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(54) Title: PREPARATION OF A POWDERY PHARMACEUTICAL COMPOSITION BY MEANS OF CRYO-MILLING

(57) Abstract: The invention relates to a method for the preparation of a powdery pharmaceutical composition comprising a pharmaceutical excipient and a pharmaceutical component, wherein the pharmaceutical excipient is a polyalkylene glycol, the method comprising the step of grinding a mixture of the pharmaceutical excipient and the pharmaceutical component at a temperature below ambient temperature.



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Preparation of a Powdery Pharmaceutical Composition by Means of Cryo-Milling

The invention relates to a method for the preparation of a powdery pharmaceutical composition comprising a pharmaceutical excipient, preferably a first pharmaceutical excipient, and a pharmaceutical component, preferably a second pharmaceutical excipient or a pharmacologically active substance, optionally together with a third constituent, preferably another pharmaceutical excipient, wherein the pharmaceutical excipient is a polyalkylene glycol, the method comprising the step of grinding a mixture of the pharmaceutical excipient and the pharmaceutical component at a temperature below ambient temperature. The powdery pharmaceutical composition is particularly useful in the manufacture of pharmaceutical dosage forms comprising at least one pharmacologically active substance. The invention further relates to a method for the manufacture of pharmaceutical dosage forms, such as tablets.

Many pharmaceutical dosage forms require homogeneous distribution of all excipients. Homogeneous distribution of excipients is required in order to maintain product quality, not only with respect to changeless drug content, but also with respect to changeless properties which are based on the presence of specific amounts of excipients such as storage stability, processability, disintegration, release profile, and the like.

Homogeneous distribution of excipients is usually achieved by vigorously mixing the excipients prior to forming the dosage form e.g. by subsequent granulation or direct compression. Blending excipients in a mixer is the method of choice for solid excipients. If one or more excipients are liquid or pasty, however, blending is more difficult to achieve, especially if the compatibility of excipients is limited, e.g. because one excipient is hydrophilic and the other excipient is hydrophobic.

Particular problems arise when the individual amounts of excipients to be mixed with one another substantially differ from one another. For example, it is rather difficult to homogeneously distribute small amounts of hydrophobic liquids, e.g. 0.5 wt.-%, in a solid mixture of hydrophilic excipients.

For example, alpha-tocopherol, which is a hydrophobic oily liquid at ambient temperature, is extensively used as antioxidant in pharmaceutical dosage forms. It is known to use alpha-tocopherol as a pre-blend with other pharmaceutical excipients in order to better distribute the comparatively small amount (e.g. 0.1 to 0.2 wt.-%) of alpha-tocopherol in the overall dosage form. Pre-blends of hydrophobic alpha-tocopherol with hydrophilic polyethylene glycol are commercially available. Such products are typically manufactured by spray-congealing. A melt of polyethylene glycol is homogenized with alpha-tocopherol and is sprayed into a drying-tower that is cooled by nitrogen gas and the congealed particles are collected. Spray congealing technology is very laborious and costly.

GB-A 1,147,210 relates to a process for making a dry, free flowing, finely divided, fat-soluble vitamin-active product, comprising (1) preparing a colloidal solution of cold water dispersible, non-gelling colloid material and water; (2) dispersing in said colloidal solution a water insoluble, fat soluble vitamin active composition to form a

first dispersion; (3) dispersing the latter in a water immiscible liquid dispersing medium to form a second dispersion; (4) extracting water at -10 to 0 °C from the latter with a water extraction agent until droplets of the first dispersion solidify to form particles; (5) separating the latter from the dispersing medium and water extraction agent at -10 to 0 °C; and (6) removing residual moisture from the solid particles.

US 4,603,143 discloses the preparation of free-flowing and stable vitamin-active powders utilizing special silicon-containing materials which are predominately in the form of substantially discrete agglomerates.

US 4,892,889 relates to a process for making a directly-compressible vitamin powder utilizing a conventional spray-dryer. The resulting powder is comprised of a fat-soluble vitamin, a water-soluble carbohydrate, and a gelatin having a bloom number between 30 and 300.

US 6,183,781 discloses a method for producing an implantable polymer/drug matrix mass, comprising the steps of (1) forming a polymer solution/drug mixture comprising a polymer dissolved in an organic solvent and a suspended labile drug; (2) removing the solvent from the polymer solution/drug mixture, thereby forming a solid polymer/drug matrix; and (3) mechanically compressing the polymer/drug matrix, thereby forming an implantable polymer/drug matrix mass.

US 6,261,599 and US 2004/0081694 disclose sustained release oral opioid analgesic dosage forms comprising a plurality of multiparticulates produced via melt extrusion techniques. The extruded material exits the extruder in form of an extruded strand.

DE 195 22 899 discloses a method for continuously sintering a granulate for the manufacture of compressed articles, particularly for tableted drug formulations. None of the components is melted in the extruder and no strand is extruded.

EP-A 0 043 254 discloses a pharmaceutical composition with a retarded liberation of an active material and a process for producing the same. An active material in finely divided form is mixed with both a finely divided high melting lipid or lipoid component and a finely divided low melting lipid or lipoid component, the resulting mixture is brought to a temperature which is above the melting point of the low melting component but below the melting point of the high melting component and the mixture, after melting of the low melting component, is allowed to cool to below the melting point thereof and subsequently worked up to give a finished pharmaceutical composition which has a controlled retarded liberation and which is safe, easy and not expensive to produce.

EP-A 229 652 discloses that certain acid compounds stabilize the potency of vitamin E compounds when processed into a dry particulate free-flowing form. A potency stabilized composition in a dry, particulate, free-flowing form is comprised of Vitamin E incorporated in a carrier whose potency has been stabilized with an effective amount of a certain acid compound. Such potency stabilizing acid compounds are hydroxy acids or amino acids, such as citric acid, ascorbic acid, methionine and cysteine.

EP-A 641 195 relates to a continuous method for the production of retarded pharmaceutical compositions by an extrusion process. A mixture of an active material, a low and high melting lipid or lipoid components is introduced by means of an extruder screw conveyor into a preheated extruder and brought to a temperature which is at most about 4 °C above the melting temperature of the low melting component at a pressure of about 200 to about 600 kPa (N/m²). The mass is extruded through a nozzle plate with a nozzle diameter of about 1.2 to about 4 mm and subsequently cooled, and if desired, granulated.

EP 2 246 063 relates to pharmaceutical compositions for the controlled and sustained release of active substance comprising a biodegradable polymer or copolymer. Furthermore, the reference relates to pharmaceutical compositions for the controlled and sustained release of at least one active substance such as peptides or hormones and analogues thereof and the manufacturing process of such pharmaceutical compositions.

WO 95/17174 discloses a process for making an ingestible, neutral tasting laxative composition by coating dioctyl sulfosuccinate with a material selected from the group consisting of C₁₄₋₁₈ fats, C₁₆₋₂₀ fatty acids, sucrose polyesters, C₁₄₋₁₈ fats and waxes, pH sensitive polymers, food gums, and combinations thereof. Preferably, two successive, different coatings are applied to the dioctyl sulfosuccinate by steps including either fluid bed coating, spray congealing, spray quenching, or spray drying.

WO 96/03979 relates to an apparatus and method for preparing solid forms with controlled release of the active ingredient according to the spray drying and spray congealing techniques by means of an atomizer utilizing the mechanical vibrations of resonant metal elements or nozzles so as to obtain very small droplets with very short spray length.

WO 98/35655 discloses a method of physically separating at least two active substances A and B in solid medicament forms, wherein a melting process is applied and active substance A is homogeneously intermingled with the higher-melting lipids or lipoid constituent and the mixture thus obtained is granulated or finely divided in another manner.

WO 2009/135680 relates to a process for preparing a powder comprising the steps of providing at least one first component being in liquid form or having a waxy consistency at ambient temperature, providing at least one second component having a melting point or melting point/range in the range from above ambient temperature to below the degradation temperature of said first component, forming a homogenous liquid mixture comprising said at least one first component and said at least one second component by stirring and heating the mixture to or keeping the mixture at a temperature in the range from above the melting point or melting point/range of said second component and below the degradation temperature of said first component, transferring the liquid mixture to at least one spray congealing unit by at least one transfer unit, which is adapted to keep the mixture in its liquid form during its transfer, spray congealing said mixture, and isolating the powder obtained upon spray congealing.

WO 2011/095314 discloses the extrusion of a mixture of melted excipients through an extruder having a certain temperature profile to allow congealing of melted solution and to exit the extruder in form of powder. However,

the powder is comparatively coarse and conventional subsequent grinding steps do not provide fine powders satisfying all requirements.

Li Lei et al., Drug Development and Industrial Pharmacy, 32(8), 2006, 991-1002 relates to the characterization of poly(ethylene oxide) in hot-melt extrusion.

Andreas Gryczke et al., Colloids and Surfaces. B, Biointerfaces, 86(2), 2011, 275-284 relates to the development and evaluation of orally disintegrating tablets containing ibuprofen granules prepared by hot melt extrusion.

The aforementioned procedures are not satisfactory in every respect. With some procedures, generally only large amounts of excipients can be employed, other procedures are quite laborious and require sophisticated equipment, still other procedures yield coarse powders. There is a demand for a simple and effective method to continuously and homogeneously incorporate incompatible pharmaceutical excipients in substantially differing amounts into pharmaceutical compositions. The method should minimize capital expenditures for new equipment, have no or reduced regulatory impact and should be flexible with respect to the chemical nature and amount of constituents that can be processed.

It is an object of the invention to provide methods for the preparation of powdery pharmaceutical compositions comprising a homogeneous mixture of at least two pharmaceutical excipients and having advantages over the methods of the prior art. The manufacture of the powdery pharmaceutical compositions should be possible in a continuous fashion and should encompass a limited number of method steps only.

This object has been achieved by the subject-matter of the patent claims.

The invention relates to a method for the preparation of a powdery pharmaceutical composition comprising a pharmaceutical excipient, preferably first pharmaceutical excipient, which is a polyalkylene glycol, more preferably polyethylene glycol, and a pharmaceutical component, preferably a second pharmaceutical excipient or a pharmacologically active substance (drug), more preferably alpha-tocopherol; optionally together with a third constituent, preferably another pharmaceutical excipient, wherein the pharmaceutical excipient is a polyalkylene glycol; the method comprising the step of

- (c) grinding a mixture of the pharmaceutical excipient and the pharmaceutical component at a temperature below ambient temperature.

It has been surprisingly found that incompatible pharmaceutical excipients and components, respectively, e.g. a hydrophilic pharmaceutical excipient, preferably first pharmaceutical excipient, which is a polyalkylene glycol, more preferably polyethylene glycol, and a hydrophobic pharmaceutical component, preferably second pharmaceutical excipient, more preferably alpha-tocopherol, can be converted into a fine powdery pharmaceutical composition in a simple grinding process below ambient temperature.

By the method according to the invention fine powders can even be obtained when the amount of the excipient and the component substantially differs from one another, e.g. when the pharmaceutical excipient is present in an

amount of 99 wt.-% or more and the pharmaceutical component is present in an amount of 1 wt.-% or less, both percentages being related to the total weight of the powdery pharmaceutical composition.

It has been surprisingly found that cryo-milling of blends comprising alpha-tocopherol and polyethylene glycol (PEG) show better results than either jet milling or sizing of extruded material. The feasibility of the method according to the invention could be demonstrated by means of different mill apparatuses (i.e. plate mills, hammer mills). Cryogenic temperatures make brittle the material to be milled and this implies that the specific energy required for milling is reduced. Additionally, cryogenic milling prevents the materials from thermal damage, hinders the occurrence of undesirable chemical reactions between phases and reduces particles aggregation. Further, the method according to the invention allows the control of the particle size by a very simple operation, namely by changing the sieve net of the mill apparatus. This flexibility makes possible the manufacture of alpha-tocopherol / PEG blends with a tailored particle size-distribution, and thereby it is possible to modulate the behavior of the powders in relation with properties such bioavailability, stability, flowability, adhesive strength, drying properties and solubility. The method according to the invention is robust and consistent to achieve particle size distribution (PSD) comparable to commercial alpha-tocopherol / PEG blends manufactured by spray-congealing, which is considered to be one of the most powerful technologies for the manufacture of solid dispersion microparticles

It has also been found that cryo-milling does not affect physical-chemical characteristics of the milled composition. Cryo-milling can be applied to a wide range of alpha-tocopherol / PEG mass ratios (0.01 wt.-% to 70 wt.-%, preferably 0.1 wt.-% to 20 wt.-%, more preferably 0.5 wt.-% to wt.-10%) whatever is the initial size of material. The method according to the invention is simple and cheaper than spray congealing processes. Further, the cryo-milled compositions do not affect physical characteristics (i.e. density, flowability, particle distribution) of resultant powder blends of drug products compared to the commercial alpha-tocopherol / PEG blends.

Figure 1 compares the particle size distribution (PSD) of alpha-tocopherol / PEG with other excipients.

Figure 2 shows the particle size distribution (PSD) of Trials 6, 7 and 8 in comparison to that of a commercial vitamin E/PEG 6000 blend.

Figure 3 shows a DSC of the commercial vitamin E/PEG 6000 blend.

Figure 4 shows a DSC of Vitamin E/PEG 4% material after cryo-milling.

Figure 5 shows a DSC of Vitamin E/PEG 14% material after cryo-milling.

Figure 6 shows the influence of the temperature on the particle size distribution (PSD).

Figure 7 shows the influence of the cryo-milling technology on the particle size distribution (PSD).

Figure 8 shows a comparison of particle size distribution (PSD) after blending.

A first aspect of the invention relates to a method for the preparation of a powdery pharmaceutical composition comprising a pharmaceutical excipient, preferably first pharmaceutical excipient, which is a polyalkylene glycol, more preferably polyethylene glycol, and a pharmaceutical component, preferably second pharmaceutical excipient, more preferably alpha-tocopherol; the method comprising the step of

- (c) grinding a mixture of the pharmaceutical excipient and the pharmaceutical component at a temperature below ambient temperature.

Preferably, the grinding in step (c) is performed in form of a cryo-milling. For the purpose of the specification, the terms "*grinding*" and "*milling*" are synonymous.

Preferably, the temperature below ambient temperature is at most 0°C, or at most -5°C, or at most -10°C, or at most -15°C, or at most -20°C, or at most -25°C, or at most -30°C, or at most -35°C, or at most -40°C, or at most -45°C, or at most -50°C, or at most -55°C, or at most -60°C, or at most -65°C, or at most -70°C, or at most -75°C, or at most -80°C, or at most -85°C, or at most -90°C, or at most -95°C, or at most -100°C. Preferably, the temperature is that of liquid nitrogen (i.e. about -196°C).

Preferably, the cryo-milling in step (c) of the method according to the invention is performed until the desired particle size and particle size distribution of the powdery pharmaceutical composition is achieved. The duration depends upon the equipment and the process parameters and can be determined by routine experimentation.

Cryo-milling in step (c) can be performed continuously or discontinuously.

Preferably, the pharmaceutical composition is subjected to cryo-milling in step (c) for at least about 10 seconds, or at least about 20 seconds, or at least about 30 seconds, or at least about 1 minute.

When cryo-milling in step (c) is performed continuously, the above time intervals refer to the mean residence time of the material within the mill.

In principle, many different mill apparatuses that are known to the skilled person can be used for cryo-milling, although some of them appear to better adapt to cryogenic conditions. Plate mills and hammer mills are preferred.

Typically, the mill is a cryo-mill, i.e. a mill capable of operating at low temperatures and being equipped with a suitable cooling system.

Preferably, the cryo-mill is equipped with a milling chamber comprising means for providing mechanical impact on the material to be milled, sometimes also referred to as "grinding jar". Depending upon the type of the cryo-mill, said mechanical impact may be provided in different forms that are known to the skilled person and that all have in common that the particle size of fine material is reduced through attrition and compressive forces at the grain size level. Suitable mills include but are not limited to ball mills, rod mills, autogenous mills, SAG mills,

pebble mills, high pressure grinding rolls, Buhrstone mills, vertical shaft impactor mills (VSI mills), tower mills. Preferred mills are ball mills, colloid mills, conical mills, disintegrators, disk mills, edge mills, gristmills, hammer mills, jet mills, pellet mills, planetary mills, plate mills, stirred mills, and vibratory mills.

Further, the cryo-mill is preferably equipped with a sieve that allows material of the desired particle size to exit the milling chamber but keeps the coarser material within the milling chamber so that it is subjected to additional mechanical impact.

Still further, the cryo-mill is preferably equipped with a feeding device supplying the cryo-mill with starting material to be milled. Both the feeding device and the milling chamber are preferably equipped with isolating protections and integrated cooling, e.g. suitable pipeline to allow refrigeration with liquid nitrogen. The grinding jar is preferably continuously cooled with liquid nitrogen from the integrated cooling system before and during the grinding process. The sample is thus embrittled and volatile components are preserved. The liquid nitrogen preferably circulates through the system and is continuously replenished from an autofill system in the exact amount which is required to maintain the temperature at about -196 °C.

In a preferred embodiment, cryo-milling is performed by means of a plate mill, e.g. a Hosokawa – Alpine (Germany). The mill preferably comprises a stainless steel milling chamber equipped with high speed rotating elements (plate beater) that apply a centrifugal force guiding the fed coarse material against a radial sieve of appropriate open sieve net. The milled material is then directly collected into a suitable container. Coarse material is preferably loaded by means of a feeding device directly in the center of the milling chamber.

In another preferred embodiment, cryo-milling is performed by means of a hammer mill, e.g. a Nuova Guseo (Italy). The mill preferably comprises a stainless steel milling chamber equipped with an horizontal rotor shaft which carries grinding elements (hammers) rotating at variable speed depending on the mill size. Coarse material is grinded by impact and attrition and finally forced through a radial sieve of appropriate open sieve net. Preferably, the milled material is then directly collected into a suitable container. The mill is preferably loaded by the top by means of an appropriate feeding device.

Milling may be performed continuously or batch-wise.

For the purpose of the specification, a "*pharmaceutical composition*" is any composition that is adapted for administration to an animal, typically oral administration of a human being.

The pharmaceutical composition according to the invention comprises a pharmaceutical excipient, preferably first pharmaceutical excipient, which is a polyalkylene glycol, more preferably polyethylene glycol, and a pharmaceutical component, preferably second pharmaceutical excipient, more preferably alpha-tocopherol.

For the purpose of specification, a "*polyalkylene glycol*" has a molecular weight of up to 50,000 g/mol, preferably up to 20,000 g/mol, whereas a "*polyalkylene oxide*" has a molecular weight of more than 50,000 g/mol, preferably more than 20,000 g/mol.

For the purpose of the specification the term "*pharmaceutical component*" encompasses both, pharmacologically active substances (drugs) as well as pharmaceutical excipients. Thus, preferably, the pharmaceutical component is selected from pharmacologically active substances and pharmaceutical excipients.

Pharmaceutical excipients are known to the skilled person (cf. e.g. R.C. Rowe et al., Handbook of Pharmaceutical Excipients, Pharmaceutical Press; 6th edition 2009; E.-M. Hoepfner et al., Fiedler - Encyclopedia of Excipients, Editio Cantor, 6th edition 2008).

For the purpose of the specification, a "*pharmaceutical excipient*" is preferably to be regarded as any pharmacologically inactive substance typically used as a carrier for the active ingredients of a medication. The pharmaceutical excipient may have a physiological effect, e.g. like a vitamin, but not a pharmacological effect, like a drug. Typical examples of pharmaceutical excipients include antiadherents, binders, coating materials, disintegrants, fillers, diluents, flavours, colorants, glidants, lubricants, preservatives, sorbents, sweeteners, and the like. Any of the foregoing excipients can be divided into sub-groups. For example, preservatives can be divided into antioxidants, buffers, antimicrobial substances and the like; whereas binders can be divided into solution binders and dry binders. Several excipients simultaneously exhibit different properties so that they can serve different purposes. For example, polyethylene glycol can be used as binder, plasticizer and the like.

Pharmacologically active substances are also known to the skilled person. In this regard, it can be referred to e.g. the Anatomical Therapeutic Chemical (ATC) classification system of the WHO.

In a preferred embodiment, the pharmaceutical component is a pharmacologically active substance (drug). Under these circumstances, the pharmaceutical composition according to the invention comprises the pharmacologically active substance already.

In another preferred embodiment, the pharmaceutical component is a second pharmaceutical excipient. Under these circumstances, the pharmaceutical composition according to the invention comprises at least two pharmaceutical excipients, namely the above pharmaceutical excipient (= first pharmaceutical excipient) and the pharmaceutical component (= second pharmaceutical excipient).

When the pharmaceutical component is a pharmacologically active substance, this is preferably selected from the group consisting of hormones and related compounds, such as estrogens, gestagens, androgens, anti-estrogens, anti-gestagens, anti-androgens; and analgesics, such as opioids, preferably selected from the group consisting of tramadol, tapentadol, oxycodone, oxymorphone, hydrocodone, hydromorphone, morphin; and the physiologically acceptable salts thereof.

When the pharmaceutical component is a second pharmaceutical excipient, the pharmaceutical composition according to the invention does not necessarily have to comprise a pharmacologically active substance (drug). Rather, the pharmaceutical composition may exclusively consist of two or more pharmaceutical excipients. Under these circumstances, the pharmaceutical composition is preferably adapted for being further processed

into a pharmaceutical dosage form by addition of a pharmacologically active substance and optionally, further pharmaceutical excipients. Thus, in a preferred embodiment, the pharmaceutical composition can be regarded as an intermediate in the preparation of a pharmaceutical dosage form, which intermediate as such does not yet contain the pharmacologically active substance of the pharmaceutical dosage form.

In a preferred embodiment, the mixture comprises a third constituent, preferably another, i.e. additional pharmaceutical excipient.

When the mixture comprises a third constituent beside the pharmaceutical excipient and the pharmaceutical component, said third constituent is preferably an additional pharmaceutical excipient, more preferably a polymer, still more preferably a polyalkylene oxide, yet more preferably a polyethylene oxide having a weight average molecular weight of at least 1 Mio g/mol, most preferably a polyethylene oxide having a weight average molecular weight of at least 4 Mio g/mol.

In a preferred embodiment, the pharmaceutical composition essentially consists of a pharmaceutical excipient, preferably first pharmaceutical excipient, which is a polyalkylene glycol, more preferably polyethylene glycol, and a pharmaceutical component, preferably second pharmaceutical excipient, more preferably alpha-tocopherol, but does not contain any further ingredients, i.e. neither further pharmaceutical excipients nor pharmacologically active substances. In another preferred embodiment, the pharmaceutical composition essentially consists of a pharmaceutical excipient, preferably first pharmaceutical excipient, which is a polyalkylene glycol, more preferably polyethylene glycol, a pharmaceutical component, preferably second pharmaceutical excipient, more preferably alpha-tocopherol, and a third constituent, preferably an additional pharmaceutical excipient, more preferably a polymer, still more preferably a polyethylene oxide, but does not contain any further ingredients, i.e. neither further pharmaceutical excipients nor pharmacologically active substances.

The pharmaceutical excipient and the pharmaceutical component are not particularly limited.

Preferably, the pharmaceutical excipient, preferably first pharmaceutical excipient, is hydrophilic and the pharmaceutical component, preferably second pharmaceutical excipient, is hydrophobic, or vice versa. When the pharmaceutical composition comprises a third constituent, this is preferably hydrophilic as well.

A skilled person knows how to distinguish hydrophobic substances from hydrophilic substances. For the purpose of the specification, hydrophilic substances preferably have a solubility in pure water at 20 °C of at least 10 g/l, more preferably at least 50 g/l, still more preferably at least 100 g/l, yet more preferably at least 200 g/l, most preferably at least 300 g/l and in particular at least 400 g/l. For the purpose of the specification, hydrophobic substances preferably have a solubility in pure water at 20 °C of at most 1 g/l, more preferably at most 0.5 g/l, still more preferably at most 1.0 g/l, yet more preferably at most 0.05 g/l, most preferably at most 0.01 g/l and in particular at most 0.005 g/l.

In a preferred embodiment, the pharmaceutical excipient, preferably first pharmaceutical excipient, has a melting point/range within the range of 60 ± 30 °C, more preferably 60 ± 25 °C, still more preferably 60 ± 20 °C, yet more preferably 60 ± 15 °C, most preferably 60 ± 10 °C, and in particular 60 ± 5.0 °C.

In a preferred embodiment, the pharmaceutical component, preferably second pharmaceutical excipient, has a melting point/range within the range of 2.0 ± 30 °C, more preferably 2.0 ± 25 °C, still more preferably 2.0 ± 20 °C, yet more preferably 2.0 ± 15 °C, most preferably 2.0 ± 10 °C, and in particular 2.0 ± 5.0 °C.

In a preferred embodiment, the pharmaceutical component, preferably second pharmaceutical excipient, has a density (at 20 °C) within the range of 0.950 ± 0.040 g/cm³, more preferably 0.950 ± 0.030 g/cm³, still more preferably 0.950 ± 0.025 g/cm³, yet more preferably 0.950 ± 0.020 g/cm³, most preferably 0.950 ± 0.015 g/cm³, and in particular 0.950 ± 0.010 g/cm³.

In a preferred embodiment,

- the pharmaceutical excipient, preferably first pharmaceutical excipient, is a polymer, more preferably a linear polymer, still more preferably a water-soluble polymer, yet more preferably a polyalkylene glycol, most preferably a polyethylene glycol; and/or
- the pharmaceutical component, preferably second pharmaceutical excipient, is an antioxidant, preferably a tocopherol component, more preferably alpha-tocopherol.

For the purpose of the specification, the term "*polyalkylene glycol*" comprises e.g. polyethylene glycol, polypropylene glycol, blends thereof and copolymers thereof.

For the purpose of the specification, "*tocopherol component*" refers to alpha-tocopherol (vitamin E) and its derivatives such as tocopherol acetate.

In a preferred embodiment, the pharmaceutical excipient, preferably first pharmaceutical excipient, is a polyalkylene glycol, preferably a polyethylene glycol, having a weight average molecular weight within the range of from $6,000\pm 5,000$ g/mol, more preferably $6,000\pm 4,000$ g/mol, still more preferably $6,000\pm 3,000$ g/mol, yet more preferably $6,000\pm 2,000$ g/mol, most preferably $6,000\pm 1,500$ g/mol, and in particular $6,000\pm 1,000$ g/mol.

Preferably, the pharmaceutical composition does not contain any pharmacologically active substance (besides the tocopherol component).

In a preferred embodiment, the relative weight ratio of the pharmaceutical excipient, preferably first pharmaceutical excipient, which is a polyalkylene glycol, more preferably polyethylene glycol, to the pharmaceutical component, preferably second pharmaceutical excipient, more preferably alpha-tocopherol, is within the range of from 1000:1 to 1:1, more preferably 900:1 to 5:1, still more preferably 800:1 to 10:1, yet more preferably 700:1 to 15:1, most preferably 600:1 to 20:1, and in particular 500:1 to 25:1.

In a preferred embodiment, the relative weight ratio of the pharmaceutical excipient, preferably first pharmaceutical excipient, which is a polyalkylene glycol, more preferably polyethylene glycol, to the pharmaceutical component, preferably second pharmaceutical excipient, more preferably alpha-tocopherol, is at most 1000:1, more preferably at most 900:1, still more preferably at most 800:1, yet more preferably at most 700:1, most preferably at most 600:1 and in particular at most 500:1.

In another preferred embodiment, the relative weight ratio of the pharmaceutical excipient, preferably first pharmaceutical excipient, which is a polyalkylene glycol, more preferably polyethylene glycol, to the pharmaceutical component, preferably second pharmaceutical excipient, more preferably alpha-tocopherol, is at least 1:1, more preferably at least 5:1, still more preferably at least 10:1, yet more preferably at least 20:1, most preferably at least 30:1 and in particular at least 50:1.

When the pharmaceutical composition comprises a third constituent, preferably another pharmaceutical excipient, the relative weight ratio of the pharmaceutical excipient, preferably first pharmaceutical excipient, which is a polyalkylene glycol, more preferably polyethylene glycol, to said third constituent, preferably another pharmaceutical excipient, preferably polyethylene oxide, is within the range of from 99:1 to 1:5, more preferably 50:1 to 1:4, still more preferably 30:1 to 1:3, yet more preferably 20:1 to 1:2, most preferably 15:1 to 1:1 and in particular 10:1 to 2:1.

Preferably, the content of the pharmaceutical excipient, preferably first pharmaceutical excipient, which is a polyalkylene glycol, more preferably polyethylene glycol, in the pharmaceutical composition is at least 50 wt.-% or at least 55 wt.-%, still more preferably at least 60 wt.-% or at least 65 wt.-%, yet more preferably at least 70 wt.-% or at least 75 wt.-%, most preferably at least 80 wt.-%, at least 82.5 wt.-%, at least 85 wt.-% or at least 87.5 wt.-%, and in particular at least 90 wt.-%, at least 91 wt.-%, at least 92 wt.-%, at least 93 wt.-%, at least 94 wt.-%, at least 95 wt.-%, at least 96 wt.-%, at least 97 wt.-%, at least 98 wt.-%, or at least 99 wt.-%, based on the total weight of the pharmaceutical composition.

Preferably, the content of the optionally present third constituent, preferably another pharmaceutical excipient, more preferably polyethylene oxide, in the pharmaceutical composition is at least 0.1 wt.-% or at least 0.2 wt.-%, still more preferably at least 0.5 wt.-% or at least 1.0 wt.-%, yet more preferably at least 2.0 wt.-% or at least 5.0 wt.-%, most preferably at least 7.5 wt.-%, at least 10 wt.-%, at least 12.5 wt.-% or at least 15 wt.-%, and in particular at least 20 wt.-%, at least 25 wt.-%, at least 30 wt.-%, at least 35 wt.-%, at least 40 wt.-%, at least 45 wt.-%, at least 50 wt.-%, at least 55 wt.-%, at least 60 wt.-%, or at least 65 wt.-%, based on the total weight of the pharmaceutical composition.

Preferably, the content of the pharmaceutical component, preferably second pharmaceutical excipient, more preferably alpha-tocopherol, in the pharmaceutical composition is at most 50 wt.-% or at most 45 wt.-%, more preferably at most 40 wt.-% or at most 35 wt.-%, still more preferably at most 30 wt.-% or at most 25 wt.-%, yet more preferably at most 20 wt.-%, at most 17.5 wt.-%, at most 15 wt.-% or at most 12.5 wt.-%, most preferably 10 wt.-%, at most 9.0 wt.-%, at most 8.0 wt.-%, at most 7.0 wt.-%, or at most 6.0 wt.-%, and in particular at most

at most 5.0 wt.-%, at most 4.0 wt.-%, at most 3.0 wt.-%, at most 2.0 wt.-%, or at most 1.0 wt.-%, based on the total weight of the pharmaceutical composition.

In a preferred embodiment, the content of the pharmaceutical component, preferably pharmacologically active ingredient, is at most 10 wt.-% or at most 9.0 wt.-%, more preferably at most 8.0 wt.-% or at most 7.0 wt.-%, still more preferably at most 6.0 wt.-% or at most 5.0 wt.-%, yet more preferably at most 4.5 wt.-%, at most 4.0 wt.-%, at most 3.5 wt.-% or at most 3.0 wt.-%, most preferably 2.5 wt.-%, at most 2.0 wt.-%, at most 1.5 wt.-%, at most 1.0 wt.-%, or at most 0.75 wt.-%, and in particular at most at most 0.5 wt.-%, at most 0.25 wt.-%, at most 0.1 wt.-%, at most 0.05 wt.-%, at most 0.01 wt.-%, at most 0.005 wt.-% or at most 0.001 wt.-%, based on the total weight of the pharmaceutical composition.

In a preferred embodiment, the content of the pharmaceutical component, preferably second pharmaceutical excipient, more preferably alpha-tocopherol, in the pharmaceutical composition is within the range of 14.0 ± 5.0 wt.-%, more preferably 14.0 ± 4.0 wt.-%, still more preferably 14.0 ± 3.0 wt.-%, yet more preferably 14.0 ± 2.0 wt.-%, most preferably 14.0 ± 1.0 wt.-%, and in particular 14.0 ± 0.5 wt.-%, based on the total weight of the pharmaceutical composition.

In another preferred embodiment, the content of the pharmaceutical component, preferably second pharmaceutical excipient, more preferably alpha-tocopherol, in the pharmaceutical composition is within the range of 12.0 ± 5.0 wt.-%, more preferably 12.0 ± 4.0 wt.-%, still more preferably 12.0 ± 3.0 wt.-%, yet more preferably 12.0 ± 2.0 wt.-%, most preferably 12.0 ± 1.0 wt.-%, and in particular 12.0 ± 0.5 wt.-%, based on the total weight of the pharmaceutical composition.

In still another preferred embodiment, the content of the pharmaceutical component, preferably second pharmaceutical excipient, more preferably alpha-tocopherol, in the pharmaceutical composition is within the range of 10.0 ± 5.0 wt.-%, more preferably 10.0 ± 4.0 wt.-%, still more preferably 10.0 ± 3.0 wt.-%, yet more preferably 10.0 ± 2.0 wt.-%, most preferably 10.0 ± 1.0 wt.-%, and in particular 10.0 ± 0.5 wt.-%, based on the total weight of the pharmaceutical composition.

In yet another preferred embodiment, the content of the pharmaceutical component, preferably second pharmaceutical excipient, more preferably alpha-tocopherol, in the pharmaceutical composition is within the range of 9.0 ± 5.0 wt.-%, more preferably 9.0 ± 4.0 wt.-%, still more preferably 9.0 ± 3.0 wt.-%, yet more preferably 9.0 ± 2.0 wt.-%, most preferably 9.0 ± 1.0 wt.-%, and in particular 9.0 ± 0.5 wt.-%, based on the total weight of the pharmaceutical composition.

In a preferred embodiment, the content of the pharmaceutical component, preferably second pharmaceutical excipient, more preferably alpha-tocopherol, in the pharmaceutical composition is within the range of 8.0 ± 5.0 wt.-%, more preferably 8.0 ± 4.0 wt.-%, still more preferably 8.0 ± 3.0 wt.-%, yet more preferably 8.0 ± 2.0 wt.-%, most preferably 8.0 ± 1.0 wt.-%, and in particular 8.0 ± 0.5 wt.-%, based on the total weight of the pharmaceutical composition.

In another preferred embodiment, the content of the pharmaceutical component, preferably second pharmaceutical excipient, more preferably alpha-tocopherol, in the pharmaceutical composition is within the range of 7.0 ± 5.0 wt.-%, more preferably 7.0 ± 4.0 wt.-%, still more preferably 7.0 ± 3.0 wt.-%, yet more preferably 7.0 ± 2.0 wt.-%, most preferably 7.0 ± 1.0 wt.-%, and in particular 7.0 ± 0.5 wt.-%, based on the total weight of the pharmaceutical composition.

In still another preferred embodiment, the content of the pharmaceutical component, preferably second pharmaceutical excipient, more preferably alpha-tocopherol, in the pharmaceutical composition is within the range of 6.0 ± 5.0 wt.-%, more preferably 6.0 ± 4.0 wt.-%, still more preferably 6.0 ± 3.0 wt.-%, yet more preferably 6.0 ± 2.0 wt.-%, most preferably 6.0 ± 1.0 wt.-%, and in particular 6.0 ± 0.5 wt.-%, based on the total weight of the pharmaceutical composition.

In yet another preferred embodiment, the content of the pharmaceutical component, preferably second pharmaceutical excipient, more preferably alpha-tocopherol, in the pharmaceutical composition is within the range of 5.0 ± 2.5 wt.-%, more preferably 5.0 ± 2.0 wt.-%, still more preferably 5.0 ± 1.5 wt.-%, yet more preferably 5.0 ± 1.0 wt.-%, most preferably 5.0 ± 0.5 wt.-%, and in particular 5.0 ± 0.25 wt.-%, based on the total weight of the pharmaceutical composition.

In another preferred embodiment, the content of the pharmaceutical component, preferably second pharmaceutical excipient, more preferably alpha-tocopherol, in the pharmaceutical composition is within the range of 4.0 ± 2.5 wt.-%, more preferably 4.0 ± 2.0 wt.-%, still more preferably 4.0 ± 1.5 wt.-%, yet more preferably 4.0 ± 1.0 wt.-%, most preferably 4.0 ± 0.5 wt.-%, and in particular 4.0 ± 0.25 wt.-%, based on the total weight of the pharmaceutical composition.

In still another preferred embodiment, the content of the pharmaceutical component, preferably second pharmaceutical excipient, more preferably alpha-tocopherol, in the pharmaceutical composition is within the range of 3.0 ± 2.5 wt.-%, more preferably 3.0 ± 2.0 wt.-%, still more preferably 3.0 ± 1.5 wt.-%, yet more preferably 3.0 ± 1.0 wt.-%, most preferably 3.0 ± 0.5 wt.-%, and in particular 3.0 ± 0.25 wt.-%, based on the total weight of the pharmaceutical composition.

In yet another preferred embodiment, the content of the pharmaceutical component, preferably second pharmaceutical excipient, more preferably alpha-tocopherol, in the pharmaceutical composition is within the range of 2.0 ± 1.5 wt.-%, more preferably 2.0 ± 1.25 wt.-%, still more preferably 2.0 ± 1.0 wt.-%, yet more preferably 2.0 ± 0.75 wt.-%, most preferably 2.0 ± 0.5 wt.-%, and in particular 2.0 ± 0.25 wt.-%, based on the total weight of the pharmaceutical composition.

In another preferred embodiment, the content of the pharmaceutical component, preferably second pharmaceutical excipient, more preferably alpha-tocopherol, in the pharmaceutical composition is within the range of 1.0 ± 0.8 wt.-%, more preferably 1.0 ± 0.6 wt.-%, still more preferably 1.0 ± 0.5 wt.-%, yet more preferably 1.0 ± 0.4 wt.-%, most preferably 1.0 ± 0.3 wt.-%, and in particular 1.0 ± 0.2 wt.-%, based on the total weight of the pharmaceutical composition.

The pharmaceutical composition is powdery. A "*powder*" is typically defined as an assembly of dry particles dispersed in air. For the purpose of the specification, "*powdery*" preferably means that the pharmaceutical composition is a dry bulk solid consisting of a large number of fine or very fine particles that may flow freely when shaken or tilted, i.e. that are not cemented together. Preferably, the texture is smooth in touch. In a preferred embodiment, the powdery pharmaceutical composition is free-flowing.

In a preferred embodiment, the powdery pharmaceutical composition is a homogeneous mixture of the pharmaceutical excipient, preferably first pharmaceutical excipient, which is a polyalkylene glycol, more preferably polyethylene glycol, and the pharmaceutical component, preferably second pharmaceutical excipient, more preferably alpha-tocopherol and the optionally present third constituent. For the purpose of the specification, "*homogeneous*" preferably means that the standard deviation (SD) as a measure of blend uniformity (BU) of the powdery pharmaceutical composition is at most 5.0 SD%, more preferably at most 4.5 SD%, still more preferably at most 4.0 SD%, yet more preferably at most 3.5 SD%, most preferably at most 3.0 SD% and in particular at most 2.5 SD%. Methods to determine blend uniformity of powders are known to the skilled person. For example, a suitable method is near infrared spectroscopy (NIR), other methods are described in the Eur. Ph.

Preferably, the particle size (grain size) of the powdery pharmaceutical composition is comparatively fine.

In a preferred embodiment, at least 90 wt.-% of the powdery pharmaceutical composition passes sieve size 4.75 mm, 3.35 mm, 2.81 mm, 2.38 mm, or 2.00 mm; more preferably 1.68 mm, 1.40 mm, 1.20 mm, 1.00 mm, or 0.853 mm; still more preferably 0.710 mm, 0.599 mm, 0.500 mm, 0.422 mm, or 0.354 mm; yet more preferably 0.297 mm, 0.251 mm, 0.211 mm, 0.178 mm, or 0.152 mm; most preferably 0.125 mm, 0.104 mm, 0.089 mm, 0.075 mm, or 0.066 mm; and in particular 0.053 mm, 0.044 mm, or 0.037 mm.

In a particularly preferred embodiment, at least 90 wt.-% of the powdery pharmaceutical composition passes sieve size 1.00 mm, 0.95 mm, 0.90 mm or 0.85 mm.

In a preferred embodiment, the powdery pharmaceutical composition is free flowing and preferably, has an average particle size of at most 100 μm , more preferably at most 90 μm , still more preferably at most 80 μm , yet more preferably at most 70 μm , most preferably at most 60 μm and in particular at most 50 μm . Method to determine the average particle size of powders are known to the skilled person. A suitable method is for example laser light scattering or sieve analysis.

In a preferred embodiment, the powdery pharmaceutical composition is characterized by a d_{10} value of 17 ± 10 μm , more preferably 17 ± 8 μm , still more preferably 17 ± 6 μm , yet more preferably 17 ± 5 μm , even more preferably 17 ± 4 μm , most preferably 17 ± 3 μm and in particular 17 ± 2 μm .

In a preferred embodiment, the powdery pharmaceutical composition is characterized by a d 50 value of 80 ± 30 μm , more preferably 80 ± 25 μm , still more preferably 80 ± 20 μm , yet more preferably 80 ± 15 μm , even more preferably 80 ± 10 μm , most preferably 80 ± 8 μm and in particular 80 ± 6 μm .

In a preferred embodiment, the powdery pharmaceutical composition is characterized by a d 90 value of 190 ± 70 μm , more preferably 190 ± 60 μm , still more preferably 190 ± 50 μm , yet more preferably 190 ± 40 μm , even more preferably 190 ± 30 μm , most preferably 190 ± 20 μm and in particular 190 ± 10 μm .

When the method according to the invention involves preceding step (b) (see below), the powder which has exited the extruder is further grinded so that the particle size and particle size distribution of the final powdery pharmaceutical composition obtained in step (c) does not correspond to the particle size and particle size distribution of the powder that has exited the extruder in step (b).

Preferably, the method according to the invention additionally comprises the preceding step of

- (b) extruding a mixture of the pharmaceutical excipient, preferably first pharmaceutical excipient, which is a polyalkylene glycol, more preferably polyethylene glycol, and the pharmaceutical component, preferably second pharmaceutical excipient, more preferably alpha-tocopherol, in an extruder at a temperature profile allowing a liquid melt of the mixture to congeal in the extruder and to exit the extruder in form of a powder.

In optional step (b) of the method according to the invention, a mixture of the pharmaceutical excipient, preferably first pharmaceutical excipient, which is a polyalkylene glycol, more preferably polyethylene glycol, and the pharmaceutical component, preferably second pharmaceutical excipient, more preferably alpha-tocopherol, optionally together with a third constituent, preferably another pharmaceutical excipient, is extruded.

Typically, extrusion is regarded as a process used to create objects of a fixed cross-sectional profile. A material is pushed or drawn through a die of the desired cross-section. Two main advantages of this process over other manufacturing processes is its ability to create very complex cross-sections and work materials that are brittle, because the material only encounters compressive and shear stresses. It also forms finished parts with an excellent surface finish.

For the purpose of the invention, however, extrusion is preferably performed in an unusual fashion, namely so that the product, i.e. the extrudate, is a powder. This can be achieved by carefully adapting the extrusion parameters, e.g. screw geometry, extrusion temperature, screw speed, throughput, pressure and the like. Preferably, the extruder is not equipped with an extrusion die so that the pressure exerted to the mixture within the extruder is comparatively low. Preferably, the extruder is equipped neither with extrusion die nor with an adapter (e.g. Y-pipe).

For the purpose of the specification the term "*extrudate*" refers to any material exiting the extruder, e.g. an extruded strand or a powder.

Preferably, the pressure just ahead of the exit (outlet orifice) of the extruder does not exceed 25 bar or 20 bar, more preferably 15 bar or 10 bar, still more preferably 8.0 bar or 6.0 bar, yet more preferably 5.0 bar or 4.0 bar, most preferably 3.0 bar or 2.0 bar, and in particular 1.5 bar or 1.0 bar. The pressure just ahead of the exit of the extruder can be measured by conventional means and many commercialized extruders are already equipped with a respective manometer at the proper position. In a preferred embodiment, however, no pressure can be measured at all and the extrusion is performed under conditions imparting as minimal pressure as possible, preferably at most 1.0 bar, more preferably at most 0.8 bar, still more preferably at most 0.6 bar, yet more preferably at most 0.4 bar, most preferably at most 0.2 bar, and in particular at most 0.1 bar.

Preferably, the design of the screw elements and the extrusion conditions are adjusted to ensure that the extruded mass, in particular after its congealing, is not compacted or, if compaction cannot be completely avoided, the degree of compaction is as low as possible. A skilled person knows how to adjust such mild extrusion conditions, e.g. by regulating the screw speed.

Preferably, the extruder has an inner diameter of 10 mm to 100 mm, more preferably 12 mm to 90 mm, still more preferably 14 mm to 80 mm, most preferably 15 mm to 70 mm and in particular 15 mm to 60 mm. In a preferred embodiment, the extruder has an inner diameter of 18 ± 10 mm, more preferably 18 ± 8 mm, still more preferably 18 ± 6 mm, yet more preferably 18 ± 4 mm, most preferably 18 ± 2 mm, and in particular 18 ± 1 mm. In another preferred embodiment, the extruder has an inner diameter of 27 ± 10 mm, more preferably 27 ± 8 mm, still more preferably 27 ± 6 mm, yet more preferably 27 ± 4 mm, most preferably 27 ± 2 mm, and in particular 27 ± 1 mm. In yet another preferred embodiment, the extruder has an inner diameter of 50 ± 10 mm, more preferably 50 ± 8 mm, still more preferably 50 ± 6 mm, yet more preferably 50 ± 4 mm, most preferably 50 ± 2 mm, and in particular 50 ± 1 mm.

Preferably, the extruder has a length of 30 cm to 250 cm, more preferably 40 cm to 240 cm, still more preferably 50 cm to 230 cm, most preferably 60 cm to 220 cm and in particular 70 cm to 210 cm.

In a preferred embodiment, the ratio of extruder length in mm and extruder diameter in mm is within the range of 25 ± 15 , more preferably 25 ± 10 , still more preferably 25 ± 8 , yet more preferably 25 ± 6 , most preferably 25 ± 4 , and in particular 25 ± 2 .

In another preferred embodiment, the ratio of extruder length in mm and extruder diameter in mm is within the range of 30 ± 15 , more preferably 30 ± 10 , still more preferably 30 ± 8 , yet more preferably 30 ± 6 , most preferably 30 ± 4 , and in particular 30 ± 2 .

In still another preferred embodiment, the ratio of extruder length in mm and extruder diameter in mm is within the range of 40 ± 15 , more preferably 40 ± 10 , still more preferably 40 ± 8 , yet more preferably 40 ± 6 , most preferably 40 ± 4 , and in particular 40 ± 2 .

Preferably, the screw geometry is adapted so that the congealed material within the extruder is exerted a sufficient impact in order to yield a powdery pharmaceutical composition exiting the extruder. Thus, the

extrusion parameters of the method according to the invention are preferably in contrast to the extrusion parameters of conventional methods where it is generally desired to manufacture a non-powdery extrusion strand having a smooth and excellent surface finish.

Typically, the screw geometry may be modified by varying the screw elements from which the screw is assembled. Conventional screw extruders are typically equipped with an extrusion axis adapted to carry a number of screw elements. Depending upon the extruder design and the design of the individual screw elements, the extrusion axis may carry about 10 to about 50 or more identical or different screw elements. In twin screw extruders (counter-rotating or co-rotating) the design of the individual screw elements must be such that contra-rotation or co-rotation about the two parallel extrusion axes is possible.

Preferably, each screw is equipped with (assembled from) at least 5, more preferably at least 10, most preferably 15 and in particular at least 20 identical or different screw elements.

The manufactures of screw extruders usually commercialize quite a number of different extrusion elements that can be employed in their extruders depending upon the individual demands of the extrusion technique. Examples of commercially available screw elements include screw transport elements, kneading elements, blank elements and the like. A skilled person is aware of typical screw elements.

Each screw element serves a particular purpose and a skilled person knows what screw element to choose in order to serve a particular purpose.

For example, a main purpose of screw transport elements is to effect transportation of the extruded material within the extruder from the inlet to the outlet and optionally, to impart the necessary pressure in front of the extrusion die. Screw transport elements can typically be divided in sub-types differing in their number of windings (threads) per standard length. For example, a screw transport element having two windings (threads) along a length of e.g. 100 mm differs from a screw transport element having three windings (threads) along the same length.

In contrast, a main purpose of kneading elements is to effect a vigorous mixing of the constituents of the extruded material without any substantial transportation. Kneading elements can typically also be divided in sub-types differing in their design and relative angle of kneaders. For example, a kneading element having two consecutive kneaders that are off-set 90° about the extrusion axis differs from a kneading element having two consecutive kneaders that are off-set 60° about the extrusion axis.

The design of the extrusion screws in the method according to the invention is not particularly limited. Preferably, however, each extrusion screw is equipped with (assembled from) a plurality of screw elements. Preferably, each extrusion screw comprises at least two different types of screw elements, more preferably at least three different types, still more preferably at least four different types, whereas every type of screw element may be represented by a single or a plurality of screw elements (i.e., of the same type). Screw elements of the

same type may be located next to one another or in alternating, regular or irregular order and sequence with screw elements of other type(s), respectively.

In a preferred embodiment, each extrusion screw comprises at least having one screw element with a pitch (axial distance for one revolution of screw flight expressed as ratio to screw diameter (D)) within the range of 1.25 ± 1.0 D, more preferably 1.25 ± 0.75 D, still more preferably 0.5 ± 0.4 D, 1.0 ± 0.5 D or 1.75 ± 0.5 D, yet more preferably 0.5 ± 0.3 D, 1.0 ± 0.4 D or 1.75 ± 0.4 D, and most preferably 0.5 ± 0.25 D, 1.0 ± 0.25 D or 1.75 ± 0.25 D.

In a preferred embodiment of the method according to the invention, each extrusion screw is equipped with (assembled from) at least two different types of screw transport elements differing, optionally *inter alia*, in their number of windings (threads) per standard length, whereas in at least a portion of the extrusion screw the type of screw transport elements having the lower number of windings (threads) is located upstream with respect to the screw transport elements having the higher number of windings (threads).

In another preferred embodiment of the method according to the invention, each extrusion screw is equipped with (assembled from) at least two different types of screw transport elements differing, optionally *inter alia*, in their chamber volume per standard length, whereas in at least a portion of the extrusion screw the type of screw transport elements having the smaller chamber volume is located upstream with respect to the screw transport elements having the larger chamber volume. For the purpose of the specification, the chamber volume is to be regarded as the space between the screw elements and the extruder wall, i.e. the inner hollow space that guides the extruded mass through the extruder.

Preferably, each extrusion screw is equipped with (assembled from) at least two different types of screw transport elements (a) and (b), whereas each type of screw transport element is represented by one or more individuals. In a preferred embodiment, the number of windings (threads) per standard length of elements (b) exceeds the number of windings (threads) of elements (a). In another preferred embodiment, the chamber volume per standard length of elements (b) exceeds the chamber volume of elements (a). In still another preferred embodiment, the pitch of elements (b) exceeds the pitch of elements (a). In yet another preferred embodiment, the conveying speed of elements (b) exceeds the conveying speed of elements (a). In another preferred embodiment, the volumetric displacement of elements (b) exceeds the volumetric displacement of elements (a). Preferably, a sequence of four consecutive elements that are independently chosen from screw transport elements of type (a) and screw transport elements of type (b) forms a portion of the extrusion screw.

In a preferred embodiment, the length of the extrusion screw corresponds to the length of the extruder so that the entire extrusion screw is mounted by the extruder block. In another preferred embodiment the length of the extrusion screw is such that it protrudes from the extruder block, typically by several cm, e.g. about 2.5, 5 or 7.5 cm.

The method according to the invention comprises the extrusion of a mixture of the pharmaceutical excipient and the pharmaceutical component in an extruder at a temperature profile allowing a liquid melt of the mixture to congeal in the extruder and to exit the extruder in form of a powder. Thus, when the extruder is a screw extruder,

its extrusion axis or axes, respectively, comprise an upstream portion that serves the purpose of extruding the not yet congealed mixture and a downstream portion that serves the purpose of extruding the congealed mixture.

In a preferred embodiment of the method according to the invention, the screw elements forming said downstream portion of the extrusion screw comprise screw elements imparting a relatively high mechanical impact on the congealed mixture in order to yield a powdery pharmaceutical composition. Thus, as far as the design of the extrusion elements in this downstream portion is concerned, extrusion conditions are comparatively harsh.

Preferably, parallel to the temperature profile in the extruder that allows the liquid melt of the mixture to congeal in the extruder and to exit the extruder in form of a powder, there is an extrusion screw profile increasing the mechanical impact exerted by the extrusion elements further supporting that the extruded material exits the extruder in form of a powder.

The extruder is preferably equipped with at least two heating elements that can be adjusted to different temperatures independently. Preferably, the extruder comprises at least three, more preferably at least four, still more preferably at least five, yet more preferably at least six, most preferably at least seven and in particular at least eight of such heating elements adjustable to different temperatures independently.

These heating elements allow adjusting the desired temperature profile within the extruder.

Preferably, the extruder is equipped with at least four consecutive heating elements H_1 , H_2 , H_3 and H_4 which are set at the corresponding temperatures T_1 , T_2 , T_3 and T_4 , respectively. H_1 is located upstream with respect to H_2 to H_4 , H_2 is located upstream with respect to H_3 and H_4 and H_3 is located upstream with respect to H_4 . Preferred embodiments of the relationship T_1 to T_4 are summarized here below: $T_1 = T_2 = T_3 = T_4$; $T_1 > T_2 = T_3 = T_4$; $T_1 = T_2 > T_3 = T_4$; $T_1 = T_2 = T_3 > T_4$; $T_1 < T_2 = T_3 = T_4$; $T_1 = T_2 < T_3 = T_4$; $T_1 = T_2 = T_3 < T_4$; $T_1 > T_2 > T_3 = T_4$; $T_1 > T_2 = T_3 > T_4$; $T_1 = T_2 > T_3 > T_4$; $T_1 < T_2 < T_3 = T_4$; $T_1 < T_2 = T_3 < T_4$; $T_1 = T_2 < T_3 < T_4$; $T_1 > T_2 > T_3 > T_4$; or $T_1 < T_2 < T_3 < T_4$.

Preferably, in step (b) of the method according to the invention, extrusion is performed by means of a screw extruder, preferably a twin screw extruder having contra-rotating or co-rotating screws. It is also possible to perform extrusion by means of a planetary gear extruder (planetary roller extruder). Suitable extruders are known to the skilled person and commercially available. A suitable twin screw extruder is for example commercialized by Leistritz, type ZSE 18PH 40 D.

A skilled person recognizes, however, that the gist of the method according to the invention can also be realized by equivalent means typically employed in order to process viscous or highly viscous masses, wherein processing typically involves heating, mixing, cooling, shearing, and/or the like. Exemplified means include roll coolers or barrel coolers, cool belts, granulators, coaters, etc.

In the course of the extrusion process, the extruded material is typically transported along the longitudinal axis of the extruder from the inlet (feeding point) to the outlet (exit). Material movement is typically effected by the rotation of the screws and by the new starting material entering the inlet of the extruder. For the purpose of the specification, two locations along the longitudinal axis of the extruder may be qualified as "upstream" and "downstream" with respect to the direction of extrusion. The location upstream is closer to the inlet of the extruder than the location downstream and vice versa, the location downstream is closer to the exit of the extruder than the location upstream.

The temperature profile within the extruder is adjusted to ensure that a liquid melt of the mixture is allowed to congeal in the extruder before it exits the extruder. Thus, according to the method of the invention, at least at one upstream location within the extruder the pharmaceutical excipient, preferably first pharmaceutical excipient, which is a polyalkylene glycol, more preferably polyethylene glycol, and the pharmaceutical component, preferably second pharmaceutical excipient, more preferably alpha-tocopherol, optionally together with a third constituent, preferably another pharmaceutical excipient, are present in the molten state. Melting is typically achieved by adjusting the temperature profile so that at said upstream location the temperature of the mixture (extruded material) is sufficiently high.

This does not necessarily mean that the temperature of the mixture (extruded material) in the extruder at said one upstream location must be above the melting points/ranges of both, the pharmaceutical excipient, preferably first pharmaceutical excipient, which is a polyalkylene glycol, more preferably polyethylene glycol, and the pharmaceutical component, preferably second pharmaceutical excipient, more preferably alpha-tocopherol, and the optionally present third constituent, preferably another pharmaceutical excipient. Depending upon the nature and the amount of the excipients it may be sufficient that the temperature is above the melting point/range of just one of the two or three ingredients so that it forms a liquid melt in which the other is (are) dissolved.

Preferably, however, the temperature of the mixture (extruded material) in the extruder at said one upstream location is above the melting points/ranges of both, the pharmaceutical excipient, preferably first pharmaceutical excipient, which is a polyalkylene glycol, more preferably polyethylene glycol, and the pharmaceutical component, preferably second pharmaceutical excipient, more preferably alpha-tocopherol, and the optionally present third constituent.

The liquid melt may be formed, i.e. generated, within the extruder by initially heating the mixture (extruded material) having a temperature below its melting point/range to a temperature above its melting point/range so that a liquid melt is formed. Alternatively, however, the liquid melt may already be fed into the extruder, i.e. the liquid melt of the pharmaceutical excipient, preferably first pharmaceutical excipient, which is a polyalkylene glycol, more preferably polyethylene glycol, and the pharmaceutical component, preferably second pharmaceutical excipient, more preferably alpha-tocopherol, optionally together with a third constituent, preferably another pharmaceutical excipient, may be formed outside the extruder and then be supplied to the inlet of the extruder so that the starting material enters the extruder already in molten liquid state. Preferably, said liquid state is maintained for a while in the course of the extrusion process.

In the course of the extrusion process and as a consequence of the temperature profile, the liquid melt is allowed to congeal in the extruder. The liquid melt congeals, i.e. solidifies to a solid material by cooling. Thus, according to the method of the invention, at least at one downstream location within the extruder the pharmaceutical excipient, preferably first pharmaceutical excipient, which is a polyalkylene glycol, more preferably polyethylene glycol, and the pharmaceutical component, preferably second pharmaceutical excipient, more preferably alpha-tocopherol, optionally together with a third constituent, preferably another pharmaceutical excipient, are present in the congealed, i.e. solidified state. Congealing is typically achieved by adjusting the temperature profile so that at said downstream location the temperature of the mixture (extruded material) is sufficiently low.

This does not necessarily mean that the temperature of the mixture (extruded material) in the extruder at said one downstream location must be below the melting points/ranges of both, the pharmaceutical excipient, preferably first pharmaceutical excipient, which is a polyalkylene glycol, more preferably polyethylene glycol, and the pharmaceutical component, preferably second pharmaceutical excipient, more preferably alpha-tocopherol, and the optionally present third constituent. Depending upon the nature and the amount of the excipients it may be sufficient that the temperature is below the melting point/range of just one of the two ingredients so that it solidifies with the other ingredient being dissolved in it.

Preferably, when the congealed mixture exits the extruder, it has a temperature of at least 5 °C, preferably at least 10 °C, more preferably at least 15 °C, still more preferably at least 20 °C, yet more preferably at least 25 °C, most preferably at least 30 °C and in particular at least 35 °C, below the melting point/temperature of the pharmaceutical excipient, preferably first pharmaceutical excipient, which is a polyalkylene glycol, more preferably polyethylene glycol, and/or the pharmaceutical component, preferably second pharmaceutical excipient, more preferably alpha-tocopherol and/or the optionally present third constituent.

In a preferred embodiment of the method according to the invention, in step (b) the temperature profile comprises a temperature gradient of temperature T_1 to temperature T_2 , where $T_1 > T_2$ and where

- T_1 is above the melting point/range of the pharmaceutical excipient, preferably first pharmaceutical excipient, which is a polyalkylene glycol, more preferably polyethylene glycol, and/or the pharmaceutical component, preferably second pharmaceutical excipient, more preferably alpha-tocopherol and/or the optionally present third constituent; and/or
- T_2 is below the melting point/range of the pharmaceutical excipient, preferably first pharmaceutical excipient, which is a polyalkylene glycol, more preferably polyethylene glycol and/or pharmaceutical component, preferably second pharmaceutical excipient, more preferably alpha-tocopherol, and/or the optionally present third constituent.

T_1 and T_2 are preferably adjusted by means of the heating elements of the extruder. Preferably T_1 and T_2 correspond to the temperatures at which the heating elements are heated.

Preferably,

- T_1 is within the range of from 25 °C to 115 °C, or 30 °C to 110 °C, more preferably 35 °C to 105 °C, or 40 °C to 100 °C, still more preferably 45 °C to 95 °C, or 50 °C to 90 °C, yet more preferably 55 °C to 85 °C, most preferably 60 °C to 80 °C, and in particular 65 °C to 75 °C; and/or
- T_2 is within the range of from -20 °C to 50 °C, more preferably -10 °C to 40 °C, still more preferably -5 °C to 35 °C, yet more preferably 0 °C to 30 °C, most preferably 5 °C to 25 °C, and in particular 10 °C to 20 °C.

In a preferred embodiment, T_1 is at least 0.5 °C or at least 1.0 °C, more preferably at least 1.5 °C or at least 2.0 °C, still more preferably at least 2.5 °C or at least 3.0 °C, yet more preferably at least 3.5 °C or at least 4.0 °C, most preferably at least 4.5 °C or at least 5.0 °C, and in particular at least 5.5 °C or at least 6.0 °C above the melting point of the pharmaceutical excipient, preferably first pharmaceutical excipient, which is a polyalkylene glycol, more preferably polyethylene glycol, and/or the pharmaceutical component, preferably second pharmaceutical excipient, more preferably alpha-tocopherol and/or the optionally present third constituent.

In another preferred embodiment, T_1 is at least 5 °C or at least 10 °C, more preferably at least 15 °C or at least 20 °C, still more preferably at least 25 °C or at least 30 °C, yet more preferably at least 35 °C or at least 40 °C, most preferably at least 45 °C or at least 50 °C, and in particular at least 55 °C or at least 60 °C above the melting point of the pharmaceutical excipient, preferably first pharmaceutical excipient, which is a polyalkylene glycol, more preferably polyethylene glycol, and/or the pharmaceutical component, preferably second pharmaceutical excipient, more preferably alpha-tocopherol and/or the optionally present third constituent.

In a preferred embodiment, T_2 is at least 1.0 °C or at least 2.0 °C, more preferably at least 3.0 °C or at least 4.0 °C, still more preferably at least 5.0 °C or at least 6.0 °C, yet more preferably at least 7.0 °C or at least 8.0 °C, most preferably at least 9.0 °C or at least 10 °C, and in particular at least 11 °C or at least 12 °C above the melting point of the pharmaceutical excipient, preferably first pharmaceutical excipient, which is a polyalkylene glycol, more preferably polyethylene glycol, and/or the pharmaceutical component, preferably second pharmaceutical excipient, more preferably alpha-tocopherol and/or the optionally present third constituent.

In another preferred embodiment, T_2 is at least 2.5 °C or at least 5.0 °C, more preferably at least 7.5 °C or at least 10 °C, still more preferably at least 12.5 °C or at least 15 °C, yet more preferably at least 17.5 °C or at least 20 °C, most preferably at least 25 °C or at least 30 °C, and in particular at least 35 °C or at least 40 °C below the melting point of the pharmaceutical excipient, preferably first pharmaceutical excipient, which is a polyalkylene glycol, more preferably polyethylene glycol, and/or the pharmaceutical component, preferably second pharmaceutical excipient, more preferably alpha-tocopherol and/or the optionally present third constituent.

In a preferred embodiment, the pharmaceutical excipient, preferably first pharmaceutical excipient, which is a polyalkylene glycol, more preferably polyethylene glycol, and the pharmaceutical component, preferably second pharmaceutical excipient, more preferably alpha-tocopherol, and the optionally present third constituent, are fed into the extruder in form of a liquid melt having a sufficiently high temperature, preferably within the range of $T_1 \pm 10$ °C, more preferably $T_1 \pm 8.0$ °C, still more preferably $T_1 \pm 6.0$ °C, yet more preferably $T_1 \pm 4.0$ °C, most preferably $T_1 \pm 2.0$ °C, and in particular $T_1 \pm 1.0$ °C.

The congealed mixture then exits the extruder in form of a powder. This means that in the extruder the liquid melt does not only congeal into a solid material but is further comminuted into a powder, at least to a certain extent.

In a preferred embodiment, the method according to the invention comprising steps (b) and (c) comprises the preceding step of

- (a) mixing the pharmaceutical excipient, preferably first pharmaceutical excipient, which is a polyalkylene glycol, more preferably polyethylene glycol, with the pharmaceutical component, preferably second pharmaceutical excipient, more preferably alpha-tocopherol, and the optionally present third constituent, outside the extruder and then feeding the resultant mixture into the extruder; or

feeding the pharmaceutical excipient, preferably first pharmaceutical excipient, which is a polyalkylene glycol, more preferably polyethylene glycol, and the pharmaceutical component, preferably second pharmaceutical excipient, more preferably alpha-tocopherol, and the optionally present third constituent, into the extruder at different feeding points, where the feeding point for the pharmaceutical excipient, preferably first pharmaceutical excipient, which is a polyalkylene glycol, more preferably polyethylene glycol, is located upstream with respect to the feeding point for the pharmaceutical component, preferably second pharmaceutical excipient, more preferably alpha-tocopherol, or vice versa.

Step (a) precedes step (b), i.e. step (b) is performed after step (a) has been completed.

Preferably, in step (a) the pharmaceutical component, preferably second pharmaceutical excipient, more preferably alpha-tocopherol, is dissolved in the molten pharmaceutical excipient, preferably first pharmaceutical excipient, which is a polyalkylene glycol, more preferably polyethylene glycol and/or the optionally present third constituent, or vice versa.

In another preferred embodiment, the method according to the invention comprises the subsequent step of

- (d) grading the powder.

Typically, the method according to the invention does not comprise any spray congealing or spray drying step. It has been surprisingly found that by the method according to the invention laborious steps that require sophisticated equipment and process control can be omitted without deteriorating product quality. Thus, in a particularly preferred embodiment, besides extrusion, the method according to the invention does not comprise any separate grinding, spray congealing or spray drying steps.

The method according to the invention can be performed batch-wise or continuously.

Preferably, the method is performed continuously and a mixture of the pharmaceutical excipient, preferably first pharmaceutical excipient, which is a polyalkylene glycol, more preferably polyethylene glycol, and the pharmaceutical component, preferably second pharmaceutical excipient, more preferably alpha-tocopherol, and

the optionally present third constituent, is automatically dosed into the extruder, preferably in form of a melt. First preliminary tests revealed that continuous dosing can be realized by standard equipment.

A further aspect of the invention relates to a method for the manufacture of a pharmaceutical dosage form comprising the method according to the invention as described above. Preferably, the pharmaceutical dosage form has a breaking strength of at least 400 N, more preferably at least 500 N, still more preferably at least 600 N, yet more preferably at least 700 N, most preferably at least 800 N and in particular at least 900 N. Dosage forms exhibiting such a high breaking strength are known from the prior art. In this regard it can be referred to e.g. WO 2005/016313, WO 2005/016314, WO 2005/063214, WO 2005/102286, WO 2006/002883, WO 2006/002884, WO 2006/002886, WO 2006/082097, WO 2006/082099, WO 2008/107149 and WO2009/092601.

Preferably, the method for the manufacture of a pharmaceutical dosage form comprises the step of formulating the powdery pharmaceutical composition comprising the first pharmaceutical excipient and the second pharmaceutical excipient and the optionally present third constituent, as described above together with

- a pharmacologically active substance, preferably an opioid, and/or
- a high molecular weight polyalkylene oxide, preferably polyethylene oxide, preferably having a weight average molecular weight of at least 200,000 g/mol, more preferably at least 500,000 g/mol, still more preferably at least 750,000 g/mol, yet more preferably at least 1,000,000 g/mol and in particular within the range of from 1,000,000 g/mol to 10,000,000 g/mol; and/or
- a cellulose ether, preferably hydroxypropylmethyl cellulose or hydroxypropylcellulose.

Thus, in the method for the manufacture of a pharmaceutical dosage form according to the invention, the powdery pharmaceutical composition is preferably employed as intermediate.

Preferably, the powdery pharmaceutical composition does not substantially alter the release of the pharmacologically active substance from the pharmaceutical dosage form, i.e. the *in vitro* release profile of the pharmaceutical dosage form is not substantially influenced by the presence of the powdery pharmaceutical composition. In this regard, "substantially" preferably means 2%, more preferably 1%, i.e. the presence of the powdery pharmaceutical composition preferably does not alter the *in vitro* release profile by more than 2% compared to a dosage form not containing the powdery pharmaceutical composition.

In a preferred embodiment, the total amount of the (first) pharmaceutical excipient contained in the pharmaceutical dosage form originates from the powdery pharmaceutical composition, i.e. preferably no further (first) pharmaceutical excipient is added in the course of manufacturing the pharmaceutical dosage form from the powdery pharmaceutical composition.

In a preferred embodiment, the pharmaceutical dosage form contains the pharmaceutical composition in such an amount that the content of the (first) pharmaceutical excipient is within the range of from 1.0 to 20 wt.-%, more preferably 2.0 to 18 wt.-%, still more preferably 4.0 to 16 wt.-%, yet more preferably 6.0 to 14 wt.-%, most

preferably 7.0 to 13 wt.-%, and in particular 8.0 to 12 wt.-%, relative to the total weight of the pharmaceutical dosage form.

The invention is further illustrated by the following examples which, however, are not to be construed as limiting its scope.

Example 1 - extrusion - manufacture of pre-blend:

alpha-tocopherol-polyethylene glycol 6000 pre-blends were manufactured by means of a twin-screw extruder, type Leistritz ZSE27.

All trials were carried out with a screw configuration without kneading elements.

Only trials of 4% alpha-tocopherol concentration with high screw speed (trial 10 and trial 11) were tested with another screw configuration, because with a lower screw speed the extruder throughput was too low. These trials are identified with „bis“.

Factors	Level -	Level 0	Level +
alpha-tocopherol content [wt.-%]	4	14	14
Feed rate [kg/h]	2	4	6
Screw speed [rpm]	30	80	130

In a 2³ full factorial design, the following three parameters were varied: alpha-tocopherol content, feed rate, and screw speed. The experimental design thus consisted of 8 runs plus three center point runs for a total of 11 runs. A total of 4 kg of alpha-tocopherol / PEG blend were manufactured in each run.

The experimental design of trials 1 to 11 is summarized in the table here below:

trial	batch	alpha-tocopherol concentration [%]	feed rate [kg/h]	speed [rpm]
1	1	14%	4	80
2			2	130
3			6	30
4			4	80
5			6	130
6			2	30
7			4	80
8	2	4%	6	30
9			2	30
10			2	130
11			6	130

No significant differences among the trials could be observed. A coarse and waxy material was obtained that was difficult to characterize.

The following particle size distribution (PSD) was determined after 500 µm screening:

alpha-tocopherol /PEG 4%	Yield after screening (<500 µm %w)
Trial 8	65.0
Trial 8 (repeated)	67.6
Trial 9	34.0
Trial 10	30.9
Trial 10bis	34.0
Trial 11	36.0
Trial 11bis	32.7

The particle size distribution (PSD) comparison of alpha-tocopherol / PEG with other excipients is also shown in Figure 1.

Trials 8 and 9 (alpha-tocopherol/PEG 4%) were repeated. alpha-tocopherol/PEG 4% trials led to fine particle size, especially in Trial 8 and in Trial 8 (repeated). Only a few coarse particles were visible.

Trial 8 showed a finer particle size than the other trials. 65 wt.-% of particle had an average diameter of less than 500 µm. Trial 8 was repeated at the end of the design of experiments confirming the results. The yield was too low for industrial application. Under these conditions, it was not possible to achieve acceptable powder state at concentration of 14 wt.-% of alpha-tocopherol.

Subsequently, cryo-milling equipments of two manufacturers were tested:

- Hosokawa – Alpine (Germany) (Example 2)
- Nuova Guseo (Italy) (Example 3)

Example 2 - cryo-milling of pre-blend - Hosokawa – Alpine:

The pre-blends of Example 1 comprising alpha-tocopherol/PEG were subsequently subjected to cry-milling in order to obtain fine powders pharmaceutical compositions.

Pre-blends:

alpha-tocopherol /PEG 6000 14%	14% material is coarse and waxy, consisting of aggregates of different size
alpha-tocopherol /PEG 6000 4%	4% material consists of fine particle size, with few coarse particles visible

Milling trials were performed on 100-UPZ (Hosokawa Alpine) varying the follows process parameters: rotation speed of the plate beater (rpm), temperature, feed rate (kg/h). Only two trials of 14% concentration (trial 9 and 10) were performed with 100 AFG Jet-Mill Micronizer (Hosokawa Alpine).

The material was charged in a screw feeding device. The material fell in a liquid nitrogen bath, and was cooled down to temperatures around -120°C. A whirling screw system transported the brittle material under liquid nitrogen to the grinding system, equipped with a plate rotating beater and a 0.5 mm sieve.

Milling in Hosokawa Alpine: Trials performed on alpha-tocopherol/PEG 4%:

trial	machine	apparatus	feed rate (kg/h)	temperature (from - to)	alpha-tocopherol content (batch)
1	100UPZ 14000 RPM	- liquid nitrogen; plate beater; sieve 0.5mm	7.5	-60°C/-70°C	4%
2	100UPZ 18000 RPM	- liquid nitrogen; plate beater; sieve 0.5mm	5.0	-100°C/-120°C	4%
3	100UPZ 18000 RPM	- liquid nitrogen; plate beater; sieve 0.5mm	12	-57°C/-62°C	4%
4	100UPZ 18000 RPM	- liquid nitrogen; plate beater; sieve 0.5mm	20	-70°C/-80°C	4%
5	100UPZ 18000 RPM	- liquid nitrogen; plate beater; sieve 0.5mm	30	-30°C/-40°C	4%

The better trial in terms of feed rate was trial 5, performed on alpha-tocopherol/PEG 4%. This batch, produced in the preliminary design of experiments, had a less fine particle size compared to the batches of trials 1 to 4, but better flow property. There were no significant differences among electric current consumption of the system before and after the addition of materials: this indicates that the system can work without trouble even at high feed rate. The standard screw feeding device allows the loading of material. There was no deposit in the milling tools.

Milling in Hosokawa Alpine: Trials performed on alpha-tocopherol/PEG 14%:

Trial	Machine	Apparatus	Feed rate (Kg/h)	Temperature (from - to)	alpha-tocopherol content (batch)
6	100UPZ 14000 RPM	- liquid nitrogen; plate beater; sieve 0.5mm	13.6	-10°C/-25°C	14%
7	100UPZ 14000 RPM	- liquid nitrogen; plate beater; sieve 0.5mm	20	-10°C/-25°C	14%
8	100UPZ 14000 RPM	- liquid nitrogen; plate beater; sieve 0.5mm	17	-10°C/-25°C	14%
9	100AFG 1000	nozzles 1.9 mm 6bar	1.4	n/a	14%
10	100AFG 2000	nozzles 1.9 mm 6bar	0.4	n/a	14%

Severe dosing problems on the screw feeder were observed, due the material dimension and the low melting temperature. Feeding was possible with a vibrating feeding system. There were no significant differences among electric current consumption of the system before and after the addition of materials: this indicates that the system can work without trouble even at high feed rate. There was no deposit in the milling tools.

After milling, a fine white powder was obtained.

Flowability test failed for nozzles 6 mm and 10 mm with stirrer on or off, as the reference (commercial spray-congealed blend). Bulk density was comparable among the trials and with the reference (commercial spray-congealed blend). Tapped density was not considered a significant parameter, due the clogging that happens for the reference material. DSC profiles of material before and after milling were similar and there were no significant differences with the DSC profile of the reference (commercial spray-congealed blend).

The bulk densities are displayed in the table here below:

alpha-tocopherol/PEG 4%	content of alpha-tocopherol	Density
		Bulk g/ml
Trial 1	4 wt.-%	0.502
Trial 2		0.511
Trial 3		0.494
Trial 4		0.475
Trial 5		0.486
Trial 6	14 wt.-%	0.440
Trial 7		0.439
Trial 8		0.433
Trial 9		0.505
Trial 10		0.404
alpha-tocopherol/PEG 14% commercial blend		0.438

The particle size distribution (PSD) of Trials 6, 7 and 8 in comparison to that of the commercial alpha-tocopherol/PEG 6000 blend is shown in Figure 2.

alpha-tocopherol/PEG 14%	d 10 (μm)	d 50 (μm)	d 90 (μm)
Trial 6	15.1	72.8	167.0
Trial 7	13.0	70.2	162.7
Trial 8	16.41	89.7	209.2
alpha-tocopherol/PEG 14% commercial blend	18.86	80.49	220.2

A DSC of the commercial alpha-tocopherol/PEG 6000 blend is shown in Figure 3.

DSC of alpha-tocopherol/PEG 4% material after cryo-milling is shown in Figure 4.

DSC of alpha-tocopherol/PEG 14% material after cryo-milling is shown in Figure 5.

Example 3 - cryo-milling of pre-blend - Nuova Guseo:

The pre-blended material of Example 1 was charged in a throttle feeding device. The material was embrittled in contact with liquid nitrogen. The cooled material fell into the grinding system, equipped with a rotating plate beater and a 0.5 and 0.8 mm sieve.

Milling trials were performed varying the follows process parameters: rotation speed (rpm), net size, and temperature. The first trial (trial 1) was performed with a screw feeding device, with severe dosing problems, due the material dimension and the low melting temperature. The parameters used in the other trials are summarized in the table:

Trial	Rpm	Net size (mm)	Temperature (°C)
2	5000	0.8	-60
3	6000	0.8	-60
4	7000	0.8	-58
5	5000	0.5	-60
6	6000	0.5	-54
7	7000	0.5	-50
8	7000	0.5	-30
9	7000	0.5	-15

After milling, a fine white-yellow powder was obtained. Flowability test failed for nozzles 6 mm and 10 mm with stirrer on or off, as for the reference (commercial spray-congealed blend). Bulk densities were similar among the trials and compared to the reference (commercial spray-congealed blend). Tapped density was not considered a significant parameter, due the clogging of the material, as well as for the reference (commercial spray-congealed blend):

alpha-tocopherol/PEG 14%	Density
	Bulk g/ml
Trial 1	0.500
Trial 2	0.518
Trial 3	0.501
Trial 4	0.491
Trial 5	0.498
Trial 6	0.485
Trial 7	0.466
Trial 8	0.466
Trial 9	0.478
alpha-tocopherol/PEG 14% commercial blend	0.438

The influence of the temperature on the particle size distribution (PSD) is shown in Figure 6.

	d 10 (μm)	d 50 (μm)	d 90 (μm)
alpha-tocopherol/PEG 14% Trial 7	15.2	86.1	174.4
alpha-tocopherol/PEG 14% Trial 8	19.6	96.5	195.0
alpha-tocopherol/PEG 14% Trial 9	21.1	109.0	251.2

The influence of the cryo-milling technology on the particle size distribution (PSD) is shown in Figure 7.

	d 10 (μm)	d 50 (μm)	d 90 (μm)
alpha-tocopherol/PEG 14% commercial blend	18.9	80.5	220.2
alpha-tocopherol/PEG 14% Trial 7 Hosokawa	19.6	96.5	195.0
alpha-tocopherol/PEG 14% Trial 7 Nuova Guseo	15.2	86.1	174.4

Relative alpha-tocopherol content within blend before and after cryo-milling:

Mill manufacturer	alpha-tocopherol content	Relative alpha-tocopherol content Before milling	Relative alpha-tocopherol content After milling
Hosokawa	4%	93.7 %	93.5 - 95.5%
	14%	111.1 %	111.2 - 111.3%

Nuova Guseo	14%	98.5 %	95.3 – 97.4%
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As can be concluded from the above data, with cryo-milling process the alpha-tocopherol did not degrade.

Example 4 - alpha-tocopherol / PEG blending trials:

4.1 The cryo-milled blends obtained in Examples 2 and 3, respectively, were blended with other ingredients of a drug product formulation. Content uniformity of distribution of alpha-tocopherol within the blend as well as physical characteristics (i.e. flowability, density, particle size distribution (PSD)) were investigated.

Experimental design

3 blending trials (same qualitative and quantitative composition) with:

Reference 14% alpha-tocopherol / PEG commercial blend

14% alpha-tocopherol / PEG material (cryo-milled by means of Hosokawa, Example 2)

14% alpha-tocopherol / PEG material (cryo-milled by means of Nuova Guseo, Example 3)

The total batch size was 48 kg.

The following blends were prepared:

	25mg	50mg	100mg	100mg BIS	150mg	200mg	250mg
API [mg/tbl]	29.12 7.28%	58.24 14.56%	116.48 29.12%	116.48 29.12%	174.72 38.83%	232.96 35.84%	291.20 41.60%
PEO [mg/tbl]	225.16 56.29%	225.16 56.29%	187.12 46.78%	179.32 44.83%	166.83 37.07%	260.39 40.06%	245.00 35.00%
HPMC [mg/tbl]	85.12 21.28%	56.00 14.00%	56.00 14.00%	56.00 14.00%	63.00 14.00%	91.00 14.00%	98.00 14.00%
PEG 6000 [mg/tbl]	56.31 14.08%	56.31 14.08%	37.54 9.39%	45.34 11.34%	42.24 9.39%	61.01 9.39%	60.80 8.69%
alpha-toc/PEG [mg/tbl]	4.29 1.07%	4.29 1.07%	2.86 0.72%	2.86 0.72%	3.21 0.71%	4.64 0.71%	5.00 0.71%

A comparison of particle size distribution (PSD) after blending is shown in Figure 8.

	d 10 (µm)	d 50 (µm)	d 90 (µm)
alpha-tocopherol/PEG 14% commercial blend	24.73	130.10	407.10
alpha-tocopherol/PEG 14% Hosokawa material	22.97	122.00	391.30
alpha-tocopherol/PEG 14% Nuova Guseo aterial	25.15	129.70	404.10

Densities and flowabilities are summarized in the table here below:

	Density			Flowability
	Bulk g/ml	Tapped g/ml (2500 taps)	Carr Index %	Stirrer 1 s/100g
alpha-tocopherol/PEG 14% commercial blend	0.455	0.583	21.82	153.5

alpha-tocopherol/PEG 14% Hosokawa material	0.447	0.582	23.21	156.3
alpha-tocopherol/PEG 14% Nuova Gusco material	0.450	0.581	22.52	161.1

alpha-tocopherol content uniformities are summarized in the table here below:

	tamper resistant formulation containing 100 mg Tapentadol and alpha-tocopherol/PEG 14% commercial blend	tamper resistant formulation containing 100 mg Tramadol and alpha-tocopherol/PEG 14% commercial blend	tamper resistant formulation containing 100 mg Tramadol and alpha-tocopherol/PEG 14% inventive blend
	alpha-Tocopherol	alpha-Tocopherol (%)	alpha-Tocopherol (%)
Top 1	97.5	94.5	98.6
Middle 1	96.9	102.2	99.3
Bottom 1	95.8	95.0	98.2
Top 2	101.0	93.7	101.0
Middle 2	97.9	98.9	97.3
Bottom 2	95.7	96.1	99.3
Top 3	101.7	94.7	99.8
Middle 3	96.9	95.2	97.8
Bottom 3	95.8	96.8	99.5
Middle 4	96.0	94.7	96.4
Average	97.4	96.2	98.7
RSD %	2.2	2.7	1.4

Weight uniformities in cut rods are summarized in the table here below:

Time (min)	alpha-tocopherol/PEG 14% commercial blend (mg/cut rods)		alpha-tocopherol/PEG 14% inventive blend (mg/cut rods)	
	Average weight	Weight RSD	Average weight	Weight RSD
Start	669.3	0.55%	668.9	0.43%
20	666.5	0.45%	669.7	0.37%
40	666.4	0.50%	670.6	0.60%
60	669.2	0.45%	669.3	0.39%
80	667.4	0.45%	669.0	0.45%
100	667.7	0.37%	666.0	0.50%
120	667.1	0.37%	669.8	0.30%
140	667.0	0.40%	668.0	0.49%

Extrusion speed for both batches: 16.8 kg/h

alpha-tocopherol content uniformities in cut rods are summarized in the table here below:

Time (min)	Estimated cut-rods manufactured (#)	alpha-tocopherol/PEG 14% commercial blend (%)	alpha-tocopherol/PEG 14% inventive blend (%)
Start	0	90.4	92.7
8	3350	90.4	93.7
16	6700	90.7	93.7
32	13400	91.2	93.1
48	20100	90.6	93.4
64	26800	89.4	92.2
80	33500	91.0	94.2
96	40200	90.7	93.0
112	46900	90.6	93.1
128	53600	90.9	93.4
Average		90.6	93.3
St.Dev.		0.48865	0.56421
CV%		0.5	0.6

Extrusion speed for both batches: 16.8 kg/h

The above experimental data demonstrate that the properties of the blends according to the invention are at least as good as the properties of a commercially available product that has been manufactured by a procedure which is significantly more laborious and expensive than the method according to the invention.

Patent claims:

1. A method for the preparation of a powdery pharmaceutical composition comprising a pharmaceutical excipient and a pharmaceutical component, wherein the pharmaceutical excipient is a polyalkylene glycol; the method comprising the step of
 - (c) grinding a mixture of the pharmaceutical excipient and the pharmaceutical component at a temperature below ambient temperature.
2. The method according to claim 1, wherein the temperature below ambient temperature is at most -10°C.
3. The method according to claim 1 or 2, wherein step (c) is performed by means of a cryo-mill, which is equipped with a cooling system and a milling chamber comprising means for providing mechanical impact on the material to be milled.
4. The method according to claim 3, wherein the cryo-mill is equipped with a sieve that allows material of the desired particle size to exit the milling chamber but keeps the coarser material within the milling chamber.
5. The method according to claim 3 or 4, wherein the cryo-mill is selected from the group consisting of ball mills, colloid mills, conical mills, disintegrators, disk mills, edge mills, gristmills, hammer mills, jet mills, pellet mills, planetary mills, plate mills, stirred mills, and vibratory mills.
6. The method according to any of the preceding claims, comprising the preceding steps of
 - (b) extruding a mixture of the pharmaceutical excipient and the pharmaceutical component in an extruder at a temperature profile allowing a liquid melt of the mixture to congeal in the extruder and to exit the extruder in form of a powder.
7. The method according to claim 6, comprising the preceding steps of
 - (a) mixing the pharmaceutical excipient with the pharmaceutical component outside the extruder and then feeding the resultant mixture into the extruder;or
feeding the pharmaceutical excipient and the pharmaceutical component into the extruder at different feeding points, where the feeding point for the pharmaceutical excipient is located upstream with respect to the feeding point for the pharmaceutical component, or vice versa.
8. The method according to claim 7, wherein in step (a) the pharmaceutical component is dissolved in the molten pharmaceutical excipient, or vice versa.
9. The method according to any of the preceding claims, comprising the subsequent step of
 - (d) grading the powder.

10. The method according to any of claims 6 to 9, wherein in step (b) the temperature profile comprises a temperature gradient of temperature T_1 to temperature T_2 , where $T_1 > T_2$ and where
 - T_1 is above the melting point/range of the pharmaceutical excipient and/or the pharmaceutical component; and/or
 - T_2 is below the melting point/range of the pharmaceutical excipient and/or the pharmaceutical component.
11. The method according to any of the preceding claims, wherein the powdery pharmaceutical composition has an average particle size of at most 100 μm .
12. The method according to any of the preceding claims, wherein the pharmaceutical excipient is hydrophilic and the pharmaceutical component is hydrophobic, or vice versa.
13. The method according to any of the preceding claims, wherein the pharmaceutical component is a second pharmaceutical excipient.
14. The method according to claim 13, wherein
 - the polyalkylene glycol is a polyethylene glycol; and/or
 - the second pharmaceutical excipient is alpha-tocopherol.
15. The method according to claim 14, wherein the relative weight ratio of the polyalkylene glycol to the tocopherol component is within the range of from 1000:1 to 5:1.

Figure 1

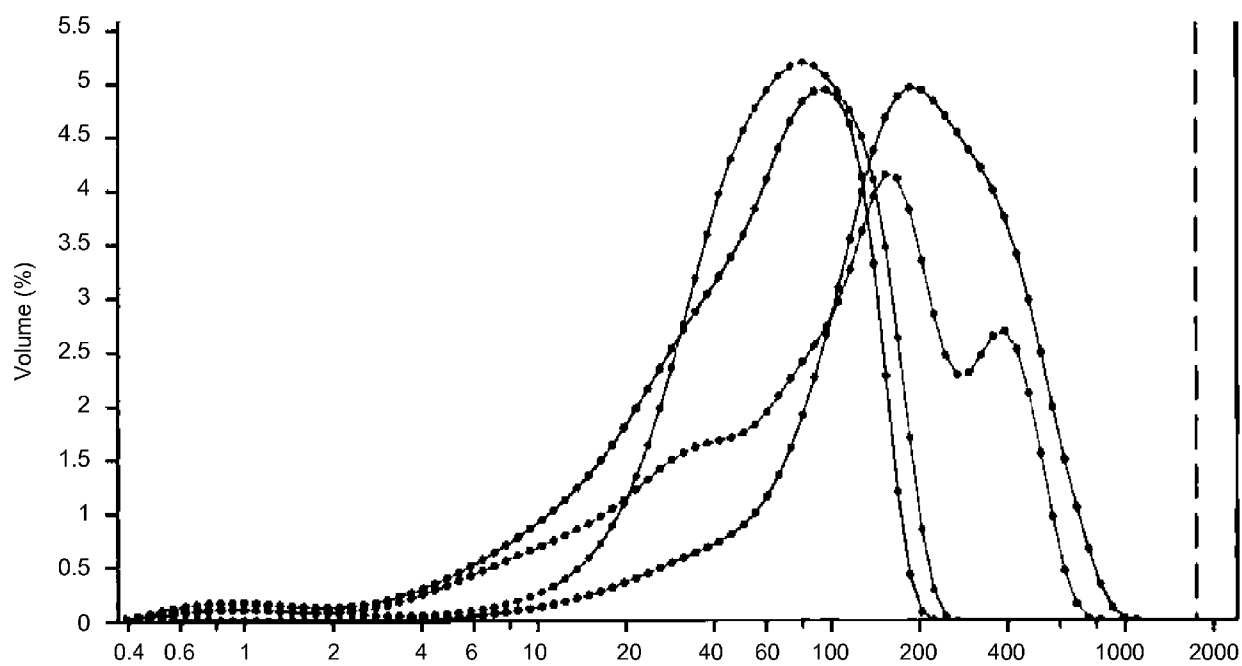


Figure 2

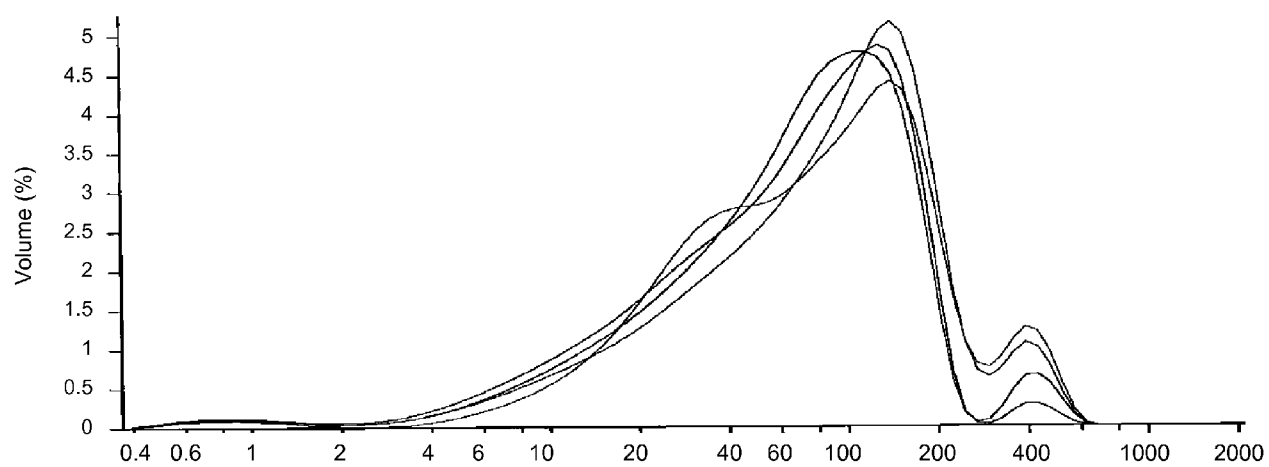


Figure 3

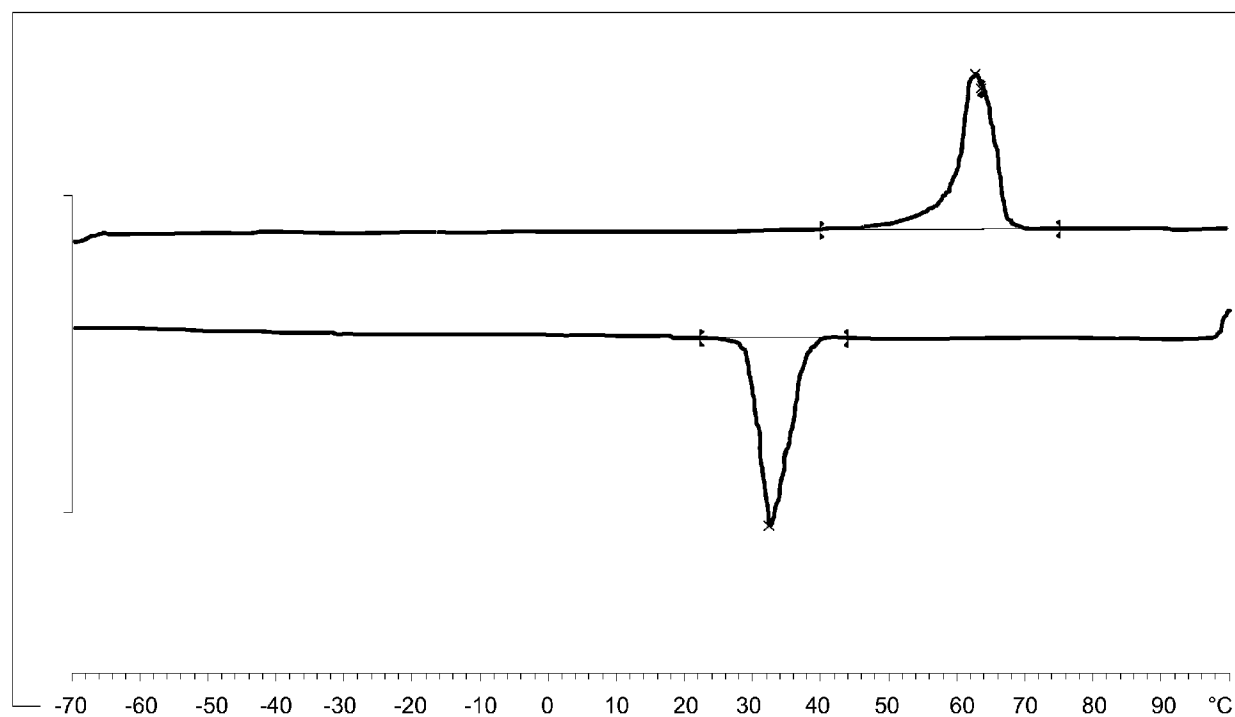


Figure 4

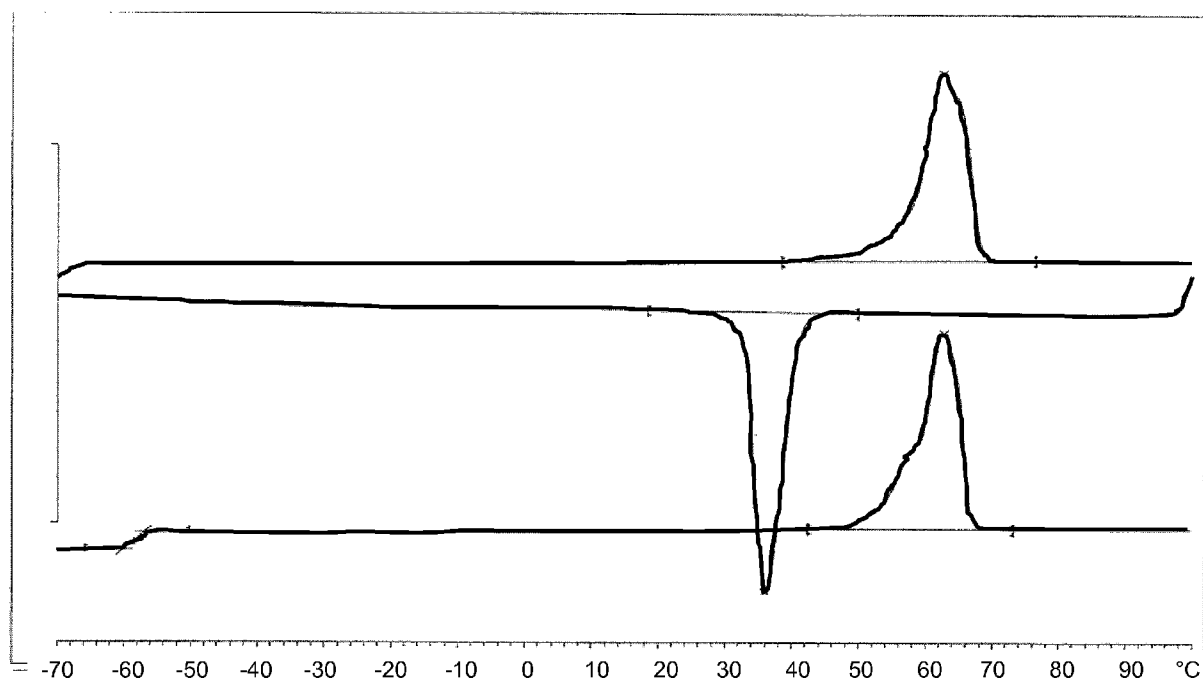


Figure 5

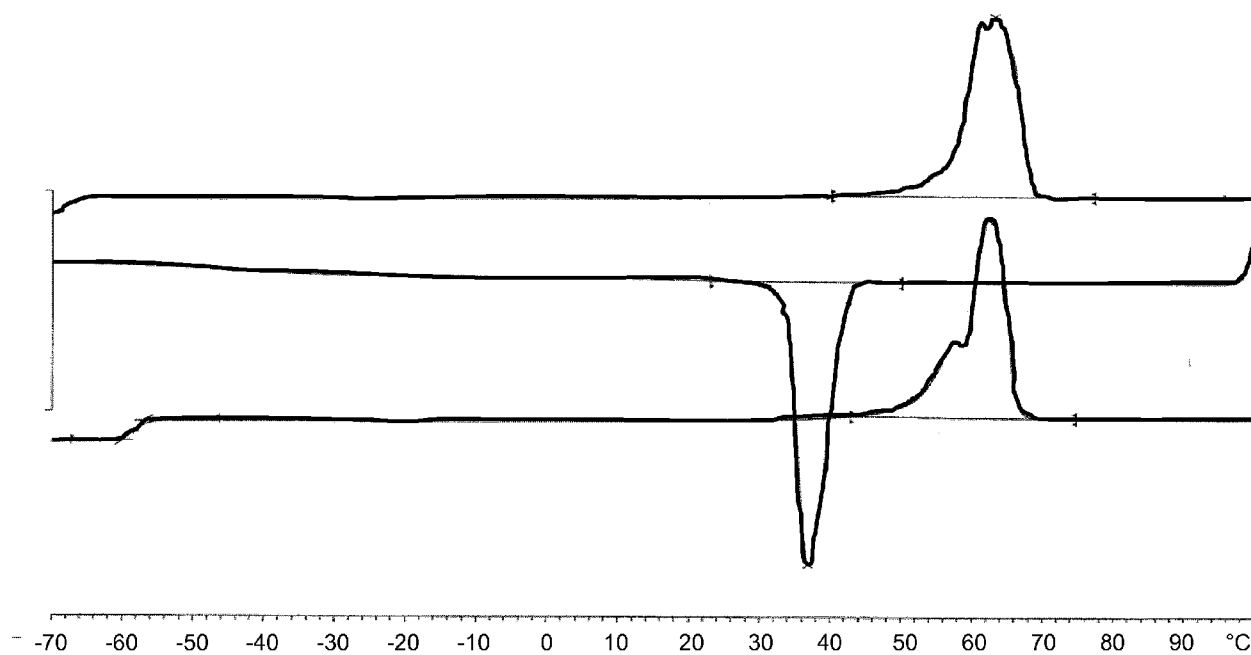


Figure 6

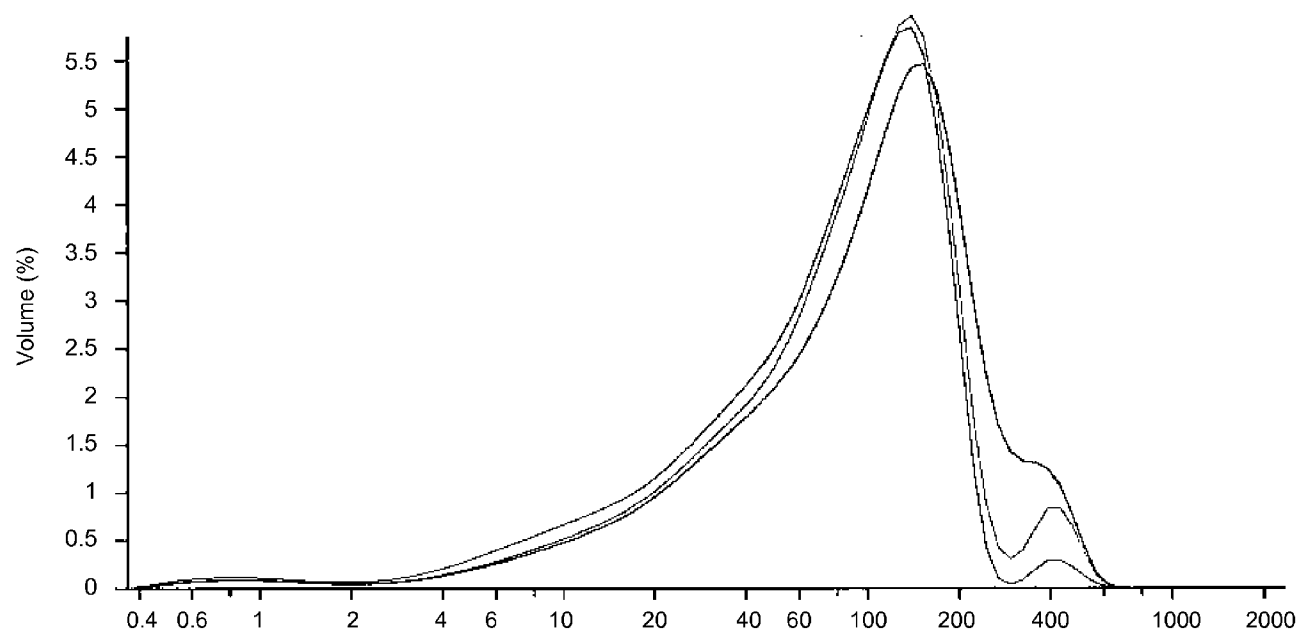


Figure 7

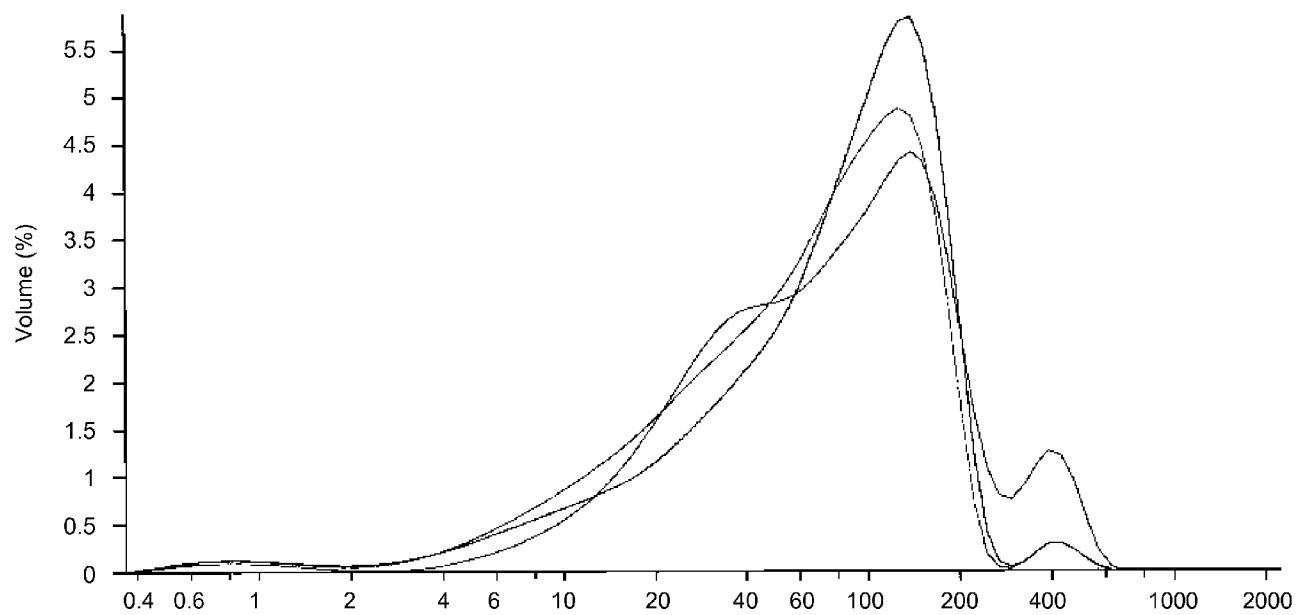
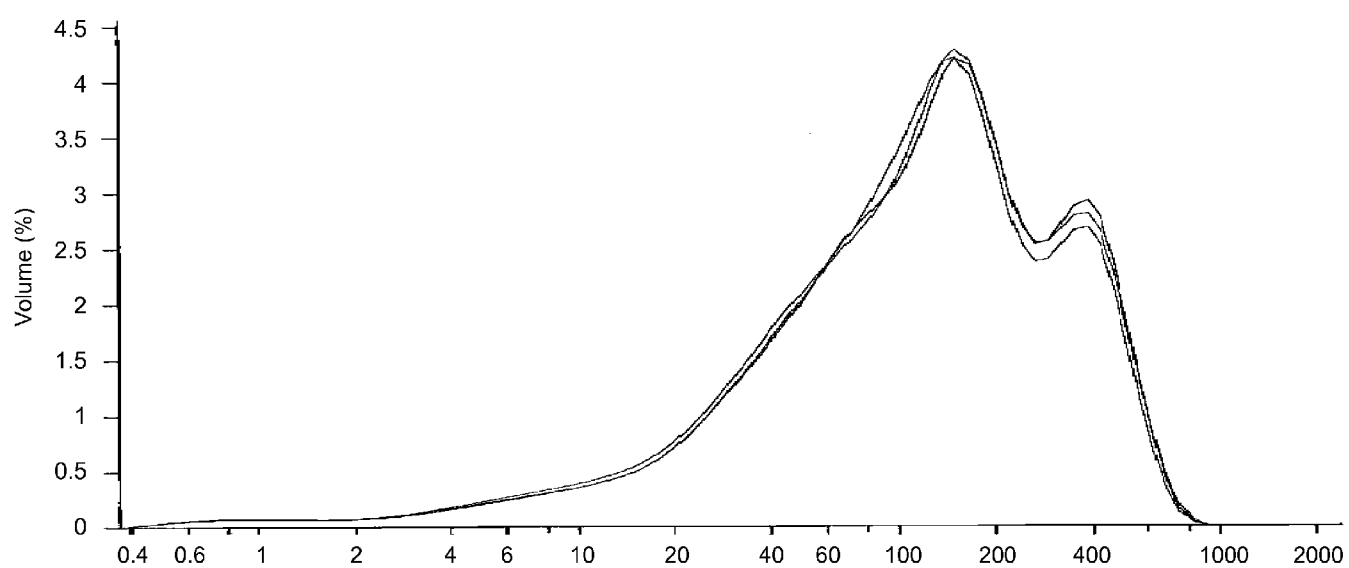


Figure 8



INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2014/075618A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/14
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, CHEM ABS Data, EMBASE, WPI Data, BIOSIS, FSTA

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	LEI LI ET AL: "Characterization of Poly(Ethylene Oxide) as a Drug Carrier in Hot-Melt Extrusion", DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, vol. 32, no. 8, 1 January 2006 (2006-01-01), pages 991-1002, XP055104632, ISSN: 0363-9045, DOI: 10.1080/03639040600559057	1,3-8, 10,12-14
Y	Hot-Melt Extrusion; page 992, column 2	1-15
Y	----- EP 2 246 063 A1 (IPSEN PHARMA SAS [FR]) 3 November 2010 (2010-11-03) example 1 ----- -/-	1-15



Further documents are listed in the continuation of Box C.



See patent family annex.

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"&" document member of the same patent family

Date of the actual completion of the international search

4 February 2015

Date of mailing of the international search report

11/02/2015

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Authorized officer

Schüle, Stefanie

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2014/075618

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 6 183 781 B1 (BURKE PAUL A [US]) 6 February 2001 (2001-02-06) column 9, line 59 - column 10, line 15 -----	1-15
Y	ANDREAS GRYZKE ET AL: "Development and evaluation of orally disintegrating tablets (ODTs) containing Ibuprofen granules prepared by hot melt extrusion", COLLOIDS AND SURFACES. B, BIOINTERFACES, ELSEVIER, AMSTERDAM, NL, vol. 86, no. 2, 5 April 2011 (2011-04-05), pages 275-284, XP028223123, ISSN: 0927-7765, DOI: 10.1016/J.COLSURFB.2011.04.007 [retrieved on 2011-04-13] page 276, paragraph 2.2 -----	1-15
Y	WO 2011/095314 A2 (GRUENENTHAL GMBH [DE]; HAUPTS MARCEL [DE]) 11 August 2011 (2011-08-11) cited in the application claims 1-15 examples -----	1-15

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2014/075618

Patent document cited in search report		Publication date		Patent family member(s)		Publication date
EP 2246063	A1	03-11-2010	CN	102413835	A	11-04-2012
			EP	2246063	A1	03-11-2010
			EP	2424558	A2	07-03-2012
			JP	2012525374	A	22-10-2012
			RU	2011148432	A	10-06-2013
			US	2015004210	A1	01-01-2015
			WO	2010125475	A2	04-11-2010

US 6183781	B1	06-02-2001	AT	221373	T	15-08-2002
			AU	718866	B2	20-04-2000
			AU	2751797	A	05-12-1997
			CA	2253667	A1	20-11-1997
			DE	69714448	D1	05-09-2002
			DE	69714448	T2	14-11-2002
			DK	0914095	T3	11-11-2002
			EP	0914095	A1	12-05-1999
			ES	2180982	T3	16-02-2003
			JP	2000513333	A	10-10-2000
			PT	914095	E	29-11-2002
			US	5817343	A	06-10-1998
			US	6183781	B1	06-02-2001
			US	2003031701	A1	13-02-2003
			WO	9742940	A1	20-11-1997

WO 2011095314	A2	11-08-2011	CN	102821757	A	12-12-2012
			EP	2531176	A2	12-12-2012
			US	2011187017	A1	04-08-2011
			WO	2011095314	A2	11-08-2011
