The following aggregate contents were obtained for its storage stability:

- After one week's open storage at 75% relative air humidity and 40°C (forced storage stability), the solution prepared from the reconstituted powder had around 5.7% aggregates.
- After one day's vacuum drying and four weeks' dry storage at 40°C, the solution prepared from the reconstituted powder had around 4.7% aggregates.

Spray drying of a 9% (w/v) LS55P
1 % (w/v) IgG1 formulation

4.5 g LS55P were dissolved in around 40 ml demineralised water (with a pH of around 7.5). As the next step, around 4.6 ml pure IgG1 with a concentration of around 109 mg/ml formulated in a pH 6 glycine-histidine buffer (see Materials) were added and diluted with demineralised water (with a pH of around 7.5) to a volume of 50 ml. The solution thus obtained contained around 9% (w/v) adjuvant or matrix and 1% (w/v) protein and was spray-dried as described above using cyclone I at an atomising air flow of around 0.67 m^3/h. The aggregate content was investigated as described above.

The following aggregate contents were obtained for its storage stability:

- After one week's open storage at 75% relative air humidity and 40°C (forced storage stability), the solution prepared from the reconstituted powder had around 2.3% aggregates.
- After one day's equilibration and four weeks' dry storage at 40°C, the solution prepared from the reconstituted powder had around 1.8% aggregates.
- After one day's vacuum drying and four weeks' dry storage at 40°C, the solution prepared from the reconstituted powder had around 1.4% aggregates.

Spray drying of a 6% (w/v) LS55P
4% (w/v) IgG1 formulation

3.0 g LS55P were dissolved in around 15 ml demineralised water (with a pH of around 7.5). As the next step, around 19.45 ml pure IgG1 with a concentration of around 102.8 mg/ml formulated in a pH 6 glycine-histidine buffer (see Materials)

were added and diluted with demineralised water (with a pH of around 7.5) to a volume of 50 ml. The solution thus obtained contained around 6% (w/v) adjuvant or matrix and 4% (w/v) protein and was spray-dried as described above using cyclone I at an atomising air flow of around 0.67 m^3/h. The aggregate content was investigated as described above.

The following aggregate contents were obtained for its storage stability:

- After one week's open storage at 75% relative air humidity and 40°C (forced storage stability), the solution prepared from the reconstituted powder had around 4.0% aggregates.

Spray drying of a 4% (w/v) LS55P
6% (w/v) IgG1 formulation

2.0 g LS55P were dissolved in around 15 ml demineralised water (with a pH of around 7.5). As the next step, around 29.18 ml pure IgG1 with a concentration of around 102.8 mg/ml formulated in a pH 6 glycine-histidine buffer (see Materials) were added and diluted with demineralised water (with a pH of around 7.5) to a volume of 50 ml. The solution thus obtained contained around 4% (w/v) adjuvant or matrix and 6% (w/v) protein and was spray-dried as described above using cyclone I at an atomising air flow of around 0.67 m^3/h. The aggregate content was investigated as described above.

The following aggregate contents were obtained for its storage stability:

- After one week's open storage at 75% relative air humidity and 40°C (forced storage stability), the solution prepared from the reconstituted powder had around 6.9% aggregates.

Spray drying of a 2.5% (w/v) LS55P
7.5% (w/v) IgG1 formulation

1.25 g LS55P were dissolved in around 10 ml demineralised water (with a pH of around 7.5). As the next step, around 38.84 ml pure IgG1 with a concentration of around 96.55 mg/ml formulated in a pH 6 glycine-histidine buffer (see Materials) were added and diluted with demineralised water (with a pH of around 7.5) to a vol-

ume of 50 ml. The solution thus obtained contained around 2.5% (w/v) adjuvant or matrix and 7.5% (w/v) protein and was spray-dried as described above using cyclone I at an atomising air flow of around 0.67 m^3/h. The aggregate content was investigated as described above.

The following aggregate contents were obtained for its storage stability:

- After one week's open storage at 75% relative air humidity and 40°C (forced storage stability), the solution prepared from the reconstituted powder had around 5.9% aggregates.
- After one day's vacuum drying and four weeks' dry storage at 40°C, the solution prepared from the reconstituted powder had around 6.1% aggregates.

Spray drying of a 1.0% (w/v) LS55P
9.0% (w/v) IgG1 formulation

0.50 g LS55P was dissolved in around 5 ml demineralised water (with a pH of around 7.5). As the next step, around 41.43 ml pure IgG1 with a concentration of around 96.55 mg/ml formulated in a pH 6 glycine-histidine buffer (see Materials) were added and diluted with demineralised water (with a pH of around 7.5) to a volume of 50 ml. The solution thus obtained contained around 1.0% (w/v) adjuvant or matrix and 9.0% (w/v) protein and was spray-dried as described above using cyclone I at an atomising air flow of around 0.67 m^3/h. The aggregate content was investigated as described above.

The following aggregate contents were obtained for its storage stability:

- After one week's open storage at 75% relative air humidity and 40°C (forced storage stability), the solution prepared from the reconstituted powder had around 10.8% aggregates.
- After one day's vacuum drying and four weeks' dry storage at 40°C, the solution prepared from the reconstituted powder had around 8.0% aggregates.

Spray drying of a 0.5% (w/v) LS55P
9.5% (w/v) IgG1 formulation

0.25 g LS55P was dissolved in around 2.5 ml demineralised water (with a pH of around 7.5). As the next step, around 46.21 ml pure IgG1 with a concentration of around 102.8 mg/ml formulated in a pH 6 glycine-histidine buffer (see Materials) were added and diluted with demineralised water (with a pH of around 7.5) to a volume of 50 ml. The solution thus obtained contained around 0.5% (w/v) adjuvant or matrix and 9.5% (w/v) protein and was spray-dried as described above using cyclone I at an atomising air flow of around 0.67 m^3/h. The aggregate content was investigated as described above.

The following aggregate contents were obtained for its storage stability:

- After one week's open storage at 75% relative air humidity and 40°C (forced storage stability), the solution prepared from the reconstituted powder had around 13.7% aggregates.

Spray drying of a 3.00% (w/v) LS55P
0.33% (w/v) IgG1 formulation

9.0 g LS55P were dissolved in around 280 ml demineralised water (with a pH of around 7.5). As the next step, around 9.73 ml pure IgG1 with a concentration of around 102.8 mg/ml formulated in a pH 6 glycine-histidine buffer (see Materials) were added and diluted with demineralised water (with a pH of around 7.5) to a volume of 300 ml. The solution thus obtained contained around 3.0% (w/v) adjuvant or matrix and 0.33% (w/v) protein and was spray-dried as described above using cyclone II at an atomising air flow of around 0.67 m^3/h. The aggregate content was investigated as described above.

The following aggregate contents were obtained for its storage stability:

- After one week's open storage at 75% relative air humidity and 40°C (forced storage stability), the solution prepared from the reconstituted powder had around 5.0% aggregates.

The MMD of the powder was determined as described above.

- The MMD of the powder after spray drying was 2.9 µm.

The MMAD and FPF of the powder were determined as described above.

- The MMAD of the powder after spray drying was 4.3 μm, and the FPF was 15.9% in relation to the powder capsule weight.

Spray drying of a 9.9% (w/v) Coupling Sugar
0.1% (w/v) IgG1 formulation

6.290 g Coupling Sugar-containing syrup (equivalent to 4.950 g Coupling Sugar) were dissolved in around 40 ml demineralised water (with a pH of around 7.5). As the next step, around 0.518 ml pure IgG1 with a concentration of around 96.55 mg/ml formulated in a pH 6 glycine-histidine buffer (see Materials) were added and diluted with demineralised water (with a pH of around 7.5) to a volume of 50 ml. The solution thus obtained contained around 9.9% (w/v) adjuvant or matrix and 0.1% (w/v) protein and was spray-dried as described above using cyclone I at an atomising air flow of around 0.67 m^3/h. The aggregate content was investigated as described above.
The following aggregate contents were obtained for its storage stability:

- After one week's open storage at 75% relative air humidity and 40°C (forced storage stability), the solution prepared from the reconstituted powder had around 14.9% aggregates.

Spray drying of a 9% (w/v) Coupling Sugar
1% (w/v) IgG1 formulation

5.71 g Coupling Sugar-containing syrup (equivalent to 4.5 g Coupling Sugar) were dissolved in around 40 ml demineralised water (with a pH of around 7.5). As the next step, around 4.6 ml pure IgG1 with a concentration of around 109 mg/ml formulated in a pH 6 glycine-histidine buffer (see Materials) were added and diluted with demineralised water (with a pH of around 7.5) to a volume of 50 ml. The solution thus obtained contained around 9% (w/v) adjuvant or matrix and 1% (w/v) protein and was spray-dried as described above using cyclone I at an atomising air flow of around 0.67 m^3/h. The aggregate content was investigated as described above.
The following aggregate contents were obtained for its storage stability:

- After one week's open storage at 75% relative air humidity and 40°C (forced storage stability), the solution prepared from the reconstituted powder had around 4.9% aggregates.
- After one day's equilibration and four weeks' dry storage at 40°C, the solution prepared from the reconstituted powder had around 3.2% aggregates.
- After one day's vacuum drying and four weeks' dry storage at 40°C, the solution prepared from the reconstituted powder had around 2.1% aggregates.

Spray drying of a 6% (w/v) Coupling Sugar
4% (w/v) IgG1 formulation

3.81 g Coupling Sugar-containing syrup (equivalent to 3.0 g Coupling Sugar) were dissolved in around 25 ml demineralised water (with a pH of around 7.5). As the next step, around 19.45 ml pure IgG1 with a concentration of around 102.8 mg/ml formulated in a pH 6 glycine-histidine buffer (see Materials) were added and diluted with demineralised water (with a pH of around 7.5) to a volume of 50 ml. The solution thus obtained contained around 6% (w/v) adjuvant or matrix and 4% (w/v) protein and was spray-dried as described above using cyclone I at an atomising air flow of around 0.67 m^3/h. The aggregate content was investigated as described above.

The following aggregate contents were obtained for its storage stability:

- After one week's open storage at 75% relative air humidity and 40°C (forced storage stability), the solution prepared from the reconstituted powder had around 5.0% aggregates.

Spray drying of a 4% (w/v) Coupling Sugar
6% (w/v) IgG1 formulation

2.54 g Coupling Sugar-containing syrup (equivalent to 2.0 g Coupling Sugar) were dissolved in around 15 ml demineralised water (with a pH of around 7.5). As the next step, around 29.18 ml pure IgG1 with a concentration of around x mg/ml formulated in a pH 6 glycine-histidine buffer (see Materials) were added and diluted with demineralised water (with a pH of around 7.5) to a volume of 50 ml. The solution thus obtained contained around 4% (w/v) adjuvant or matrix and 6% (w/v) protein and was

spray-dried as described above using cyclone I at an atomising air flow of around 0.67 m^3/h. The aggregate content was investigated as described above.

The following aggregate contents were obtained for its storage stability:

- After one week's open storage at 75% relative air humidity and 40°C (forced storage stability), the solution prepared from the reconstituted powder had around 9.9% aggregates.

Spray drying of a 2.5% (w/v) Coupling Sugar
7.5% (w/v) IgG1 formulation

1.59 g Coupling Sugar-containing syrup (equivalent to 1.250 g Coupling Sugar) was dissolved in around 8 ml demineralised water (with a pH of around 7.5). As the next step, around 38.84 ml pure IgG1 with a concentration of around 96.56 mg/ml formulated in a pH 6 glycine-histidine buffer (see Materials) were added and diluted with demineralised water (with a pH of around 7.5) to a volume of 50 ml. The solution thus obtained contained around 2.5% (w/v) adjuvant or matrix and 7.5% (w/v) protein and was spray-dried as described above using cyclone I at an atomising air flow of around 0.67 m^3/h. The aggregate content was investigated as described above.

The following aggregate contents were obtained for its storage stability:

- After one week's open storage at 75% relative air humidity and 40°C (forced storage stability), the solution prepared from the reconstituted powder had around 10.8% aggregates.

Spray drying of a 1.0% (w/v) Coupling Sugar
9.0% (w/v) IgG1 formulation

0.653 g Coupling Sugar-containing syrup (equivalent to 0.50 g Coupling Sugar) was dissolved in around 5 ml demineralised water (with a pH of around 7.5). As the next step, around 41.43 ml pure IgG1 with a concentration of around 96.56 mg/ml formulated in a pH 6 glycine-histidine buffer (see Materials) were added and diluted with demineralised water (with a pH of around 7.5) to a volume of 50 ml. The solution thus obtained contained around 1.0% (w/v) adjuvant or matrix and 9.0% (w/v) protein and

was spray-dried as described above using cyclone I at an atomising air flow of around 0.67 m^3/h. The aggregate content was investigated as described above.

The following aggregate contents were obtained for its storage stability:

- After one week's open storage at 75% relative air humidity and 40°C (forced storage stability), the solution prepared from the reconstituted powder had around 13.1% aggregates.

Spray drying of a 9% (w/v) Coupling Sugar S
1% (w/v) IgG1 formulation

5.86 g Coupling Sugar S-containing syrup (equivalent to 4.5 g Coupling Sugar S) were dissolved in around 40 ml demineralised water (with a pH of around 7.5). As the next step, around 4.6 ml pure IgG1 with a concentration of around 109 mg/ml formulated in a pH 6 glycine-histidine buffer (see Materials) were added and diluted with demineralised water (with a pH of around 7.5) to a volume of 50 ml. The solution thus obtained contained around 9% (w/v) adjuvant or matrix and 1% (w/v) protein and was spray-dried as described above using cyclone I at an atomising air flow of around 0.67 m^3/h. The aggregate content was investigated as described above.

The following aggregate contents were obtained for its storage stability:

- After one week's open storage at 75% relative air humidity and 40°C (forced storage stability), the solution prepared from the reconstituted powder had around 5.4% aggregates.

Example 2

Spray drying of an 8% (w/v) trehalose 1% (w/v) L-isoleucine
1% (w/v) IgG1 formulation

4.0 g trehalose and 0.5 g L-isoleucine were dissolved in around 40 ml demineralised water (with a pH of around 7.5) in an ultrasonic bath. As the next step, around 4.6 ml pure IgG1 with a concentration of around 109 mg/ml formulated in a pH 6 glycine-histidine buffer (see Materials) were added and diluted with demineralised water (with a pH of around 7.5) to a volume of 50 ml. The solution thus obtained contained around 9% (w/v) adjuvant or matrix and 1% (w/v) protein and was spray-dried as de-

scribed above using cyclone I at an atomising air flow of around 0.67 m^3/h. The aggregate content was investigated as described above.

- After one week's open storage at 75% relative air humidity and 40°C (forced storage stability), the solution prepared from the reconstituted powder had around 22.2% aggregates.

Spray drying of a 2.66% (w/v) LS90P 0.33% (w/v) L-isoleucine
0.33% (w/v) IgG1 formulation

4.0 g LS90P and 0.50 g L-isoleucine were dissolved in around 140 ml demineralised water (with a pH of around 7.5) in an ultrasonic bath. As the next step, around 4.864 ml pure IgG1 with a concentration of around 102.8 mg/ml formulated in a pH 6 glycine-histidine buffer (see Materials) were added and diluted with demineralised water (with a pH of around 7.5) to a volume of 150 ml. The solution thus obtained contained around 3.00% (w/v) adjuvant or matrix and 0.33% (w/v) protein and was spray-dried as described above using cyclone II at an atomising air flow of around 0.67 m^3/h. The aggregate content was investigated as described above.

The following aggregate contents were obtained for its storage stability:

- After one week's open storage at 75% relative air humidity and 40°C (forced storage stability), the solution prepared from the reconstituted powder had around 0.7% aggregates.
- After 1 and 3 months' storage at 2-8°C (3 months' stability), the solution prepared from the reconstituted powder had around 0.7% and 1.0% aggregates respectively.
- After 1 and 3 months' storage at 25°C (3 months' stability), the solution prepared from the reconstituted powder had around 0.8% and 1.1% aggregates respectively.
- After 1 and 3 months' storage at 40°C (3 months' stability), the solution prepared from the reconstituted powder had around 0.6% and 1.1% aggregates respectively.

The MMAD and FPF of the powder were determined as described above.

- The MMAD of the powder after spray drying was 7.3 µm, and the FPF was 28.1% in relation to the powder capsule weight.

Spray drying of an 8% (w/v) LS55P 1% (w/v) L-isoleucine
1% (w/v) IgG1 formulation

4.00 g LS90P and 0.50 g L-isoleucine were dissolved in around 40 ml demineralised water (with a pH of around 7.5) in an ultrasonic bath. As the next step, around 4.60 ml pure IgG1 with a concentration of around 109 mg/ml formulated in a pH 6 glycine-histidine buffer (see Materials) were added and diluted with demineralised water (with a pH of around 7.5) to a volume of 50 ml. The solution thus obtained contained around 9% (w/v) adjuvant or matrix and 1% (w/v) protein and was spray-dried as described above using cyclone I at an atomising air flow of around 0.67 m^3/h. The aggregate content was investigated as described above.

- After one week's open storage at 75% relative air humidity and 40°C (forced storage stability), the solution prepared from the reconstituted powder had around 5.5% aggregates.
- After one day's equilibration and four weeks' dry storage at 40°C, the solution prepared from the reconstituted powder had around 1.8% aggregates.
- After one day's vacuum drying and four weeks' dry storage at 40°C, the solution prepared from the reconstituted powder had around 1.8% aggregates.

Spray drying of a 2.66% (w/v) LS55P 0.33% (w/v) L-isoleucine
0.33% (w/v) IgG1 formulation

8.0 g LS55P and 1 g L-isoleucine were dissolved in around 280 ml demineralised water (with a pH of around 7.5) in an ultrasonic bath. As the next step, around 9.7 ml pure IgG1 with a concentration of around 102.8 mg/ml formulated in a pH 6 glycine-histidine buffer (see Materials) were added and diluted with demineralised water (with a pH of around 7.5) to a volume of 300 ml. The solution thus obtained contained around 3% (w/v) adjuvant or matrix and 0.33% (w/v) protein and was spray-dried as described above using cyclone II at an atomising air flow of around 0.67 m^3/h. The aggregate content was investigated as described above.

- After one week's open storage at 75% relative air humidity and 40°C (forced storage stability), the solution prepared from the reconstituted powder had around 5.9% aggregates.

- After 1 and 3 months' storage at 2-8°C (3 months' stability), the solution prepared from the reconstituted powder had around 1.6% aggregates respectively.
- After 1 and 3 months' storage at 25°C (3 months' stability), the solution prepared from the reconstituted powder had around 1.6% and 1.8% aggregates respectively.
- After 1 and 3 months' storage at 40°C (3 months' stability), the solution prepared from the reconstituted powder had around 1.6% and 1.8% aggregates respectively.

The MMAD and FPF of the powder were determined as described above.

- The MMAD of the powder after spray drying was 4.9 μm, and the FPF was 34.7% in relation to the powder capsule weight.

Spray drying of an 8% (w/v) Coupling Sugar 1% (w/v) L-isoleucine 1% (w/v) IgG1 formulation

5.08 g Coupling Sugar-containing syrup (equivalent to 4.0 g Coupling Sugar) and 0.50 g L-isoleucine were dissolved in around 40 ml demineralised water (with a pH of around 7.5) in an ultrasonic bath. As the next step, around 4.60 ml pure IgG1 with a concentration of around 109 mg/ml formulated in a pH 6 glycine-histidine buffer (see Materials) were added and diluted with demineralised water (with a pH of around 7.5) to a volume of 50 ml. The solution thus obtained contained around 9% (w/v) adjuvant or matrix and 1% (w/v) protein and was spray-dried as described above using cyclone I at an atomising air flow of around 0.67 m^3/h. The aggregate content was investigated as described above.

- After one week's open storage at 75% relative air humidity and 40°C (forced storage stability), the solution prepared from the reconstituted powder had around 7.1% aggregates.
- After one day's equilibration and four weeks' dry storage at 40°C, the solution prepared from the reconstituted powder had around 2.5% aggregates.
- After one day's vacuum drying and four weeks' dry storage at 40°C, the solution prepared from the reconstituted powder had around 1.1% aggregates.

Spray drying of an 8% (w/v) Coupling Sugar S 1% (w/v) L-isoleucine 1% (w/v) IgG1 formulation

5.21 g Coupling Sugar S-containing syrup (equivalent to 4.0 g Coupling Sugar S) and 0.50 g L-isoleucine were dissolved in around 40 ml demineralised water (with a pH of around 7.5) in an ultrasonic bath. As the next step, around 4.60 ml pure IgG1 with a concentration of around 109 mg/ml formulated in a pH 6 glycine-histidine buffer (see Materials) were added and diluted with demineralised water (with a pH of around 7.5) to a volume of 50 ml. The solution thus obtained contained around 9% (w/v) adjuvant or matrix and 1% (w/v) protein and was spray-dried as described above using cyclone I at an atomising air flow of around 0.67 m^3/h. The aggregate content was investigated as described above.

- After one week's open storage at 75% relative air humidity and 40°C (forced storage stability), the solution prepared from the reconstituted powder had around 6.8% aggregates.

Example 3

Spray drying of a 3% (w/v) trehalose 6% (w/v) L-citrulline 1% (w/v) IgG1 formulation

1.50 g trehalose and 3.00 g L-citrulline were dissolved in around 40 ml demineralised water (with a pH of around 7.5) in an ultrasonic bath. As the next step, around 4.6 ml pure IgG1 with a concentration of around 109 mg/ml formulated in a pH 6 glycine-histidine buffer (see Materials) were added and diluted with demineralised water (with a pH of around 7.5) to a volume of 50 ml. The solution thus obtained contained around 9% (w/v) adjuvant or matrix and 1% (w/v) protein and was spray-dried as described above using cyclone I at an atomising air flow of around 0.67 m^3/h. The aggregate content was investigated as described above.

- After one week's open storage at 75% relative air humidity and 40°C (forced storage stability), the solution prepared from the reconstituted powder had around 5.9% aggregates.

Spray drying of a 3% (w/v) LS55P 6% (w/v) L-citrulline 1% (w/v) IgG1 formulation

1.50 g LS55P and 3.00 g L-citrulline were dissolved in around 40 ml demineralised water (with a pH of around 7.5) in an ultrasonic bath. As the next step, around 4.60 ml pure IgG1 with a concentration of around 109 mg/ml formulated in a pH 6 glycine-histidine buffer (see Materials) were added and diluted with demineralised water (with a pH of around 7.5) to a volume of 50 ml. The solution thus obtained contained around 9% (w/v) adjuvant or matrix and 1% (w/v) protein and was spray-dried as described above using cyclone I at an atomising air flow of around 0.67 m^3/h. The aggregate content was investigated as described above.

- After one week's open storage at 75% relative air humidity and 40°C (forced storage stability), the solution prepared from the reconstituted powder had around 2.9% aggregates.
- After one day's equilibration and four weeks' dry storage at 40°C, the solution prepared from the reconstituted powder had around 1.8% aggregates.
- After one day's vacuum drying and four weeks' dry storage at 40°C, the solution prepared from the reconstituted powder had around 1.3% aggregates.

Spray drying of a 3% (w/v) Coupling Sugar 6% L-citrulline 1% (w/v) IgG1 formulation

1.91 g Coupling Sugar-containing syrup (equivalent to 1.5 g Coupling Sugar) and 3.00 g L-citrulline were dissolved in around 40 ml demineralised water (with a pH of around 7.5) in an ultrasonic bath. As the next step, around 4.60 ml pure IgG1 with a concentration of around 109 mg/ml formulated in a pH 6 glycine-histidine buffer (see Materials) were added and diluted with demineralised water (with a pH of around 7.5) to a volume of 50 ml. The solution thus obtained contained around 9% (w/v) adjuvant or matrix and 1% (w/v) protein and was spray-dried as described above using cyclone I at an atomising air flow of around 0.67 m^3/h. The aggregate content was investigated as described above.

- After one week's open storage at 75% relative air humidity and 40°C (forced storage stability), the solution prepared from the reconstituted powder had around 3.9% aggregates.
- After one day's equilibration and four weeks' dry storage at 40°C, the solution prepared from the reconstituted powder had around 1.4% aggregates.
- After one day's vacuum drying and four weeks' dry storage at 40°C, the solution prepared from the reconstituted powder had around 1.3% aggregates.

Spray drying of a 3% (w/v) Coupling Sugar S 6% L-citrulline
1% (w/v) IgG1 formulation

1.95 g Coupling Sugar S-containing syrup (equivalent to 1.5 g Coupling Sugar S) and 3.00 g L-citrulline were dissolved in around 40 ml demineralised water (with a pH of around 7.5) in an ultrasonic bath. As the next step, around 4.60 ml pure IgG1 with a concentration of around 109 mg/ml formulated in a pH 6 glycine-histidine buffer (see Materials) were added and diluted with demineralised water (with a pH of around 7.5) to a volume of 50 ml. The solution thus obtained contained around 9% (w/v) adjuvant or matrix and 1% (w/v) protein and was spray-dried as described above using cyclone I at an atomising air flow of around 0.67 m^3/h. The aggregate content was investigated as described above.

- After one week's open storage at 75% relative air humidity and 40°C (forced storage stability), the solution prepared from the reconstituted powder had around 3.1% aggregates.

Example 4

Spray drying of a 2.66% (w/v) trehalose 0.33% (w/v) tri-isoleucine
0.33% (w/v) IgG1 formulation

8.0 g trehalose and 1 g tri-isoleucine were dissolved in around 280 ml demineralised water (with a pH of around 7.5) in an ultrasonic bath. As the next step, around 12.30 ml pure IgG1 with a concentration of around 96.55 mg/ml formulated in a pH 6 glycine-histidine buffer (see Materials) were added and diluted with demineralised water (with a pH of around 7.5) to a volume of 300 ml. The solution thus obtained contained

around 3% (w/v) adjuvant or matrix and 0.33% (w/v) protein and was spray-dried as described above using cyclone II at an atomising air flow of around 0.67 m^3/h. The aggregate content was investigated as described above.

- After one week's open storage at 75% relative air humidity and 40°C (forced storage stability), the solution prepared from the reconstituted powder had around 26.7% aggregates.

Spray drying of a 2.66% (w/v) raffinose 0.33% (w/v) tri-isoleucine 0.33% (w/v) IgG1 formulation

8.0 g raffinose and 1 g tri-isoleucine were dissolved in around 140 ml demineralised water (with a pH of around 7.5) in an ultrasonic bath. As the next step, around 4.87 ml pure IgG1 with a concentration of around 102.8 mg/ml formulated in a pH 6 glycine-histidine buffer (see Materials) were added and diluted with demineralised water (with a pH of around 7.5) to a volume of 300 ml. The solution thus obtained contained around 3% (w/v) adjuvant or matrix and 0.33% (w/v) protein and was spray-dried as described above using cyclone II at an atomising air flow of around 0.67 m^3/h. The aggregate content was investigated as described above.

- After one week's open storage at 75% relative air humidity and 40°C (forced storage stability), the solution prepared from the reconstituted powder had around 12.6% aggregates.

Spray drying of a 2.66% (w/v) hydroxyethyl starch (HES) 0.33% (w/v) tri-isoleucine 0.33% (w/v) IgG1 formulation

8.0 g HES and 1 g tri-isoleucine were dissolved in around 140 ml demineralised water (with a pH of around 7.5) in an ultrasonic bath at around 80°C with stirring. As the next step, around 4.87 ml pure IgG1 with a concentration of around 102.8 mg/ml formulated in a pH 6 glycine-histidine buffer (see Materials) were added to the previously refrigerated turbid solution and diluted with demineralised water (with a pH of around 7.5) to a volume of 150 ml. The solution thus obtained contained around 3% (w/v) adjuvant or matrix and 0.33% (w/v) protein and was spray-dried as described

above using cyclone II at an atomising air flow of around 0.67 m^3/h. The aggregate content was investigated as described above.

- After one week's open storage at 75% relative air humidity and 40°C (forced storage stability), the solution prepared from the reconstituted powder had around 18.6% aggregates.
- After 1 and 3 months' open storage at around 43% relative air humidity and 25°C (open 3 months' stability), the solution prepared from the reconstituted powder had around 11.9% and 15.4% aggregates respectively.

Spray drying of a 2.00% (w/v) saccharose 0.66% (w/v) lactose 0.33% (w/v) tri-isoleucine 0.33% (w/v) IgG1 formulation

6.0 g saccharose, 2.0 g lactose, and 1 g tri-isoleucine were dissolved in around 280 ml demineralised water (with a pH of around 7.5) in an ultrasonic bath. As the next step, around 9.73 ml pure IgG1 with a concentration of around 102.8 mg/ml formulated in a pH 6 glycine-histidine buffer (see Materials) were added and diluted with demineralised water (with a pH of around 7.5) to a volume of 300 ml. The solution thus obtained contained around 3% (w/v) adjuvant or matrix and 0.33% (w/v) protein and was spray-dried as described above using cyclone II at an atomising air flow of around 0.67 m^3/h. The aggregate content was investigated as described above.

- After one week's open storage at 75% relative air humidity and 40°C (forced storage stability), the solution prepared from the reconstituted powder had around 8.8% aggregates.

Spray drying of a 2.66% (w/v) saccharose 0.33% (w/v) tri-isoleucine 0.33% (w/v) IgG1 formulation

8.0 g saccharose and 1 g tri-isoleucine were dissolved in around 280 ml demineralised water (with a pH of around 7.5) in an ultrasonic bath. As the next step, around 9.73 ml pure IgG1 with a concentration of around 102.8 mg/ml formulated in a pH 6 glycine-histidine buffer (see Materials) were added and diluted with demineralised water (with a pH of around 7.5) to a volume of 300 ml. The solution thus obtained contained around 3% (w/v) adjuvant or matrix and 0.33% (w/v) protein and was spray-dried as

described above using cyclone II at an atomising air flow of around 0.67 m^3/h. The aggregate content was investigated as described above.

- After one week's open storage at 75% relative air humidity and 40°C (forced storage stability), the solution prepared from the reconstituted powder had around 5.6% aggregates.

Spray drying of a 2.66% (w/v) LS90P 0.33% (w/v) tri-isoleucine 0.33% (w/v) IgG1 formulation

4.0 g LS90P and 0.50 g tri-isoleucine were dissolved in around 140 ml demineralised water (with a pH of around 7.5). As the next step, around 4.864 ml pure IgG1 with a concentration of around 102.8 mg/ml formulated in a pH 6 glycine-histidine buffer (see Materials) were added and diluted with demineralised water (with a pH of around 7.5) to a volume of 150 ml. The solution thus obtained contained around 3.00% (w/v) adjuvant or matrix and 0.33% (w/v) protein and was spray-dried as described above using cyclone II at an atomising air flow of around 0.67 m^3/h. The aggregate content was investigated as described above.

The following aggregate contents were obtained for its storage stability:

- After one week's open storage at 75% relative air humidity and 40°C (forced storage stability), the solution prepared from the reconstituted powder had around 2.3% aggregates.
- After 1 and 3 months' storage at 2-8°C (3 months' stability), the solution prepared from the reconstituted powder had around 0.7% and 1.0% aggregates respectively.
- After 1 and 3 months' storage at 25°C (3 months' stability), the solution prepared from the reconstituted powder had around 0.8% and 1.4% aggregates respectively.
- After 1 and 3 months' storage at 40°C (3 months' stability), the solution prepared from the reconstituted powder had around 0.9% and 2.2% aggregates respectively.
- After 1 and 3 months' open storage at around 29% relative air humidity and 25°C, the solution prepared from the reconstituted powder had around 0.4% and 0.7% aggregates respectively.
- After 1 and 3 months' open storage at around 43% relative air humidity and 25°C, the solution prepared from the reconstituted powder had around 0.5% and 0.6% aggregates respectively.

The MMD of the powder was determined as described above.

- The MMD of the powder after spray drying was 4.7 μm.

The MMAD and FPF of the powder were determined as described above.

- The MMAD of the powder after spray drying was 4.8 μm, and the FPF was 53.2% in relation to the powder capsule weight.

Spray drying of a 2.66% (w/v) LS90P 0.33% (w/v) tri-isoleucine 0.33% (w/v) IgG1 formulation

4.0 g LS90P and 0.50 g tri-isoleucine were dissolved in around 140 ml demineralised water (with a pH of around 7.5). As the next step, around 4.864 ml pure IgG1 with a concentration of around 102.8 mg/ml formulated in a pH 6 glycine-histidine buffer (see Materials) were added and diluted with demineralised water (with a pH of around 7.5) to a volume of 150 ml. The solution thus obtained contained around 3.00% (w/v) adjuvant or matrix and 0.33% (w/v) protein and was spray-dried as described above using cyclone II at an atomising air flow of around 1.05 m^3/h. The aggregate content was investigated as described above.

The following aggregate contents were obtained for its storage stability:

- After one week's open storage at 75% relative air humidity and 40°C (forced storage stability), the solution prepared from the reconstituted powder had around 2.2% aggregates.
- After 1 and 3 months' storage at around 29% relative air humidity and 25°C (open 3 months' stability), the solution prepared from the reconstituted powder had around 0.5% and 0.6% aggregates respectively.
- After 1 and 3 months' storage at around 43% relative air humidity and 25°C (open 3 months' stability), the solution prepared from the reconstituted powder had around 0.5% and 0.7% aggregates respectively.

The MMD of the powder was determined as described above.

- The MMD of the powder after spray drying was 2.7 μm.

The MMAD and FPF of the powder were determined as described above.

- The MMAD of the powder after spray drying was 3.6 μm, and the FPF was 58.0% in relation to the powder capsule weight.

Spray drying of a 2.66% (w/v) LS90P 0.33% (w/v) tri-isoleucine
0.33% (w/v) IgG1 formulation

4.0 g LS90P and 0.50 g tri-isoleucine were dissolved in around 140 ml demineralised water (with a pH of around 7.5). As the next step, around 4.864 ml pure IgG1 with a concentration of around 102.8 mg/ml formulated in a pH 6 glycine-histidine buffer (see Materials) were added and diluted with demineralised water (with a pH of around 7.5) to a volume of 150 ml. The solution thus obtained contained around 3.00% (w/v) adjuvant or matrix and 0.33% (w/v) protein and was spray-dried as described above using cyclone II at an atomising air flow of around 1.74 m^3/h. The aggregate content was investigated as described above.

The following aggregate contents were obtained for its storage stability:

- After one week's open storage at 75% relative air humidity and 40°C (forced storage stability), the solution prepared from the reconstituted powder had around % aggregates.
- After 1 and 3 months' storage at around 29% relative air humidity and 25°C (open 3 months' stability), the solution prepared from the reconstituted powder had around 0.5% and 0.6% aggregates respectively.
- After 1 and 3 months' storage at around 43% relative air humidity and 25°C (open 3 months' stability), the solution prepared from the reconstituted powder had around 0.5% and 0.8% aggregates respectively.

The MMD of the powder was determined as described above.

- The MMD of the powder after spray drying was 2.6 µm.

The MMAD and FPF of the powder were determined as described above.

- The MMAD of the powder after spray drying was 3.3 µm, and the FPF was 58.9% in relation to the powder capsule weight.

Spray drying of a 1.60% (w/v) LS90P 0.20% (w/v) tri-isoleucine
0.20% (w/v) IgG1 formulation

4.0 g LS90P and 0.50 g tri-isoleucine were dissolved in around 220 ml demineralised water (with a pH of around 7.5). As the next step, around 4.864 ml pure IgG1 with a concentration of around 102.8 mg/ml formulated in a pH 6 glycine-histidine buffer

(see Materials) were added and diluted with demineralised water (with a pH of around 7.5) to a volume of 250 ml. The solution thus obtained contained around 1.80% (w/v) adjuvant or matrix and 0.20% (w/v) protein and was spray-dried as described above using cyclone II at an atomising air flow of around 0.67 m^3/h. The aggregate content was investigated as described above.

The following aggregate contents were obtained for its storage stability:

- After one week's open storage at 75% relative air humidity and 40°C (forced storage stability), the solution prepared from the reconstituted powder had around 2.2% aggregates.
- After 1 and 3 months' storage at around 29% relative air humidity and 25°C (open 3 months' stability), the solution prepared from the reconstituted powder had around 0.5% and 0.5% aggregates respectively.
- After 1 and 3 months' storage at around 43% relative air humidity and 25°C (open 3 months' stability), the solution prepared from the reconstituted powder had around 0.7% and 0.7% aggregates respectively.

The MMD of the powder was determined as described above.

- The MMD of the powder after spray drying was 3.2 µm.

The MMAD and FPF of the powder were determined as described above.

- The MMAD of the powder after spray drying was 3.9 µm, and the FPF was 55.6% in relation to the powder capsule weight.

Spray drying of a 2.833% (w/v) LS90P 0.166% (w/v) tri-isoleucine 0.33% (w/v) IgG1 formulation

4.25 g LS90P and 0.25 g tri-isoleucine were dissolved in around 140 ml demineralised water (with a pH of around 7.5). As the next step, around 4.864 ml pure IgG1 with a concentration of around 102.8 mg/ml formulated in a pH 6 glycine-histidine buffer (see Materials) were added and diluted with demineralised water (with a pH of around 7.5) to a volume of 150 ml. The solution thus obtained contained around 3.00% (w/v) adjuvant or matrix and 0.33% (w/v) protein and was spray-dried as described above using cyclone II at an atomising air flow of around 0.67 m^3/h. The aggregate content was investigated as described above.

The following aggregate contents were obtained for its storage stability:

- After one week's open storage at 75% relative air humidity and 40°C (forced storage stability), the solution prepared from the reconstituted powder had around 1.5% aggregates.
- After 1 and 3 months' storage at around 29% relative air humidity and 25°C (open 3 months' stability), the solution prepared from the reconstituted powder had around 0.5% and 0.5% aggregates respectively.
- After 1 and 3 months' storage at around 43% relative air humidity and 25°C (open 3 months' stability), the solution prepared from the reconstituted powder had around 0.5% and 0.6% aggregates respectively.

The MMD of the powder was determined as described above.

- The MMD of the powder after spray drying was 4.8 µm.

The MMAD and FPF of the powder were determined as described above.

- The MMAD of the powder after spray drying was 5.2 µm, and the FPF was 45.7% in relation to the powder capsule weight.

Spray drying of a 2.9166% (w/v) LS90P 0.0833% (w/v) tri-isoleucine 0.33% (w/v) IgG1 formulation

4.375 g LS90P and 0.125 g tri-isoleucine were dissolved in around 140 ml demineralised water (with a pH of around 7.5). As the next step, around 4.864 ml pure IgG1 with a concentration of around 102.8 mg/ml formulated in a pH 6 glycine-histidine buffer (see Materials) were added and diluted with demineralised water (with a pH of around 7.5) to a volume of 150 ml. The solution thus obtained contained around 3.00% (w/v) adjuvant or matrix and 0.33% (w/v) protein and was spray-dried as described above using cyclone II at an atomising air flow of around 0.67 m^3/h. The aggregate content was investigated as described above.

The following aggregate contents were obtained for its storage stability:

- After one week's open storage at 75% relative air humidity and 40°C (forced storage stability), the solution prepared from the reconstituted powder had around 1.2% aggregates.
- After 1 and 3 months' storage at around 29% relative air humidity and 25°C (open 3 months' stability), the solution prepared from the reconstituted powder had around 0.4% and 0.5% aggregates respectively.

- After 1 and 3 months' storage at around 43% relative air humidity and 25°C (open 3 months' stability), the solution prepared from the reconstituted powder had around 0.5% and 0.6% aggregates respectively.

The MMD of the powder was determined as described above.

- The MMD of the powder after spray drying was 4.2 μm.

The MMAD and FPF of the powder were determined as described above.

- The MMAD of the powder after spray drying was 6.1 μm, and the FPF was 39.6% in relation to the powder capsule weight.

Spray drying of a 2.66% (w/v) LS55P 0.33% (w/v) tri-isoleucine 0.33% (w/v) IgG1 formulation

8.0 g LS55P and 1 g tri-isoleucine were dissolved in around 280 ml demineralised water (with a pH of around 7.5) in an ultrasonic bath. As the next step, around 9.73 ml pure IgG1 with a concentration of around 102.8 mg/ml formulated in a pH 6 glycine-histidine buffer (see Materials) were added and diluted with demineralised water (with a pH of around 7.5) to a volume of 300 ml. The solution thus obtained contained around 3% (w/v) adjuvant or matrix and 0.33% (w/v) protein and was spray-dried as described above using cyclone II at an atomising air flow of around 0.67 m^3/h. The aggregate content was investigated as described above.

- After one week's open storage at 75% relative air humidity and 40°C (forced storage stability), the solution prepared from the reconstituted powder had around 2.1% aggregates.
- After 1 and 3 months' storage at 2-8°C (3 months' stability), the solution prepared from the reconstituted powder had around 0.8% and 1.5% aggregates respectively.
- After 1 and 3 months' storage at 25°C (3 months' stability), the solution prepared from the reconstituted powder had around 0.9% and 1.5% aggregates respectively.
- After 1 and 3 months' storage at 40°C (3 months' stability), the solution prepared from the reconstituted powder had around 1.3% and 2.6% aggregates respectively.
- After 1 and 3 months' storage at around 43% relative air humidity and 25°C (open 3 months' stability), the solution prepared from the reconstituted powder had around 1.0% and 1.0% aggregates respectively.

The MMD of the powder was determined as described above.

- The MMD of the powder after spray drying was 3.4 μm.

The MMAD and FPF of the powder were determined as described above.

- The MMAD of the powder after spray drying was 3.9 μm, and the FPF was 58.3% in relation to the powder capsule weight.
- After one month's storage at around 43% relative air humidity and 25°C (open 3 months' stability), the MMAD was 3.8 μm, and the FPF was 59.6% in relation to the powder capsule weight.

Spray drying of a 2.833% (w/v) LS55P 0.166% (w/v) tri-isoleucine 0.33% (w/v) IgG1 formulation

8.5 g LS90P and 0.5 g tri-isoleucine were dissolved in around 280 ml demineralised water (with a pH of around 7.5) in an ultrasonic bath. As the next step, around 9.73 ml pure IgG1 with a concentration of around 102.8 mg/ml formulated in a pH 6 glycine-histidine buffer (see Materials) were added and diluted with demineralised water (with a pH of around 7.5) to a volume of 300 ml. The solution thus obtained contained around 3% (w/v) adjuvant or matrix and 0.33% (w/v) protein and was spray-dried as described above using cyclone II at an atomising air flow of around 0.67 m^3/h. The aggregate content was investigated as described above.

- After one week's open storage at 75% relative air humidity and 40°C (forced storage stability), the solution prepared from the reconstituted powder had around 3.4% aggregates.
- After 1 and 3 months' storage at around 43% relative air humidity and 25°C (open 3 months' stability), the solution prepared from the reconstituted powder had around 1.3% and 1.5% aggregates respectively.

The MMD of the powder was determined as described above.

- The MMD of the powder after spray drying was 2.9 μm.

The MMAD and FPF of the powder were determined as described above.

- The MMAD of the powder after spray drying was 4.4 μm, and the FPF was 58.6% in relation to the powder capsule weight.

Spray drying of a 2.9166% (w/v) LS55P 0.0833% (w/v) tri-isoleucine 0.33% (w/v) IgG1 formulation

8.75 g LS90P and 0.25 g tri-isoleucine were dissolved in around 280 ml demineralised water (with a pH of around 7.5). As the next step, around 9.73 ml pure IgG1 with a concentration of around 102.8 mg/ml formulated in a pH 6 glycine-histidine buffer (see Materials) were added and diluted with demineralised water (with a pH of around 7.5) to a volume of 300 ml. The solution thus obtained contained around 3% (w/v) adjuvant or matrix and 0.33% (w/v) protein and was spray-dried as described above using cyclone II at an atomising air flow of around 0.67 m^3/h. The aggregate content was investigated as described above.

- After one week's open storage at 75% relative air humidity and 40°C (forced storage stability), the solution prepared from the reconstituted powder had around 4.4% aggregates.
- After 1 and 3 months' storage at around 43% relative air humidity and 25°C (open 3 months' stability), the solution prepared from the reconstituted powder had around 0.7% and 0.8% aggregates respectively.

The MMD of the powder was determined as described above.

- The MMD of the powder after spray drying was 2.9 µm.

The MMAD and FPF of the powder were determined as described above.

- The MMAD of the powder after spray drying was 4.4 µm, and the FPF was 58.6% in relation to the powder capsule weight.

Example 5

Production of further powders according to the invention

Spray drying of a 3.33% (w/v) lysozyme formulation

5 g lysozyme were dissolved in around 140 ml demineralised water (with a pH of around 7.5) and diluted with demineralised water (with a pH of around 7.5) to a volume of 150 ml. The solution thus obtained was spray-dried as described above using cyclone II.

The residual monomer content was determined as described above. After forced storage, the solution prepared from the reconstituted powder had a residual monomer con-

tent of 35.3%. The MMD of the powder was determined as described above. The MMD of the powder was 3.2 μm. The MMAD and FPF of the powder were determined as described above. The MMAD was 4.0 μm, and the FPF was 70.4% in relation to the powder capsule weight.

Spray drying of a 3.00% (w/v) LS90P
0.33% (w/v) lysozyme formulation

9.0 g LS90P were dissolved in around 280 ml demineralised water (with a pH of around 7.5) in an ultrasonic bath. As the next step, 1 g lysozyme was added and diluted with demineralised water (with a pH of around 7.5) to a volume of 300 ml. The solution thus obtained was spray-dried as described above using cyclone II.
The residual monomer content was determined as described above. After forced storage, the solution prepared from the reconstituted powder had a residual monomer content of 62.1%. The MMD of the powder was determined as described above. The MMD of the powder was 4.0 μm. The MMAD and FPF of the powder were determined as described above. The MMAD was 3.7 μm, and the FPF was 24.7% in relation to the powder capsule weight.

Spray drying of a 2.66% (w/v) LS90P 0.33% (w/v) isoleucine
0.33% (w/v) lysozyme formulation

8.0 g LS90P and 1 g isoleucine were dissolved in around 280 ml demineralised water (with a pH of around 7.5) in an ultrasonic bath. As the next step, 1 g lysozyme was added and diluted with demineralised water (with a pH of around 7.5) to a volume of 300 ml. The solution thus obtained was spray-dried as described above using cyclone II.
The residual monomer content was determined as described above. After forced storage, the solution prepared from the reconstituted powder had a residual monomer content of 47.9%. The MMD of the powder was determined as described above. The MMD of the powder was 3.9 μm. The MMAD and FPF of the powder were determined as described above. The MMAD was 4.1 μm, and the FPF was 29.0% in relation to the powder capsule weight.

Spray drying of a 2.66% (w/v) LS90P 0.33% (w/v) tri-isoleucine 0.33% (w/v) lysozyme formulation

8.0 g LS90P and 1 g tri-isoleucine were dissolved in around 280 ml demineralised water (with a pH of around 7.5) in an ultrasonic bath. As the next step, 1 g lysozyme was added and diluted with demineralised water (with a pH of around 7.5) to a volume of 300 ml. The solution thus obtained was spray-dried as described above using cyclone II.

The residual monomer content was determined as described above. After forced storage, the solution prepared from the reconstituted powder had a residual monomer content of 47.9%. The MMD of the powder was determined as described above. The MMD of the powder was 2.7 μm. The MMAD and FPF of the powder were determined as described above. The MMAD was 3.6 μm, and the FPF was 58.6% in relation to the powder capsule weight.

Spray drying of a 3.33% (w/v) calcitonin formulation

1 g calcitonin was dissolved in around 25 ml demineralised water (with a pH of around 7.5) and diluted with demineralised water (with a pH of around 7.5) to a volume of 30 ml. The solution thus obtained was spray-dried as described above using cyclone II.

The aggregate content was investigated as described above.

- After 3 months' storage at 2-8°C (3 months' stability), the solution prepared from the reconstituted powder had around 4.1% aggregates respectively.
- After 3 months' storage at 25°C (3 months' stability), the solution prepared from the reconstituted powder had around 4.9% aggregates respectively.
- After 3 months' storage at 40°C (3 months' stability), the solution prepared from the reconstituted powder had around 7.4% aggregates respectively.

The MMAD and FPF of the powder were determined as described above. The MMAD was 3.9 μm, and the FPF was 59.0% in relation to the powder capsule weight.

Spray drying of a 3.166% (w/v) LS90P
0.166% (w/v) calcitonin formulation

4.750 g LS90P were dissolved in around 140 ml demineralised water (with a pH of around 7.5). As the next step, 0.250 g calcitonin was added and diluted with demineralised water (with a pH of around 7.5) to a volume of 150 ml. The solution thus obtained was spray-dried as described above using cyclone II.

The aggregate content was investigated as described above.

- After 3 months' storage at 2-8°C (3 months' stability), the solution prepared from the reconstituted powder had around 3.6% aggregates respectively.
- After 3 months' storage at 25°C (3 months' stability), the solution prepared from the reconstituted powder had around 3.9% aggregates respectively.
- After 3 months' storage at 40°C (3 months' stability), the solution prepared from the reconstituted powder had around 4.6% aggregates respectively.

The MMD of the powder was determined as described above. The MMD of the powder was 2.6 µm. The MMAD and FPF of the powder were determined as described above. The MMAD was 4.3 µm, and the FPF was 47.3% in relation to the powder capsule weight.

Spray drying of a 2.833% (w/v) LS90P 0.33% (w/v) isoleucine
0.166% (w/v) calcitonin formulation

4.250 g LS90P and 0.50 g isoleucine were dissolved in around 140 ml demineralised water (with a pH of around 7.5) in an ultrasonic bath. As the next step, 0.250 g calcitonin was added and diluted with demineralised water (with a pH of around 7.5) to a volume of 150 ml. The solution thus obtained was spray-dried as described above using cyclone II.

The aggregate content was investigated as described above.

- After 3 months' storage at 2-8°C (3 months' stability), the solution prepared from the reconstituted powder had around 3.3% aggregates respectively.
- After 3 months' storage at 25°C (3 months' stability), the solution prepared from the reconstituted powder had around 3.6% aggregates respectively.

- After 3 months' storage at 40°C (3 months' stability), the solution prepared from the reconstituted powder had around 3.6% aggregates respectively.

The MMD of the powder was determined as described above. The MMD of the powder was 2.8 μm. The MMAD and FPF of the powder were determined as described above. The MMAD was 4.4 μm, and the FPF was 49.2% in relation to the powder capsule weight.

Spray drying of a 2.866% (w/v) LS90P 0.33% (w/v) tri-isoleucine 0.166% (w/v) calcitonin formulation

4.250 g LS90P and 0.50 g tri-isoleucine were dissolved in around 140 ml demineralised water (with a pH of around 7.5) in an ultrasonic bath. As the next step, 0.250 g calcitonin was added and diluted with demineralised water (with a pH of around 7.5) to a volume of 150 ml. The solution thus obtained was spray-dried as described above using cyclone II.

The aggregate content was investigated as described above.

- After 3 months' storage at 2-8°C (3 months' stability), the solution prepared from the reconstituted powder had around 3.3% aggregates respectively.
- After 3 months' storage at 25°C (3 months' stability), the solution prepared from the reconstituted powder had around 3.6% aggregates respectively.
- After 3 months' storage at 40°C (3 months' stability), the solution prepared from the reconstituted powder had around 3.9% aggregates respectively.

The MMD of the powder was determined as described above. The MMD of the powder was 2.5 μm. The MMAD and FPF of the powder were determined as described above. The MMAD was 3.5 μm, and the FPF was 60.4% in relation to the powder capsule weight.

Example 6

Freeze drying of a 5% (w/v) IgG1 formulation

Pure IgG1 with a concentration of around 109 mg/ml formulated in a pH 6 glycine-histidine buffer (see Materials) was diluted with demineralised water (with a pH of around 7.5) to a content of 50 mg/ml and freeze-dried in the absence of any other ad-

juvants. The solution had a volume of 50 ml and was distributed in commercial 2R vials before freeze drying. The lyophilisate was lyophilised in the 2R vials by means of a spatula and further treated as described above.

The aggregate content was investigated as described above.

- After one week's open storage at 75% relative air humidity and 40°C (forced storage stability), the solution prepared from the reconstituted powder had around 20.5% aggregates.
- After one day's equilibration and four weeks' dry storage at 40°C, the solution prepared from the reconstituted powder had around 15.3% aggregates.
- After one day's vacuum drying and four weeks' dry storage at 40°C, the solution prepared from the reconstituted powder had around 12.6% aggregates.

Freeze drying of a 4.5% (w/v) mannitol
0.5% (w/v) IgG1 formulation

2.25 g mannitol were dissolved in around 40 ml demineralised water (with a pH of around 7.5). As the next step, 2.3 ml pure IgG1 with a concentration of around 109 mg/ml formulated in a pH 6 glycine-histidine buffer (see Materials) was diluted with demineralised water (with a pH of around 7.5) to a content of 50 mg/ml. The solution thus obtained contained around 4.5% (w/v) adjuvant or matrix and 0.5% (w/v) protein, was distributed in commercial 2R vials, and was freeze-dried as described above. The lyophilisate was lyophilised in the 2R vials by means of a spatula and further treated as described above. The aggregate content was investigated as described above.

The following aggregate contents were obtained for its storage stability:

- After one week's open storage at 75% relative air humidity and 40°C (forced storage stability), the solution prepared from the reconstituted powder had around 34.0% aggregates.
- After one day's equilibration and four weeks' dry storage at 40°C, the solution prepared from the reconstituted powder had around 11.6% aggregates.
- After one day's vacuum drying and four weeks' dry storage at 40°C, the solution prepared from the reconstituted powder had around 6.2% aggregates.

Freeze drying of a 4.5% (w/v) LS55P
0.5% (w/v) IgG1 formulation

2.25 g LS55P were dissolved in around 40 ml demineralised water (with a pH of around 7.5). As the next step, 2.3 ml pure IgG1 with a concentration of around 109 mg/ml formulated in a pH 6 glycine-histidine buffer (see Materials) was diluted with demineralised water (with a pH of around 7.5) to a content of 50 mg/ml. The solution thus obtained contained around 4.5% (w/v) adjuvant or matrix and 0.5% (w/v) protein, was distributed in commercial 2R vials, and was freeze-dried as described above. The lyophilisate was lyophilised in the 2R vials by means of a spatula and further treated as described above. The aggregate content was investigated as described above.

The following aggregate contents were obtained for its storage stability:

- After one week's open storage at 75% relative air humidity and 40°C (forced storage stability), the solution prepared from the reconstituted powder had around 2.5% aggregates.
- After one day's equilibration and four weeks' dry storage at 40°C, the solution prepared from the reconstituted powder had around 2.6% aggregates.
- After one day's vacuum drying and four weeks' dry storage at 40°C, the solution prepared from the reconstituted powder had around 1.2% aggregates.

Freeze drying of a 4.5% (w/v) Coupling Sugar
0.5% (w/v) IgG1 formulation

2.25 g Coupling Sugar were dissolved in around 40 ml demineralised water (with a pH of around 7.5). As the next step, 2.3 ml pure IgG1 with a concentration of around 109 mg/ml formulated in a pH 6 glycine-histidine buffer (see Materials) was diluted with demineralised water (with a pH of around 7.5) to a content of 50 mg/ml. The solution thus obtained contained around 4.5% (w/v) adjuvant or matrix and 0.5% (w/v) protein, was distributed in commercial 2R vials, and was freeze-dried as described above. The lyophilisate was lyophilised in the 2R vials by means of a spatula and further treated as described above. The aggregate content was investigated as described above.

The following aggregate contents were obtained for its storage stability:

- After one week's open storage at 75% relative air humidity and 40°C (forced storage stability), the solution prepared from the reconstituted powder had around 5.5% aggregates.
- After one day's equilibration and four weeks' dry storage at 40°C, the solution prepared from the reconstituted powder had around 4.6% aggregates.
- After one day's vacuum drying and four weeks' dry storage at 40°C, the solution prepared from the reconstituted powder had around 1.5% aggregates.

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Claims

1. Composition containing at least one antibody or one functional antibody derivative thereof and one or more 1,4 O-linked saccharose derivatives selected from the compounds: 1,4 O-linked D-Gal-saccharose (lactosucrose), 1,4 O-linked D-Glu-saccharose (glucosyl sucrose), or 1,4 O-linked Glu-Glu-saccharose (maltosyl sucrose).

2. Composition according to claim 1, characterised in that the composition is a **pharmaceutical** composition.

3. Composition according to claim 1, characterised in that the antibody is a **therapeutic** antibody or a derivative thereof.

4. Composition according to claims 1 to 3, characterised in that the antibody is a **monoclonal** antibody or a derivative thereof.

5. Composition according to claims 1 to 4, characterised in that it contains lactosucrose as 1,4 O-linked saccharose derivative.

6. Composition according to claim 5, characterised in that the composition additionally contains one or more mono-, di- and/or polysaccharides.

7. Composition according to claim 6, characterised in that the composition additionally contains lactose and saccharose.

8. Composition according to any one of claims 5 to 7, characterised in that the fraction of lactosucrose amounts to at least 55% (w/w) in relation to the sugar fraction contained in the composition.

9. Composition according to claims 1 to 4, characterised in that it contains a mixture of glucosyl sucrose and maltosyl sucrose.

10. Composition according to claim 9, characterised in that the composition additionally contains one or more mono-, di- and/or polysaccharides.

11. Composition according to claim 10, characterised in that the composition additionally contains fructose, glucose, and/or saccharose.

12. Composition according to any one of claims 9 to 11, characterised in that the total fraction of glucosyl sucrose and maltosyl sucrose amounts to at least 25% (w/w) in relation to the sugar fraction contained in the composition.

13. Composition according to claim 12, characterised in that the respective fraction of glucosyl sucrose and maltosyl sucrose amounts to at least 18% (w/w) in relation to the sugar fraction contained in the composition.

14. Composition according to any one of claims 1 to 13, characterised in that the sugar fraction containing at least one 1,4 O-linked saccharose derivative amounts to between 25 and 99.99% (w/w) of the dry weight of the composition.

15. Composition according to any one of claims 1 to 11, characterised in that the fraction of antibody or antibody derivative amounts to between 0.1 and 75% (w/w) of the dry weight of the composition and that the sum of the weight percentages amounts to max 100% (w/w).

16. Composition according to any one of claims 1 to 15, characterised in that the dry weight of the composition contains between 60 and 90% (w/w) sugar and up to 40% (w/w) of an antibody or antibody derivative, whereby the fraction of lactosucrose, maltosyl sucrose, and/or glucosyl sucrose amounts to at least 20%

(w/w) of the dry weight of the composition and that the sum of the weight percentages amounts to max 100% (w/w).

17. Composition according to any one of claims 1 to 16, characterised in that the composition contains one or more pharmaceutically compatible adjuvants and/or one or more salts.

18. Composition according to claim 17, characterised in that the adjuvant is an amino acid or peptide.

19. Composition according to claim 18, characterised in that the amino acid is isoleucine.

20. Composition according to claim 18, characterised in that the peptide is a di- or tri-peptide.

21. Composition according to claim 18, characterised in that the peptide is an isoleucine-containing peptide.

22. Composition according to claim 20 or 21, characterised in that the peptide is di- or tri-isoleucine.

23. Composition according to claim 19, characterised in that the dry weight of the composition contains between 60 and 99% (w/w) of at least one 1,4 O-linked saccharose derivative or a sugar mixture that contains at least one 1,4 O-linked saccharose derivative and between 1 and 40% (w/w) isoleucine.

24. Composition according to any one of claims 20 to 23, characterised in that the dry weight of the composition contains between 60 and 99% (w/w) of at least one 1,4 O-linked saccharose derivative or of a sugar mixture that contains at least one 1,4 O-linked saccharose derivative, and between 1 and 40% (w/w) of a peptide.

25. Composition according to any one of claims 1 to 24, characterised in that the composition is an aqueous solution, semi-solid preparation, or powder.

26. Powder according to claim 25, characterised in that the particles in the powder have an MMD between 1 and 10 μm.

27. Powder according to claim 25 or 26, characterised in that the particles in the powder have an MMAD between 1 and 5 μm

28. Powder according to claim 25 or 26, characterised in that the particles in the powder have an MMAD of less than 10 μm.

29. Powder according to claim 25 or 26, characterised in that the particles in the powder have an MMAD of between 0.5 - 10 μm.

30. Process for production of a powder according to any one of claims 25 to 29, characterised in that

a) an antibody or functional antibody derivative is dissolved / suspended in an aqueous solution / suspension;

b) one or more 1,4 O-linked saccharose derivatives selected from the combinations lactosucrose, glucosyl sucrose, or maltosyl sucrose or a sugar mixture containing at least one of these 1,4 O-linked saccharose derivatives is / are dissolved / suspended in an aqueous solution / suspension;

c) where an antibody or functional antibody derivative and 1,4 O-linked saccharose derivative or the sugar mixture containing at least one 1,4 O-linked saccharose derivative are dissolved / suspended in different solutions / suspensions, these are mixed;

d) the solution / suspension containing the antibody or functional antibody derivative and the 1,4 O-linked saccharose derivative(s) are dried.

31. Process according to claim 30, characterised in that the drying process is freeze or spray drying.

32. Process according to claim 30 or 31, characterised in that the 1,4 O-linked saccharose derivative is lactosucrose.

33. Process according to claim 32, characterised in that the solution or suspension additionally contains one or more mono-, di- or polysaccharides.

34. Process according to claim 33, characterised in that the solution to be dried additionally contains lactose and saccharose.

35. Process according to any one of claims 32 to 34, characterised in that the fraction of lactosucrose amounts to at least 55% (w/w) of the sugar fraction present in the solution to be dried.

36. Process according to claim 30 or 31, characterised in that the 1,4 O-linked saccharose derivative is a mixture of glucosyl sucrose and maltosyl sucrose.

37. Process according to claim 36, characterised in that the solution to be dried additionally contains one or more mono-, di- or polysaccharides.

38. Process according to claim 36 or 37, characterised in that the solution to be dried contains fructose, saccharose and/or glucose.

39. Process according to any one of claims 36 to 38, characterised in that the total fraction of glucosyl sucrose and maltosyl sucrose amounts to at least 25% (w/w) of that present in the solution to be dried.

40. Process according to claim 39, characterised in that the respective fraction of glucosyl sucrose and maltosyl sucrose amounts to at least 18% (w/w) of that present in the solution to be dried.

41. Process according to any one of claims 30 to 40, characterised in that the sugar fraction containing at least one 1,4 O-linked saccharose derivative amounts to between 25 and 99.99% (w/w) of the dry weight of the solution to be dried.

42. Process according to any one of claims 30 to 40, characterised in that the fraction of antibody or antibody derivative amounts to between 0.1 and 75% (w/w) of the dry weight of the solution to be dried, whereby the sum of the weight percentages amounts to max 100% (w/w).

43. Process according to any one of claims 30 to 42, characterised in that the solution to be dried contains one or more pharmaceutically compatible adjuvants and/or one or more salts.

44. Process according to claim 43, characterised in that the adjuvant is an amino acid or peptide.

45. Process according to claim 44, characterised in that the amino acid is isoleucine.

46. Process according to claim 44, characterised in that the peptide is a di- or tri-peptide.

47. Process according to claim 44, characterised in that the peptide is an isoleucine-containing peptide.

48. Process according to claim 44, 46 or 47, characterised in that the peptide is tri-isoleucine.

49. Process according to claim 41 or 42, characterised in that the dry weight of the solution to be dried contains between 60 and 90% (w/w) of at least one 1,4 O-linked saccharose derivative or a sugar mixture containing at least one 1,4 O-linked saccharose derivative and between 1 and 19.99% (w/w) amino acid and that the sum of the weight percentages amounts to max 100% (w/w).

50. Process according to any one of claims 41 or 42, characterised in that the dry weight of the solution to be dried contains between 60 and 90% (w/w) of at least one 1,4 O-linked saccharose derivative or a sugar mixture containing at least one 1,4 O-linked saccharose derivative and between 1 and 19.99% of a peptide.

51. The powder according to any one of claims 25 to 29 for use as of a medicinal drug.

52. The spray-dried powder according to any one of claims 26 to 29 for use as a medicinal inhalant.