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[54] PROCESS FOR THE PREPARATION OF AN INTERMEDIATE POWDER FORMULATION AND A FINAL SOLID DOSAGE FORM UNDER USAGE OF A SPRAY CONGEALING STEP 製備中間體粉末製劑的工藝及利用噴霧冷凝步驟的最終固體劑量形狀

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(54) **PROCESS FOR THE PREPARATION OF AN INTERMEDIATE POWDER FORMULATION AND A FINAL SOLID DOSAGE FORM UNDER USAGE OF A SPRAY CONGEALING STEP**

VERFAHREN FÜR DIE ZUBEREITUNG EINES PULVERFÖRMIGEN ZWISCHENPRODUKTS UND EINER ENDGÜLTIGEN FESTEN DARREICHUNGSFORM ANHAND EINES SPRÜHERSTARRUNGSSCHRITTES

PROCÉDÉ DE PRÉPARATION D'UNE FORMULATION DE POUDRE INTERMÉDIAIRE ET D'UNE FORME GALÉNIQUE SOLIDE FINALE EN UTILISANT UNE ÉTAPE DE CONGÉLATION PAR PULVÉRISATION

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Description

[0001] The present invention pertains to a process of homogenously distributing a liquid, in particular a relatively small amount of a liquid, more in particular a relatively small amount of an oily substance, within a solid material so that a powder product is obtained which is suited to be used in the manufacture of a pharmaceutical composition, in particular a solid dosage form, such as for example a tablet, comprising at least one pharmaceutically active ingredient. The invention further pertains to a process for preparing a solid dosage form, such as a tablet, for pharmaceutical use.

[0002] Usually, with solid oral dosage forms all excipients have to be homogenously distributed therein. Whereas typically solid excipients, irrespective of their relative amounts, can be homogenously mixed without facing any significant problems, it is rather critical to homogenously distribute liquids, more in particular relatively small amounts of an oil, in a solid mixture. For some solid formulations it might even be desirable to homogenously incorporate therein less than 1 %, even less than 0.5 wt-% of an oil, e.g. vitamin E. However, it is not always feasible to melt the entire formulation in order to achieve homogenous mixing.

[0003] According to US 4,603,143 a free-flowing vitamin E or vitamin E acetate containing powder is obtained by adding a liquid form of a vitamin E or vitamin E acetate in an amount sufficient to yield a content of about 40 to about 60 wt-% to a silicon-containing adsorbent in the form of substantially discrete non-amorphous agglomerates. At least 50 % of said agglomerates have to have a minimum length, width, or both of 300 microns. This process does not require any spray-drying technique. It has been observed that the mixing process as such generates some heat while the liquid vitamin is adsorbed on the surface of the adsorbent powder thereby improving the absorption process.

[0004] In GB 1,147,210 problems associated with spray-drying processes in the preparation of dry, finely divided, solid, fat-soluble, vitamin-active products shall be overcome by first preparing a colloidal solution from cold water dispersible, non-gelling colloidal material and water, dispersing therein a water-insoluble, fat-soluble, vitamin-active composition to form a first dispersion, then dispersing said first dispersion in a water immiscible dispersing medium whereby a second dispersion is formed. In the following water is extracted at a temperature in the range from -10 to 0°C by use of a water extracting agent until said colloidal material solidifies, whereby finely divided, solid particles, containing said water-insoluble, fat-soluble vitamin-active composition dispersed therein is formed. Then, at a temperature in the range from -10 to 0°C solid particles are separated from said dispersing medium. Finally, substantially all residual moisture is removed from said solid particles. According to GB 1,147,210 with vitamin E as the fat-soluble vitamin-active component a finely divided product is obtained having a particle size distribution such that 91.5 wt-% of a product is in the range from -30 mesh to +120 mesh (US screen sizes).

[0005] In EP 229 652 B1 it is disclosed that dry potency stabilized, particulate, free-flowing tocopherol compositions which contain 20 to 60 wt-% of tocopherol in its free tocopherol form and 40 to 80 wt-% of a carrier, based on the total weight of carrier and tocopherol, can be obtained by forming an emulsion or slurry therefrom which in addition has to contain a potency stabilizer in an amount from 2 to 50 wt-% based on the total weight of stabilizer and tocopherol. This emulsion or slurry is subjected to spray-drying. Suitable potency stabilizers are reported to be ascorbic acid, a mixture of ascorbic acid and cysteine and a mixture of citric acid and cysteine. The preferred particle size of the spray-dried product lies in the range from 200 to 500 μm.

[0006] According to US 4,892,889 a spray-dried vitamin powder suitable for the preparation of direct-compression vitamin tablets is obtained by spray-drying in a conventional spray-dryer a mixture comprising a fat-soluble vitamin, gelatin having a bloom number between 30 and 300, a water-soluble carbohydrate, and an effective amount of water to permit spray-drying. The final powder shall contain from 20 to 60 wt-% of the fat-soluble vitamin, from 6 to 46 wt-% of the gelatin, and an effective amount of said carbohydrate to prevent extrusion.

[0007] In US 4,262,017 a process for the preparation of a vitamin E dry powder having a high content of vitamin E is disclosed which requires dissolving sodium or potassium caseinate in a very specific residual liquor from the production of lactose. The obtained solution has to be mixed with oily vitamin E acetate in a pressure homogenizer to form a dispersion which is subjected to spray-drying to form a powder containing lactose, sodium or potassium caseinate and vitamin E acetate. The final powder product has to contain from 10 to 60 wt-% of vitamin E acetate.

[0008] In WO 96/03979 A1 solid dosage forms exhibiting controlled release of an active ingredient can be obtained by spray drying or spray congealing if an atomizing device is employed which uses mechanical vibrations of resonant metal elements or nozzles. According to a preferred embodiment, the resonant metal element comprises an appropriately shaped sonotrode. With the method according to WO 96/03979 A1 the overall dimension of the equipment necessary to obtain solid dosage forms with controlled release can be minimized.

[0009] Document WO 98/35655 A2 discloses a process for incorporating at least two incompatible active ingredients into a solid dosage form in such a manner that these ingredients are not in contact with each other. This is accomplished by first distributing the first active ingredient into a lipid or lipoid component having a higher melting point and subsequently mixing the second active ingredient with said granulated higher melting lipid which contains the first active ingredient and with another lipid or lipoid component having a lower melting point. The weight ratio of the higher melting lipid and the lower melting lipid has to be in the range from 1:5 to 5:1. It is described that the first active ingredient can be

incorporated into the higher melting lipid or lipoid component by way of spray congealing.

[0010] According to WO 99/12864 A2 stearic acid wax, glyceryl fatty acid esters, glyceryl monostearate and lauric acid wax after having been mixed with an active pharmaceutical agent can be subjected to spray congealing. Similarly, in WO 95/17174 A1 it is disclosed to spray congeal a mixture comprising a material selected from the group consisting of C_{14-18} fats, C_{16-20} fatty acids, and C_{14-18} waxes, and dioctylsulfosuccinate.

[0011] WO2005/053656, US5126151, EP0477135, US5707636, EP0261616 reveal compositions with a waxy or oily character and a process for the formation of particles under use of spray congealing.

[0012] With the aforementioned established procedures generally only large amounts of vitamin E or derivatives thereof can be employed. It, thus, would have been desirable to be also in the position to homogenously incorporate oily compounds such as vitamin E in rather small amounts into solid excipients used for the manufacture of tablets.

[0013] Therefore, it has been an object of the present invention to provide a process for homogenously incorporating a component being in liquid form at ambient temperature or having a waxy consistency, in particular small amounts of such a component, such as for example a waxy or, in particular, oily substance, into a solid component, in particular relatively large amounts of a solid component. The process for homogenously incorporating a liquid into a solid component is preferably also a continuous process enabling the processing of larger amount on an industrial scale. The thus obtained powder with a good, an acceptable blend uniformity (uniform distribution, preferably a relative standard deviation up to 6% (see below in example 5), of the component being in liquid form at ambient temperature or having a waxy consistency in the obtained powder) can then be used for the manufacture of a solid dosage form, in particular a solid dosage form for pharmaceutical use, such as a tablet, capsule, bead, pellet. Further, it has been an object of the present invention to provide a method for manufacturing a solid dosage form, such as for example a tablet, which comprises a component being in liquid form at ambient temperature or having a waxy consistency, in particular relatively small amounts of such a component, e.g. an oily substance, being homogeneously distributed within said solid dosage form. The thus obtained solid dosage form, in particular the tablet, has a good, an acceptable content uniformity for the said component. It has been another object of the present invention to provide a versatile basis for the production of a solid dosage form while keeping various pathways open to arrive at a final solid dosage form thereby furnishing a greater flexibility.

[0014] According to one aspect the problem underlying the present invention has been solved by a process for preparing a powder comprising the steps according to claim 1.

[0015] In the meaning of the present invention the at least one first component being in liquid form at ambient temperature or having a waxy consistency at ambient temperature represents an organic molecule, including oligomers and polymers, i.e. not an inorganic compound. These compounds degrade, that is, loose their original structure when exposed to heat, e.g. by rupture of single or double bonds or by oxidation and/or polymerization reactions. For a specific compound a certain amount of energy/heat is needed to initiate degradation. This is known to a person skilled in the art and is, for example, well reflected in WO 2005/053656 A1. Further, in the meaning of the present invention the at least one first component is provided in liquid form at ambient temperature or has a waxy consistency at ambient temperature. That is, said first component is employed, e.g. when in the form of an oil, having an inner structure remote from a crystal.

[0016] According to one embodiment, the homogenous liquid mixture comprises at least 50 wt % of said at least one second component and 50 wt % or less of said at least one first component; in particular the homogenous liquid mixture comprises at least 75 wt % of said at least one second component and 25 wt % or less of said at least one first component; more in particular the homogenous liquid mixture comprises at least 90 wt % of said at least one second component and 10 wt % or less of said at least one first component; even more in particular the homogenous liquid mixture comprises at least 92 wt % of said at least one second component and 8 wt % or less of said at least one first component; even further in particular the homogeneous liquid mixture comprises at least 94 wt % of said at least one second component and 6 wt % or less of said at least one first component; more in particular the homogeneous liquid mixture comprises at least 96 wt % of said at least one second component and 4 wt % or less of said at least one first component. According to another embodiment, the homogenous liquid mixture comprises from about 92 wt % to about 99.9 wt %, in particular from about 94 wt % to about 99.5 wt %, more in particular from about 94 wt% to about 98 wt % or from about 95 wt % to about 99 wt % or from about 96 wt% to about 99 wt% or from about 95 wt% to about 98 wt % or from about 96 wt % to about 98 wt % of the at least one second component, and from about 0.1 wt % to about 8 wt %, in particular from about 0.5 wt % to about 6 wt %, more in particular from about 2 wt % to about 6 wt % or from about 1 wt % to about 5 wt % or from about 1 wt % to about 4 wt % or from about 2 wt % to about 5 wt % or from about 2 wt % to about 4 wt % of the at least one first component.

[0017] According to another embodiment the process for preparing a powder product further comprises keeping the isolated powder at a temperature below the melting point or melting range of said second component, in particular until it is used in the production of a solid dosage form.

[0018] Said first component preferably is in liquid form at ambient temperature, in particular has an oily consistency at ambient temperature. Ambient temperature in the meaning of the invention typically comprises temperatures in the range from about 18°C to about 25°C, and in particular in the range from 20°C to 25°C. A first component being liquid in the meaning of the present invention also includes compounds or mixtures of compounds which are viscous at ambient

temperature allowing, for example, to be transferred through a feed line, if need be, by way of pressure.

[0019] Suitable oily or waxy first components include, for example, vegetable, animal, mineral and synthetic oils or waxes, e.g. silicon oils or waxes, poloxamers liquid at room temperature, polyethyleneglycols with molecular weight < 3000, and mixtures thereof. Mineral oils or waxes for example include paraffin oil or wax, in particular an iso-paraffin oil or wax. Suitable silicon oils comprise dimethicone, substituted and linear dimethicone, simethicone, cyclomethicone and mixtures thereof. Suitable vegetable oils comprise lineseed oil, palm oil, olive oil, castor oil, rapeseed oil, soy oil, peanut oil, coconut oil, sunflower oil or turnip seed oil or mixtures thereof. Oils in the meaning of the present invention further comprise alkyl esters of fatty acid esters, wherein the alkyl group has from 1 to 30 carbon atoms and the fatty acid has from 12 to 28 carbon atoms, long chain fatty alcohols or fatty acids (e.g. octyl dodecanol, oleyl alcohol, oleic acid). A particular sub-group are the C_{1-4} alkyl esters of C_{16-18} fatty acids, for example the methyl, ethyl or isopropyl esters of palmitic, heptadecanoic, myristic or stearic acid. Also included are fatty acid glycerides and fatty acid partial glycerides. Suitable waxes in the meaning of the present invention refer to oil-soluble materials which have a waxy consistency and have an onset of melting in the temperature range from 15 °C to 40 °C, such as for example lecithine. In a preferred embodiment the first component comprises or represents at least one vitamin oil, lecithine, simethicone or a mixture thereof. In a further preferred embodiment the first component comprises or represents a component selected from vitamin oil, lecithine or simethicone. In a most preferred embodiment the first component comprises or represents a vitamin oil, such as for example tocopherol and/or a tocopherol derivative. Tocopherol comprises alpha-, beta-, gamma-, delta-, and epsilon-tocopherol (determined by the number of methyl groups on the chromanol ring), including its stereoisomeric forms. Various mixtures of the aforementioned tocopherol compounds can also be used. Among the aforementioned components alpha-tocopherol is most preferred. Suitable tocopherol derivatives include tocopherol esters such as dl-tocopheryl acetate. Tocopherol and tocopherol derivatives can be used as active ingredients and/or antioxidants with the powders obtained by spray congealing.

[0020] Preferably, said first component is a liquid anti-oxidant, e.g. alpha-tocopherol.

[0021] Said second component preferably is a component with a melting point or melting range of or above 37°C but which is not too high, in order to reduce energy input during the spray congealing process. Preferably, the second component does not thermally degrade shortly above its melting point. Exemplary, the melting point or melting range of the second component ranges from above ambient temperature to 120 °C, in particular ranges from >40 °C to 120°C, more in particular ranges from 50°C to 120°C, even more in particular ranges from 55°C to 120°C. Preferably, the melting point or melting range of the second component should not exceed 90°C, preferably the melting point or melting range of the second component ranges from >40°C to 90°C, more preferably from 45°C to 90°C; even more preferably from 48°C to 77 °C. Preferably, the second component is a component which cools down rapidly. Suitable components to be used as second component comprise hydrophilic polymers such as for example polyalkylene glycol, in particular polyethylene glycol, poly(alkylene oxide), in particular poly(ethylene oxide), poly(vinylalcohol), hydroxymethyl cellulose, hydroxyethyl cellulose, hydroxylpropyl cellulose, hydroxypropyl methylcellulose, carboxy methyl cellulose, and mixtures thereof; waxes or waxy material, such as for example yellow or white wax USP, glyceryl tristearate, carnauba wax, hydrogenated vegetable oil e.g. hydrogenated castor oil, cetyl alcohol, lanolin alcohol, glyceryl monostearate optionally in combination with aminoalkyl methacrylate copolymer E, beeswax, microcrystalline waxes (or microwaxes), gelucire 50/13, polyoxylglycerides, e.g. stearoyl macrogolglycerides, glyceryl behenate, e.g. Compritol 888 ATO®, glyceryl palmitostearate, e.g. Precirol ATO 5®, Vitamin E TPGS (tocopherol glyceryl succinate), and/or mixtures thereof. Preferable components to be used as second component comprise polyalkylene glycol, in particular polyethylene glycol, poly(alkylene oxide), in particular poly(ethylene oxide), waxes or waxy material, such as for example yellow or white wax USP, glyceryl tristearate, carnauba wax, hydrogenated vegetable oil e.g. hydrogenated castor oil, cetyl alcohol, lanolin alcohol, glyceryl monostearate optionally in combination with aminoalkyl methacrylate copolymer E, beeswax, microcrystalline waxes (or microwaxes), gelucire 50/13, polyoxylglycerides, e.g. stearoyl macrogolglycerides, glyceryl behenate, e.g. Compritol 888 ATO®, glyceryl palmitostearate, e.g. Precirol ATO 5®, Vitamin E TPGS (tocopherol glyceryl succinate), and/or mixtures thereof.

[0022] The at least one second component preferably comprises at least one polyalkylene glycol, in particular polyethylene glycol, such as polyethylene glycol 3000 to 20000, preferably polyethylene glycol 6000 (PEG 6000). More preferably, the at least one second component consists of polyalkylene glycol, in particular polyethylene glycol, such as polyethylene glycol 3000 to 20000, preferably polyethylene glycol 6000 (PEG 6000).

[0023] Preferably, said second component is a component sensitive to oxidation, e.g polyalkylene glycol, in particular polyethylene glycol, more in particular PEG 6000.

[0024] Said homogenous liquid mixture is, according to one embodiment of the present process for preparing a powder, obtained by adding said at least one first component to said at least one second component, which is present in liquid form due to heating.

[0025] Said homogenous liquid mixture preferably comprises, or in particular consists of, tocopherol, in particular alpha-tocopherol, as the first component and polyalkylene glycol, in particular polyethylene glycol, more in particular PEG 6000, as the second component.

[0026] Spray congealing as such is well known in the art. In the spray congealing process a substance or mixture in its molten state is sprayed into a chamber by use of a so-called atomizing gas to form small droplets. In the spraying chamber, the temperature is below that of the melting point of the sprayed molten substance or mixture so that the small droplets solidify to form a powdered product. With the process of the present invention, it has been found that upon spray congealing a liquid, even very low amounts of the first component, in particular a component being in liquid form, e.g. an oily substance, can be homogeneously distributed within, in particular within the bulk mass of, the second component which is in solid state at ambient temperature. The equipment that can be used for spray congealing is known to a person skilled in the art.

[0027] In the spray congealing step usually a heated atomizing gas, preferably an inert gas, e.g. nitrogen, is used with the spray congealing unit having a temperature at the spraying nozzle in the range from about 60°C to about 120°C , in particular from about 80°C to about 120°C, in particular from about 95°C to about 110°C. Preferably, with the spray congealing unit an atomizing gas rate in the range from about 20 kg/h to about 50 kg/h, in particular from about 25 kg/h to about 45 kg/h, is employed. According to a further aspect of the process for preparing a powder, the process gas, e.g. nitrogen gas, used with the spray congealing unit for cooling the sprayed droplets has a temperature in the range from about 0°C to about 15°C, in particular from about 2°C to about 12°C. The spray congealing unit preferably comprises at least one spraying nozzle, preferably a two fluid nozzle, said spraying nozzle preferably having a diameter in the range from about 1 mm to about 4 mm, in particular from about 1,5 mm to about 3 mm, more in particular from about 1,5 mm to about 2 mm. It is considered to be within the skills of the skilled person to recognize the most appropriate parameters of the spray congealing process taking into account the type of apparatus used, the desired viscosity of the homogeneous mixture, the thermostability of the mixture, the size of the batch and the like.

[0028] In one embodiment of the process, said transfer unit comprises at least one, in particular one, feed line and at least one, in particular one, pump, wherein at least said feed line is adapted to be heatable. Said at least one second component preferably is at least partially melted in the transfer unit, in particular in the feed line. In this embodiment, the at least one first component is preferably added to the molten second component prior to entering the spray nozzle, e.g. the at least one first component is added to the molten second component in the feed vessel or the feed line. Preferably, the feed vessel is adapted to be heatable. Preferably, both the feed vessel and the feed line is heated.

[0029] Accordingly, the powder obtained with the present invention preferably comprises, more particularly consists of, at least 75 wt % of polyalkylene glycol, in particular polyethylene glycol, more in particular PEG 6000, and 25 wt % or less of tocopherol, in particular alpha-tocopherol; more in particular the powder comprises, more particularly consists of, at least 90 wt % of polyalkylene glycol, in particular polyethylene glycol, more in particular PEG 6000, and 10 wt % or less of tocopherol, in particular alpha-tocopherol; even more in particular the powder comprises, more particularly consists of, at least 92 wt % of polyalkylene glycol, in particular polyethylene glycol, more in particular PEG 6000, and 8 wt % or less of tocopherol, in particular alpha-tocopherol. According to another embodiment, the powder obtained with the present invention preferably comprises, more particularly consists of, from about 92 wt % to about 99.9 wt %, in particular from about 94 wt % to about 99.5 wt %, more in particular from about 96 wt % to about 99 wt %, even more in particular from about 96 wt % to about 98 wt % of polyalkylene glycol, in particular polyethylene glycol, more in particular PEG 6000, and from about 0.1 wt % to about 8 wt %, in particular from about 0.5 wt % to about 6 wt %, more in particular from about 1 wt % to about 4 wt %, even more in particular from about 2 wt % to about 4 wt % of tocopherol, in particular alpha-tocopherol. According to yet another embodiment, the powder obtained with the present invention preferably comprises, more particularly consists of, from about 92 wt % to about 99.9 wt %, in particular from about 94 wt % to about 99.5 wt %, more in particular from about 94 wt % to about 98 wt % or from about 95 wt % to about 99 wt % or from about 96 wt % to about 99 wt % or from about 95 wt % to about 98 wt % or from about 96 wt % to about 98 wt % of the at least one second component, and from about 0.1 wt % to about 8 wt %, in particular from about 0.5 wt % to about 6 wt %, more in particular from about 2 wt % to about 6 wt % or from about 1 wt % to about 5 wt % or from about 1 wt % to about 4 wt % or from about 2 wt % to about 5 wt % or from about 2 wt % to about 4 wt % of the at least one first component.

[0030] In another embodiment, the powder product obtained with the process of the invention preferably has a particle size distribution (PSD) d_{50} in the range from about 40 μm to about 300 μm, in particular from about 40 μm to about 200 μm, more in particular in the range from about 50 μm to about 180 μm. In case the product particles obtained with the process of the present invention are not essentially spherical in shape, the particle size of such irregularly shaped particles is determined by taking the diameter of a sphere which has essentially the same volume as said irregularly shaped particle. The particle size can, for example, be determined by laser diffraction techniques. The average particle size d_{50} is regularly defined as the size or diameter where 50 mass-% of the particles of the powder have larger diameter and where the other 50 mass-% have a smaller diameter.

[0031] A powder obtainable by or obtained with the process of the invention is particularly suited for the preparation of a pharmaceutical solid dosage form, such as for example a capsule or tablet, containing at least one pharmaceutically active ingredient. Therefore, the present invention also relates to the use of a powder obtainable by or obtained with the process of the invention for the preparation of a solid dosage form containing at least one pharmaceutically active

ingredient.

[0032] With the powder obtained according to the process of the present invention a solid dosage form for pharmaceutical use can be prepared containing less than 1 wt %, in particular less than 0.4 wt %, e.g. in the range from about 0.05 to about 0.3 wt % or in the range from about 0.1 to about 0.15 wt %, of said first component based on the total weight of the solid dosage form. Preferably, the first component is homogeneously/uniformly distributed in said solid dosage form.

[0033] According to another aspect the problem underlying the present invention has been solved by a process for the preparation of a solid dosage form, in particular a tablet, comprising the steps of

a) providing at least one pharmaceutically active ingredient (component a),
b) providing the powder according to the above spray congealing process according to the invention (component b),
c) providing at least one third component (component c),
d) forming a mixture comprising components a, and b and c),
e) transforming said mixture into a solid dosage form.

[0034] It is evident that in case the pharmaceutically active ingredient is a component being in liquid form at ambient temperature or having a waxy consistency at ambient temperature, that the pharmaceutically active ingredient can be incorporated in the powder according to the spray congealing process of the present invention and hence, the present invention also comprises a process for the preparation of a solid dosage form comprising the steps of

a) providing the powder according to the above spray congealing process according to the invention, wherein the first component, in particular the first liquid component, is a pharmaceutically active ingredient and wherein the at least one second component is as defined above, (component a),
b) providing at least one third component (component b),
c) forming a mixture comprising components a) and b),
d) transforming said mixture into a solid dosage form.

[0035] The mixture under c) can for instance be formed by blending e.g. in a fluid bed or by wet- , dry- or melt-granulation in a high or low shear granulator, or by slugging (roller compactor).

[0036] Suitable pharmaceutically active ingredients are those which exert a local physiological effect, as well as those which exert a systemic effect, after oral administration. Examples of suitable active ingredients encompass:

analgesic and anti-inflammatory drugs (NSAIDs, fentanyl, indomethacin, ibuprofen, ketoprofen, nabumetone, paracetamol, piroxicam, tramadol, tapentadol, COX-2 inhibitors such as celecoxib and rofecoxib) ;
anti-arrhythmic drugs (procainamide, quinidine, verapamil);
antibacterial and antiprotozoal agents (amoxicillin, ampicillin, benzathine penicillin, benzylpenicillin, cefaclor, cefadroxil, cefprozil, cefuroxime axetil, cephalexin, chloramphenicol, chloroquine, ciprofloxacin, clarithromycin, clavulanic acid, clindamycin, doxyxycline, erythromycin, flucloxacillin sodium, halofantrine, isoniazid, kanamycin sulphate, lincomycin, mefloquine, minocycline, nafcillin sodium, nalidixic acid, neomycin, norfloxacin, ofloxacin, oxacillin, phenoxymethyl-penicillin potassium, pyrimethamine-sulfadoxime, streptomycin); anti-coagulants (warfarin) ;
antidepressants (amitriptyline, amoxapine, butriptyline, clomipramine, desipramine, dothiepin, doxepin, fluoxetine, reboxetine, amineptine, selegiline, gepirone, imipramine, lithium carbonate, mianserin, milnacipran, nortriptyline, paroxetine, sertraline ; 3-[2-[3,4-dihydrobenzofuro[3,2-c]pyridin-2(1H)-yl]ethyl]-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one); anti-diabetic drugs (glibenclamide, metformin) ;
anti-epileptic drugs (carbamazepine, clonazepam, ethosuximide, gabapentin, lamotrigine, levetiracetam, phenobarbitone, phenytoin, primidone, tiagabine, topiramate, valpromide, vigabatrin) ;
antifungal agents (amphotericin, clotrimazole, econazole, fluconazole, flucytosine, griseofulvin, itraconazole, ketoconazole, miconazole nitrate, nystatin, terbinafine, voriconazole) ; antihistamines (astemizole, cinnarizine, cyproheptadine, decarboethoxyloratadine, fexofenadine, flunarizine, levocabastine, loratadine, norastemizole, oxatomide, promethazine, terfenadine) ;
anti-hypertensive drugs (captopril, enalapril, ketanserin, lisinopril, minoxidil, prazosin, ramipril, reserpine, terazosin) ;
anti-muscarinic agents (atropine sulphate, hyoscine) ;
antineoplastic agents and antimetabolites (platinum compounds, such as cisplatin, carboplatin; taxanes, such as paclitaxel, docetaxel; tecans, such as camptothecin, irinotecan, topotecan; vinca alkaloids, such as vinblastine, vindecine, vincristine, vinorelbine; nucleoside derivatives and folic acid antagonists such as 5-fluorouracil, capecitabine, gemcitabine, mercaptopurine, thioguanine, cladribine, methotrexate; alkylating agents, such as the nitrogen mustards, e.g. cyclophosphamide, chlorambucil, chlormethine, iphosphamide, melphalan, or the nitro-soureas, e.g. carmustine, lomustine, or other alkylating agents, e.g. busulphan, dacarbazine, procarbazine, thiotepa; antibiotics,

such as daunorubicin, doxorubicin, idarubicin, epirubicin, bleomycin, dactinomycin, mitomycin; HER 2antibody, such as trastuzumab; podophyllotoxin derivatives, such as etoposide, teniposide; farnesyl transferase inhibitors; anthrachinon derivatives, such as mitoxantron; hdm2 antagonists; HDAC inhibitors; cMet inhibitors) ; anti-migraine drugs (alniditan, naratriptan, sumatriptan) ;
anti-Parkinsonian drugs (bromocryptine mesylate, levodopa, selegiline) ;
antipsychotic, hypnotic and sedating agents (alprazolam, buspirone, chlordiazepoxide, chlorpromazine, clozapine, diazepam, flupenthixol, fluphenazine, flurazepam, 9-hydroxyrisperidone, lorazepam, mazapertine, olanzapine, oxazepam, pimozide, pipamperone, piracetam, promazine, risperidone, selfotel, seroquel, sertindole, sulpiride, temazepam, thiothixene, triazolam, trifluperidol, ziprasidone, zolpidem) ;
anti-stroke agents (lubeluzole, lubeluzole oxide, riluzole, aptiganel, eliprodil, remacemide) ; antitussive (dextromethorphan, laevodropropizine) ;
antivirals (acyclovir, ganciclovir, loviride, tivirapine, zidovudine, lamivudine, zidovudine + lamivudine, didanosine, zalcitabine, stavudine, abacavir, lopinavir, amprenavir, nevirapine, efavirenz, delavirdine, indinavir, nelfinavir, ritonavir, saquinavir, adefovir, hydroxyurea, etravirine, darunavir, rilpivirine) ;
beta-adrenoceptor blocking agents (atenolol, carvedilol, metoprolol, nebivolol, propanolol) ; cardiac inotropic agents (amrinone, digitoxin, digoxin, milrinone) ;
corticosteroids (beclomethasone dipropionate, betamethasone, budesonide, dexamethasone, hydrocortisone, methylprednisolone, prednisolone, prednisone, triamcinolone) ;
disinfectants (chlorhexidine) ;
diuretics (acetazolamide, frusemide, hydrochlorothiazide, isosorbide) ;
enzymes;
essential oils (anethole, anise oil, caraway, cardamom, cassia oil, cineole, cinnamon oil, clove oil, coriander oil, dementholised mint oil, dill oil, eucalyptus oil, eugenol, ginger, lemon oil, mustard oil, neroli oil, nutmeg oil, orange oil, peppermint, sage, spearmint, terpineol, thyme) ; gastro-intestinal agents (cimetidine, cisapride, clebopride, diphenoxylate, domperidone, famotidine, lansoprazole, loperamide, loperamide oxide, mesalazine, metoclopramide, mosapride, nizatidine, norcisapride, olsalazine, omeprazole, pantoprazole, perprazole, prucalopride, rabeprazole, ranitidine, ridogrel, sulphasalazine) ;
haemostatics (aminocaproic acid);
lipid regulating agents (atorvastatin, lovastatin, pravastatin, probucol, simvastatin) ;
local anaesthetics (benzocaine, lignocaine) ;
opioid analgesics (buprenorphine, codeine, dextromoramide, dihydrocodeine, hydrocodone, oxycodone, morphine);
parasympathomimetics and anti-dementia drugs (ATT-082, eptastigmine, galanthamine, metrifonate, milameline, neostigmine, physostigmine, tacrine, donepezil, rivastigmine, sabcomeline, talsaclidine, xanomeline, memaritine, lazabemide);
peptides and proteins (antibodies, becaplermin, cyclosporine, erythropoietin, immunoglobulins, insuline);
sex hormones (oestrogens : conjugated oestrogens, ethinyloestradiol, mestranol, oestradiol, oestriol, oestrone ; progestogens ; chlormadinone acetate, cyproterone acetate, 17-deacetyl norgestimate, desogestrel, dienogest, dydrogesterone, ethynodiol diacetate, gestodene, 3-keto desogestrel, levonorgestrel, lynestrenol, medroxy-progesterone acetate, megestrol, norethindrone, norethindrone acetate, norethisterone, norethisterone acetate, norethynodrel, norgestimate, norgestrel, norgestrienone, progesterone, quingestanol acetate) ;
stimulating agents (sildenafil) ;
vasodilators (amlodipine, buflomedil, amyl nitrite, diltiazem, dipyridamole, glyceryl trinitrate, isosorbide dinitrate, lidoflazine, molsidomine, nicardipine, nifedipine, oxpentifylline, pentaerythritol tetranitrate); their N-oxides, their pharmaceutically acceptable acid or base addition salts, their solvates and their stereochemically isomeric forms.

[0037] Pharmaceutically acceptable acid addition salts comprise the acid addition salt forms which can conveniently be obtained by treating the base form of the active ingredient with appropriate organic and anorganic acids. Suitable acids are for example, hydrohalic acids, e.g. hydro-chloric, hydrobromic and the like; sulfuric acid; nitric acid; phosphoric acid and the like; or organic acids, for example, acetic, propanoic, hydroxyacetic, 2-hydroxypropanoic, 2-oxopropanoic, oxalic, malonic, succinic, maleic, fumaric, malic, tartaric, 2-hydroxy-1,2,3-propanetricarboxylic, methanesulfonic, ethanesulfonic, benzenesulfonic, 4-methyl-benzenesulfonic, cyclohexanesulfonic, 2-hydroxybenzoic, 4-amino-2-hydroxybenzoic and the like acids. Conversely the salt form can be converted by treatment with alkali into the free base form.

[0038] Active ingredients containing an acidic proton may be converted into their non-toxic metal or amine addition salt forms by treatment with appropriate organic and inorganic bases. Appropriate base addition salt forms comprise, for example, the ammonium salts, the alkali and earth alkaline metal salts, e.g. the lithium, sodium, potassium, magnesium, calcium salts and the like, salts with organic bases, e.g. primary, secondary and tertiary aliphatic and aromatic amines such as methylamine, ethylamine, propylamine, isopropylamine, the four butylamine isomers, dimethylamine, diethylamine, diethanolamine, dipropylamine, diisopropylamine, din-butylamine, pyrrolidine, piperidine, morpholine, tri-

methylamine, triethylamine, tripropylamine, quinuclidine, pyridine, quinoline and isoquinoline, the benzathine, *N*-methyl-D-glucamine, 2-amino-2-(hydroxymethyl)-1,3-propanediol, hydrabamine salts, and salts with amino acids such as, for example, arginine, lysine and the like.

[0039] The term solvate comprises the hydrates and solvent addition forms which the active ingredients are able to form, as well as the salts thereof. Examples of such forms are e.g. hydrates, alcoholates and the like.

[0040] The *N*-oxide forms of the active ingredients comprise those active ingredients wherein one or several tertiary nitrogen atoms are oxidized to the so-called *N*-oxide.

[0041] The term "stereochemically isomeric forms" defines all the possible stereoisomeric forms which the active ingredients may possess. More in particular, stereogenic centers may have the R- or S-configuration or cis or trans configuration, and active ingredients containing one or more double bonds may have the E- or Z-configuration.

[0042] Preferably, the pharmaceutically active ingredient is an analgesic compound, in particular an opioid or opioid derivative, such as for example tapentadol or a pharmaceutically acceptable acid addition salt thereof, such as for example tapentadol HCl.

[0043] Suitable first and second components for obtaining the powder according to the present spray congealing process according to the invention as defined in the process for the preparation of a solid dosage form are as defined hereinabove for the spray congealed powder.

[0044] Said at least one third component may comprise a hydrophilic polymer, preferably selected from the group consisting of in particular poly(ethylene oxide), poly(vinyl alcohol), hydroxymethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose and carboxy methylcellulose. In a preferred embodiment said hydrophilic polymer comprises poly(alkylene oxide), in particular poly(ethylene oxide) and/or a cellulose derivative, in particular hydroxypropyl methylcellulose. In another preferred embodiment said hydrophilic polymer comprises and in particular essentially consists of poly(alkylene oxide), in particular poly(ethylene oxide), and a cellulose derivative, in particular hydroxypropyl methylcellulose.

[0045] Preferably, said at least one third component is a component sensitive to oxidation, e.g. poly(alkylene oxide).

[0046] Said at least one third component may also comprise one or more hydrophilic polymers constituting a controlled release matrix preferably releasing the pharmaceutically active ingredient gradually, slowly or continuously. Said polymers swell upon contact with aqueous fluid following administration, regularly resulting in a viscous, drug release regulating gellayer. The viscosity of the polymers preferably ranges from 150 to 100,000 mPa.s (apparent viscosity of a 2 % aqueous solution at 20°C). Examples of such polymers are

- alkylcelluloses, such as, methylcellulose;
- hydroxyalkylcelluloses, for example, hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose and hydroxybutylcellulose;
- hydroxyalkyl alkylcelluloses, such as, hydroxyethyl methylcellulose and hydroxypropyl methylcellulose;
- carboxyalkylcelluloses, such as, carboxymethylcellulose;
- alkali metal salts of carboxyalkylcelluloses, such as, sodium carboxymethylcellulose;
- carboxyalkylalkylcelluloses, such as, carboxymethylethylcellulose;
- carboxyalkylcellulose esters;
- other natural, semi-synthetic, or synthetic polysaccharides, such as, alginic acid, alkali metal and ammonium salts thereof, carrageenans, galactomannans, tragacanth, agar-agar, gummi arabicum, guar gummi, xanthan gummi, starches, pectins, such as sodium carboxy-methylamylopectin, chitin derivates such as chitosan, polyfructans, inulin;
- polyacrylic acids and the salts thereof;
- polymethacrylic acids and the salts thereof, methacrylate copolymers;
- polyvinylalcohol;
- polyvinylpyrrolidone, copolymers of polyvinylpyrrolidone with vinyl acetate;
- combinations of polyvinylalcohol and polyvinylpyrrolidone;
- polyalkylene oxides such as polyethylene oxide and polypropylene oxide and copolymers of ethylene oxide and propylene oxide.

[0047] Preferable hydrophilic polymers are polysaccharides, more in particular cellulose derivatives and most in particular cellulose ether derivatives.

[0048] Most preferred cellulose ether derivatives are hydroxypropyl methylcellulose and hydroxypropyl cellulose, in particular hydroxypropyl methylcellulose.

[0049] Different viscosity grades of hydroxypropyl cellulose and hydroxypropyl methylcellulose are commercially available.

[0050] Hydroxypropyl methylcellulose preferably has a viscosity grade ranging from about 3,500 mPa.s to about 100,000 mPa.s, in particular ranging from about 4,000 mPa.s to about 20,000 mPa.s and most in particular a viscosity grade of about 6,500 mPa.s to about 15,000 mPa.s (apparent viscosity of a 2% aqueous solution at 20°C). Exemplary

hydroxypropyl methylcellulose are e.g. hypromellose 2208 (DOW, Antwerp, Belgium) or hypromellose 2910. It is considered to be in the knowledge of the skilled person to recognise the appropriate viscosity or substitution grade of hydroxypropyl methylcellulose.

[0051] Hydroxypropyl cellulose having a viscosity lower than 1,500 mPa.s (apparent viscosity of a 2% aqueous solution at 20°C) is preferred, in particular hydroxypropyl cellulose having a viscosity in the range from about 150 to about 700 mPa.s, preferably from 200 to 600 mPa.s, e.g. Klucel EF® (Hercules, Wilminton, USA).

[0052] The hydrophilic polymers constituting the matrix mainly provide for the controlled, in particular gradual, slow or continuous, pharmacokinetic release profile of the preparation. Depending on the amount of polymers processed in the preparation, the release profile can be tuned. Preferably, the amount of hydrophilic polymer in the present formulation ranges from about 0.01 to about 80% (w/w), in particular from about 10% to about 80% (w/w), or from about 20% to about 80% (w/w), or from about 30% to about 80% (w/w) or from about 40% to about 80% (w/w). In addition, when using a combination of polymers, the ratio of said polymers also influences the release profile of the preparation. For example, when using one or more hydrophilic polymers, preferably cellulose derivatives, more in particular hydroxypropyl cellulose and hydroxypropyl methylcellulose, the weight percentage (% w/w) of hydroxypropyl methylcellulose preferably ranges from 0 to about 16%; the weight percentage of hydroxypropyl cellulose preferably ranges between about 25% and about 62%. The ratio of hydroxypropyl cellulose to hydroxypropyl methylcellulose preferably ranges from 1:5 to 5:1, more preferable from 1:1 to 5:1, and most preferred from 3:1 to 5:1.

[0053] A combination of different polymers offers the possibility of combining different mechanisms by which the active ingredient is released from the matrix. Such combination facilitates control of the pharmacokinetic release profile of the preparation at will. Three main mechanisms exist by which an active ingredient can be released from a hydrophilic matrix : dissolution, erosion and diffusion. An active ingredient will be released by the dissolution mechanism when it is homogeneously dispersed in a matrix network of a soluble polymer. The network will gradually dissolve in the gastro-intestinal tract, thereby gradually releasing its load. The matrix polymer can also gradually be eroded from the matrix surface, likewise releasing the active ingredient in time. When an active ingredient is processed in a matrix made up of an insoluble polymer, it will be released by diffusion : the gastro-intestinal fluids penetrate the insoluble, sponge-like matrix and diffuse back out loaded with drug.

Release of one or more active ingredients from a matrix containing hydroxypropyl cellulose and hydroxypropyl methylcellulose occurs by a combined set of release mechanisms. Due to the higher solubility of hydroxypropyl methylcellulose compared with hydroxypropyl cellulose, the former will gradually dissolve and erode from the matrix, whereas the latter will more act as a sponge-like matrix former releasing the active ingredient mainly by diffusion.

[0054] Said at least one third component may also comprise pharmaceutically acceptable formulating agents in order to promote the manufacture, compressibility, appearance and taste of the preparation. These formulating agents comprise, for example, diluents or fillers, glidants, binding agents, granulating agents, anti-caking agents, lubricants, flavors, sweeteners, dyes, pigments and preservatives.

[0055] The filler may be selected from soluble fillers, for example, sucrose, lactose, trehalose, maltose, mannitol, sorbitol, inulin, and from insoluble fillers, for example, dicalcium or tricalcium phosphate, dicalcium carbonate, talc, microcrystalline cellulose, silicified microcrystalline cellulose. An interesting filler is lactose, in particular, lactose monohydrate. Different grades of lactose can be used. One type of lactose preferably used in the present invention is lactose monohydrate, in particular 200 mesh (e.g. available from DMV, Veghel, the Netherlands). Another preferred lactose monohydrate type is characterised in that 98 %(w/w) of the particles have a diameter smaller than 250 μm, 30 % (w/w) to 60 % (w/w) of the particles have a diameter of 100 μm and at maximum 15 % (w/w) of the particles have a diameter of smaller than 45 μm. Such lactose monohydrate can for example be purchased as lactose monohydrate of the type DCL 11 from DMV, Veghel, the Netherlands. The notation DCL refers to "Direct Compression Lactose". The number 11 is a reference number of the manufacturer. Another interesting filler is mannitol, such as for instance fine grade mannitol or direct compression mannitol (Roquette).

[0056] The weight percentage of filler preferably ranges between 0% to about 54% (w/w), in particular between about 6 % and about 54 % (w/w).

[0057] Among the formulating agents that further may be comprised in the solid dosage form there may be mentioned agents such as polyvidone; starch; acacia gum; gelatin; seaweed derivatives, e.g. alginic acid, sodium and calcium alginate; cellulose derivatives, e.g. ethylcellulose, hydroxypropylmethylcellulose, having useful binding and granulating properties; glidants such as colloidal silica, starch or talc; lubricants such as magnesium stearate and/or palmitate, calcium stearate, stearic acid, polyethylene glycol, liquid paraffin, sodium or magnesium lauryl sulphate; antiadherents such as talc and corn starch.

[0058] In addition to the pharmaceutical acceptable formulating agents described above, cyclodextrins or derivatives thereof may also be included to improve the dissolution rate of the active ingredient. The cyclodextrins which can be used includes the pharmaceutically acceptable unsubstituted and substituted cyclodextrins known in the art, more particularly α, P or y cyclodextrins or the pharmaceutically acceptable derivatives thereof, such as for example β-cyclodextrin ethers, e.g. dimethyl-β-cyclodextrin and polyethers, e.g. hydroxypropyl β-cyclodextrin and hydroxyethyl β-cyclodextrin,

being examples. Another suitable type of substituted cyclodextrins is sulfobutylcyclodextrins. This type is also envisaged in the present invention.

[0059] Suitable sweeteners include sucrose, glucose, fructose or intense sweeteners, i.e. agents with a high sweetening power when compared to sucrose (e.g. at least 10 times sweeter than sucrose). Suitable intense sweeteners comprise aspartame, saccharin, sodium or potassium or calcium saccharin, acesulfame potassium, sucralose, alitame, xylitol, cyclamate, neomate, neohesperidine dihydrochalcone or mixtures thereof, thaumatin, palatinit, stevioside, rebaudioside, Magnasweet ®.

[0060] Suitable flavours include fruit flavours such as tutti frutti, cherry, raspberry, black currant or strawberry flavour, or stronger flavours, such as Caramel Chocolate flavour, caramel sweet tone, Mint Cool flavour, Fantasy flavour, vanilla, grenadine, guarana, masking flavour (Givaudan, in particular masking flavour 11031-31) and the like. Combinations of flavours may also be used.

[0061] Suitable dyes or pigments include iron oxides or aluminium lakes.

[0062] The solid dosage form which can be obtained by the above-described process comprises a tablet, a tablet precursor, a capsule, pellets, beads, and an extrudate.

[0063] Transforming the mixture of the components into a solid dosage form as indicated under point

e) respectively d) of the above-described processes can be done by using pharmaceutically acceptable processes known to the person skilled in the art, such as for example granulation, tabletting including direct compression, slugging, capsule filling, extrusion, pelletization and the like.

[0064] One embodiment of the present invention therefore relates to a process for the preparation of a solid dosage form, in particular a tablet, comprising the steps of

a) providing the powder according to the above spray congealing process of the present invention (component a),
b) providing at least one first, in particular solid, pharmaceutically active ingredient (component b) and/or providing at least one second pharmaceutically active ingredient, in particular in the form of the first component, with said powder of step a),
c) providing at least one third component (component c),
d) forming a mixture therefrom,
e) meltextruding said mixture,
f) collecting the extruded product, and
g) compressing the extruded product into a solid dosage form, in particular a tablet.

[0065] Preferably, in one embodiment said first pharmaceutically active ingredient, said powder and said third component are solid at ambient temperature.

[0066] Upon melt extrusion the extruded product usually is present in the form of at least one strand representing one possible form of the tablet precursor. Alternatively, it is also possible to cut the extruded product, in particular the strand, into individual pieces which represent another form of tablet precursor in the meaning of the present invention. These individual pieces preferably have or approximate the length dimension of the tablet which can be shaped therefrom. It is found to be advantageous for certain embodiments that the strand is cooled below 45 °C, below ambient temperature, particularly to temperatures below 10°C prior to cutting.

[0067] The process for preparing a solid dosage form in the meaning of the invention preferably requires that at least components a), b) and c) respectively a) and c) are homogenously mixed prior to transforming the mixture into a solid dosage form, in particular prior to melt extrusion, preferably while at least components a) and b) and said third component c), respectively a) and said third component are in their solid states.

[0068] With the process for the preparation of a solid dosage form, preferably an extrudate, preferably at least 5 wt % of said pharmaceutically active ingredient, at least 20 wt % of said at least one third component, in particular comprising, more in particular consisting of, poly(ethylene oxide) and hydroxypropyl methylcellulose, and at least 3 wt % of the spray congealed powder, in particular comprising, more in particular consisting of, a vitamin oil and polyalkylene glycol, in particular tocopherol and PEG 6000 are used. Those powders are particularly preferred as spray congealed powders which comprise 50 wt % or less, in particular 25 wt % or less, more in particular 10 wt % or less, even more in particular 8 wt % or less, even further in particular 6 wt % or less or 4 wt % or less, of said first component, based on the total weight of the spray congealed powder.

[0069] According to another aspect of the object of the present invention, there is taught a process for the preparation of a tablet for pharmaceutical application as an oral dosage form comprising the steps of providing at least one tablet precursor obtained according to a process of the present invention, in particular obtained according to the melt extrusion process of the present invention as described hereinabove, subjecting said tablet precursor to a tablet punch, and collecting the tablet or tablets from the tablet punch after the punching step/ compression step. According to one mode

of executing said process, the tablet precursor is cut from the extrudate in the form of an individual piece, in particular approximating the dimensions of the final tablet, said piece is transferred to the tablet press and subjected to the punching step/ compression step, whereupon the punched tablet is collected from the tablet punch. Alternatively, the tablet precursor in the form of an extruded strand is transferred to the tablet press and is as such subjected to the punching step/compression step, whereupon the punched tablets are collected from the tablet punch. In another embodiment, the process for the preparation of the tablet includes that the extruded tablet precursor in the form of a cut individual piece or the tablet precursor in the form of a strand is subjected to the punching step/compression step when still being warm from the melt extrusion process. Alternatively, this process includes that the tablet precursor in the form of a cut individual piece or the tablet precursor in the form of a strand is subjected to the punching step/compression step while having a temperature above ambient temperature and below the melting point or melting range of said at least one second and said at least one third component in said tablet precursor. It is of course also possible that the tablet precursor in the form of a cut individual piece or the tablet precursor in the form of a strand is subjected to the punching step/compression step while having a temperature below ambient temperature, in particular below 15° C.

[0070] From the above it can be derived that according to one embodiment, the present invention also relates to a process for producing a tablet comprising the steps of

a) providing a powder according to a process comprising the steps of providing at least one first component being in liquid form at ambient temperature, in particular having a viscous liquid consistency, such as for example an oil; or having a waxy consistency at ambient temperature, in particular a component which is a solid or semi-solid at ambient temperature and which has an onset of melting in the temperature range from 15 °C to 40 °C,, providing at least one second component having a melting point or melting range in the range from above ambient temperature to below the degradation temperature of said first component, in particular in the range from above ambient temperature to 120 °C, more in particular in the range from >40 °C to 120°C, even more in particular in the range from 50°C to 120°C, even further in particular in the range from 55°C to 120°C or not above 90°C, 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 range of said second component and below the degradation temperature of said first component, in particular in the range from above the melting point or melting range of said second component to 120 °C, more preferably not above 90°C, 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 (component a),
b) providing at least one pharmaceutically active ingredient (component b),
c) providing at least one third component (component c),
d) forming a mixture comprising components a, and b and c,
e) meltextruding said mixture,
f) collecting the extruded product, in particular in the form of at least one strand or in the form of individual pieces obtained by cutting said at least one strand;
g) subjecting said extruded product, in particular in the form of at least one strand or in the form of individual pieces obtained by cutting said at least one strand, to a tablet press; and
h) collecting the tablet or tablets from the tablet press after the punching step/compression step.

[0071] In a preferred embodiment, the at least one first component is one component, in particular alpha tocopherol, and the at least one second component is one component, in particular polyalkylene glycolpolyalkylene glycol, more in particular poly(ethylene) glycol, even more in particular PEG 6000.

[0072] The present invention also relates to a solid dosage form, in particular a tablet, obtainable by or obtained with the process as described hereinabove. Said solid dosage form can also be a tablet precursor such as the product resulting from the above described melt extrusion process, said tablet precursor can be further compressed into a tablet.

[0073] With the present invention it has surprisingly been found that even very low amounts of a liquid or waxy compound such as e.g. an oil, can be homogeneously distributed in a material which is solid at ambient temperature in order to form a powder product, preferably having a small particle size distribution and being suited to be used for the preparation of a solid dosage form, in particular a pharmaceutical tablet. With the process of the present invention, it is now advantageously possible to incorporate even tiny amounts of excipients not being solid at ambient temperature, but being liquid or waxy, into a solid dosage form, e.g. a tablet in a homogenous manner. Furthermore, it is possible to finely adjust these very small amounts of products being liquid or waxy at ambient temperature in the final formulations. For example, it is possible to finely adjust the amount of vitamin E/tocopherol in a tablet formulation in the range of from about 0.05 to about 0.5 wt-% based on the weight of the tablet, the property profile of said tablet can be optimized, for example, in terms of storage stability and ease of formulation. The advantageous storage stability feature not only is an advantage for the tablet itself but also for the tablet precursor being used in the tablet punching step/compression step.

That is, there is no need to immediately subject the extruded tablet precursor to the tablet punching step/compression step, thereby greatly enlarging the mode of operation for the tablet manufacturer. It is, for example, even possible to ship the tablet precursor of the present invention from one production facility to another production site without affecting the efficacy of the final pharmaceutical tablet formulation. It is another benefit of the present invention that the powder products obtained by the spray congealing process of the present invention regularly do not tend to be sticky at ambient temperature.

[0074] The features disclosed in the description as well as in the claims can be used essential alone or in every combination for the realization of the invention in different embodiments. The different embodiments described for the spray congealing process also apply for the process for the preparation of a solid dosage form. As used herein, the term "about" means ± 10% of the value.

Examples:

Example 1:

[0075] Preparation of spray congealed powder having the following composition:

DL-alpha-tocopherol (Vitamin E)	4.00 wt-%
Polyethylene Glycol 6000 (PEG 6000)	96.00 wt-%

Melt preparation process:

[0076] The required amounts of Vitamin E and PEG 6000 were weighed out.An appropriately sized stainless steel feed tank with mixer fitted with a Chromalox Micro Therm temperature control system was purged with nitrogen.PEG 6000 was slowly added into the feed tank.Once partially melted, it was agitated with a mixer to promote melting.Once PEG 6000 was completely added and melted, a melt temperature of 80°C was maintained. The tank was continuously purged with nitrogen.Vitamin E was added into the molten PEG 6000.It was continued to mix for at least 10 minutes before spray congealing started. Agitation was kept throughout the spray congealing process.

Spray congealing process:

[0077] The thermal controllers for the feed lines were set at 90°C and pre-heated for at least 30 minutes.

[0078] The spray congealing process was started :

Apparatus : Niro-PSD-2® (two-fluid nozzle with orifice diameter of 2.0 mm)
Atomization gas : nitrogen (80 °C)
Atomization gas pressure 1.0 bar
Process gas : nitrogen, flow rate 425 CMH
Feed rate : 9 kg/h
Outlet temperature: 10°C
Condenser temperature : 0 °C.

Collection of spray congealed powder

[0079] Spray congealed powder was collected from the cyclone in product drums (purged with nitrogen for a minimum of 5 minutes before sealing).

Example 2 (comparative examples)

Preparation of powder containing vitamin E

[0080] The aim was to divide a small amount of vitamin E into a powder blend. The powder blend consisted of Tapentadol HCl, Polyethylene Oxide 7M, Hydroxypropyl methylcellulose and Polyethylene glycol 6000.

a)) absorbing Vitamin E on a solid carrier

[0081] One way of incorporating a small amount of a liquid such as Vitamin E into a powder is first absorbing the liquid

to a solid carrier, then blending with the remaining of the solid excipients. If the dilution is important, it can be performed geometrically, e.g the Vitamin E containing carrier is mixed with one or more solid powder(s) (to obtain a certain dilution) and the blend obtained is diluted again with the same or other solid powder(s).

[0082] First it was tried to absorb the vitamin E on one of the excipients, namely polyethylene oxide PEO) 7 M which is a major component of the powder blend. It was tried to coat 1 part of Vitamin E on 9 parts of PEO. Distribution of the Vitamin E onto the PEO 7M was not successful.

b) Therefore, a carrier was introduced, i.e. a powder specifically used for its large surface area so that the amount needed can be as little as possible in order not to interfere too much with the original formulation characteristics.

[0083] Neusilin (synthetic amorphous magnesium aluminium metasilicate) was selected as solid carrier for absorption of the Vitamin E due to its high specific surface and proposed chemically inert nature. Two available Neusilin grades (Fuji Chemical Industry Co.), US2 and UFL2, were used to screen absorption capability for the Vitamin E.

[0084] The Vitamin E-Neusilin blends were prepared in a Pro-C-epT Mi-Pro lab-scale high shear granulator with a bowl of 250 ml, without heated jacketing and without employing the Mini-Pro's dosing syringe and closed loop system. The Neusilin, Vitamine E and Fe_2O_3 were weighed and transferred into the granulation bowl and sheared to the point the product quality did not improve anymore. Fe_2O_3 was added in a 1% concentration as a colorant to monitor visually the homogenicity of the blends. The Vitamin E was heated to about 40°C to reduce viscosity and thus allow better weighing and distribution.

Vitamin E on Neusilin (1:1 w:w)

[0085] US2 type Neusilin gave an extremely poor distribution of the Vitamin E with he formation of very large lumps.

[0086] Initial aspect of the coated ULF2 was that of successful absorption of the Vitamin onto the Neusilin ULF2, although some small lumps were also present. Over time however the mixture started to agglomerate strongly. Within 1 day, the effect was already pronounced, after several days the agglomeration was such that a large particle sized granulate was formed instead of coated powder.

[0087] Because of the clear difference in distribution of Vitamin E with Neusilin grades US2 and UFL2, further experiments to prepare premix and further dilutions were only performed with ULF2.

c) Preparation of a premix (dilution of coated carrier (Vitamin E on Neusilin) with further excipients)

[0088] The Vitamin E coated Neusilin ULF2 (1:1 w:w) was sieved through a 75μm sieve and 1g of coated carrier was first blended with 24g of poly(ethylene oxide) (PEO) 7M as inert excipient (= 1/25 dilution step) (premix). Next, 2.5 g of this premix was blended again with 47.5g PEO 7M (= 1/20 dilution step) (end mixture) to come to a 1/500 dilution ratio. The blends were prepared using the Turbula mixer.

[0089] The aspect of the premix and end mixture was homogenous to the eye. These mixtures were re-examined after more than a week and remained stable whereas the undiluted neusilin-Vitamin E agglomerated completely over time as indicated before. In this experiment, a very fine sieve (75μm sieve) was used which is not practical on industrial scale.

Vitamin E on Neusilin ULF2 (1:2.5 w:w)

[0090] To improve blend quality Neusilin lumps must be avoided. This includes the formation of lumps in the granulator as well as preventing the post-production agglomeration tendency. Therefore the ratio of Neusilin was increased to try to stabilize the carrier/Vitamin E mixture. To help prevent lump formation the Vitamin E was added with a syringe instead of weighed onto the neusilin as a whole. Additionally, the option of immediate dilution of the coated carrier in the PEO was tried. Furthermore the necessity of sieving was evaluated. To this end a single batch of Neusilin was coated, split in 4 fractions, of which 2 were not processed further but one was sieved (500μm sieve) and 2 fractions used to produce premixes with again one premix being sieved (coated carrier was sieved over 500μm sieve (more adapted to production scale compared to 75μm sieve) and then diluted (1/25 dilution) with PEO).

[0091] Heating of Vitamin E (40°C) was found to be necessary to bring viscosity down enough to allow filling of the syringe. By using the syringe, formation of lumps was greatly reduced since previously Vitamin E could adhere to the granulator walls and thus cause lumps after bowl discharge.

[0092] Increasing the amount of Neusilin helped to reduce the degree of agglomerate formation but still did not sufficiently prevent it. When the obtained powder was sieved, it was initially clear of agglomerates but already after one day was no longer distinguishable from the unsieved carrier.

[0093] It was seen that the distribution of the Vitamin E in the premix was limited to a crude dispersion of carrier

agglomerates. Also the distinction between colored agglomerates and near white PEO slightly increased over time, indicating an unstable system.

Vitamin E on Neusilin ULF2 with EtOH (1:2.5:0.8 w:w):

[0094] To further improve the Vitamin E distribution on Neusilin with minimizing aggregate formation, a Vitamin E miscible solvent was selected in order to greatly modify the viscosity of the thick, oily Vitamin E. In this experiment 2.77g Vitamin E was mixed with 2.22g Ethanol 96° prior to the filling of the dosing syringe. The mixing took place in the Mi-Pro using a 250ml bowl. The Vitamin E/ ethanol solution was injected in the bowl containing 7.1g Neusilin UFL2 and ca 100mg iron oxide. As indicated for the previous experiment, 4 fractions were made from a single coating batch. Two fractions were the unprocessed coated carrier of which only one was sieved through a 500 μm sieve and two fractions were further diluted to premixes with again one being sieved (coated carrier was sieved over 500μm sieve and then diluted with PEO). The premixes consisted of 1 part coated Neusilin with 19 parts PEO 7M to give a dilution factor of 1/20 for the premix. All fractions were dried overnight at 30°C under a 250 mbar vacuum.

[0095] Using the ethanol, the Vitamin E did not need to be heated anymore to allow filling of the syringe which is considered an advantage since Vitamin E is a strong anti-oxidant, best not exposed too much to heat. Technically the carrier coating can now be done completely without lump formation in the granulation bowl. With time however the undiluted carrier started to agglomerate whether previously sieved or not. The aspect of the premixes looked homogenous under magnification. Post-drying the fractions did not really seem to create additional agglomeration in the samples.

[0096] In further experiments it was shown that satisfactory result can also be obtained with less ethanol.

[0097] From these experiments it is clear that the carrier system with Vitamin E on Neusilin (synthetic amorphous magnesium aluminium metasilicate) is not stable as such since the finely powdered Neusilin tends to agglomerate strongly over time. The use of ethanol as solvent is beneficial to improve the distribution of the Vitamin E in the powder, even though it is introducing an organic solvent in the manufacturing process which might have detrimental safety implications. In conclusion, the incorporation of Vitamin E in a solid powder by mixing was only possible through the use of a carrier and a solvent as a vehicle. The coated carrier powder obtained was not physically stable and needed to be diluted immediately with a portion of a excipient making up the formulation composition (in the above experiments, a portion of the PEO).

Example 3

Spray congealing Vitamin E and PEG 6000

[0098] PEG 6000 was weighed and molten on an off-line heating plate. Only slightly before the experiments took place an appropriate amount of Vitamin E was added and mechanically mixed with the PEG 6000. The mixture was heated to about 75 to 80°C and transferred to the spraying nozzle of a Mobile Minor spray dryer by heated feed lines.

[0099] The mixture was sprayed through a two-fluid nozzle with N_2 pre-heated at 100°C. The cooling gas was also N_2 which had an in-let temperature of 11 to 13°C and out-let temperature in the range of 20-26°C. After spraying the particles were collected in the cyclone of the spray-dryer.

[0100] Experiments were conducted with different concentrations of Vitamin E (1%, 2% or 4% (w/w) of actual Vitamin E content. Spray congealing of the Vitamin E with PEG 6000 was successful. The spray congealed product was obtained in a finely powdered state without being sticky or having much agglomeration. Loss of product in the spray chamber was also minimal since high yields were obtained. The aspect of the Vitamin E-PEG was homogenous in color and no brownish zones, indicative of separated Vitamin E, were spotted in the powders or against the chamber walls.

Example 4

Stability tests

[0101] Powders prepared by absorbing vitamin E on a carrier or the powders prepared by spray congealing (prepared according to example 3) were placed in glass bottles and stored under different conditions (5°C and 30°C/75% Relative Humidity). The concentration of "active" Vitamin E (Vitamin E which still has anti-oxidative activity) was determined by HPLC assay and the appearance of the powders was visually inspected.

[0102] The following coated carrier blends were tested :

Table 1 : Compositions and calculated contents for Neusilin powder 1 and Neusilin powder 2

Neusilin powder 1	MATERIAL	QUANTITY (g)	PERCENTAGE
Carrier	Vitamin E	4.0	30.0 %
	Ethanol	1.3	10.0 %
	Neusilin ULF2	8.0	60.2 %
Premix	Carrier	12.0	6.7 %
	PEO 7M	168.0	93.3 %
Calculated[a]	Vitamin E	3.60	2.0 %
	Neusilin ULF2	7.22	4.0 %
	PEO 7M	168.0	94.0 %

Neusilin powder 2	MATERIAL	QUANTITY (g)	PERCENTAGE
Carrier	Vitamin E	4.0	30.0 %
	Ethanol	1.3	10.0 %
	Neusilin ULF2	8.0	60.2 %
Premix	Carrier	12.0	6.7 %
	PEO 7M	168.0	93.3 %
Calculated[b]	Vitamin E	3.60	2.0 %
	Ethanol	1.20	0.7 %
	Neusilin ULF2	7.22	4.0 %
	PEO 7M	168.0	93.3 %

[a]Calculations assume that all the EtOH has been removed from the mixture.
[b]Calculations assume that the full amount of EtOH is still present in the premix.

[0103] The blends were prepared as follows:

In a first process step all the neusilin was coated with the Vitamin E / EtOH mixture in the Mi-Pro (0.25L bowl, impeller speed 200-400 rpm, chopper speed 500-650 rpm for 45 minutes). After emptying the bowl, fraction 1 was made by blending 5g of the coated neusilin with 70g PEO 7M in the Pro-C-epT (12 minutes at 250 rpm impeller speed in the 0.25L bowl). When this was in turn emptied, fraction 2 was made with 4.5g coated Neusilin and 63.0g PEO 7M (16 minutes at 250 rpm impeller speed in the 0.25L bowl). Fraction 1 and 2 have the same relative compositions but the difference is that fraction 2 (=Neusilin powder 1) was post-dried at 25°C under a vacuum of 300 mbar for 16 hours, whereas fraction 1 (=Neusilin powder 2) was not.

[0104] The neusilin based premixes were found to be unstable. In fact, the Vitamin E content dropped so much already after one month at 30°C/75%RH that the study of those samples was discontinued.

[0105] Spray congealed powder prepared as described above (see Example 3) were also subjected to the same conditions. For each Vitamin E concentration (1%, 2% and 4% w/w) a small and a large particle size fraction was tested. Particle size was adjusted by amending the feed rate, nozzle diameter and/or N_2 rate during the spray congealing process).

[0106] The results are gathered in the below Table 2:

	Condition	Time	Appearance	Active VitE content (HPLC assay)
Spray congealed powder PEG 6000 with 1%w/w Vit E: large particle size (average d50 : 73 μm)		Initial	PASS	97.7
	5 °C,	After 1 month	PASS	97.2
		After 3 month	PASS	95.1
	30 °C/75% RH	After 1 month	PASS	92.1
		After 3 month	PASS	82.4
Spray congealed powder PEG 6000 with 1%w/w Vit E: small particle size (average d50 : 40 μm)		Initial	PASS	110.8
	5 °C	After 1 month	PASS	110.4
		After 3 month	PASS	115.5
	30 °C/75% RH	After 1 month	PASS	103.4
		After 3 month	PASS	85.1
Spray congealed powder PEG 6000 with 2%w/w Vit E: large particle size (average d50 : 43 μm)		Initial	PASS	95.1
	5 °C	After 1 month	PASS	94.7
		After 3 month	PASS	100.8
	30 °C/75% RH	After 1 month	PASS	91.1
		After 3 month	PASS	81.1
Spray congealed powder PEG 6000 with 2%w/w Vit E: small particle size (average d50 : 12 μm)		Initial	PASS	82.5
	5 °C	After 1 month	PASS	85.2
		After 3 month	PASS	86.9
	30 °C/75% RH	After 1 month	PASS	81.9
		After 3 month	PASS	85.0

(continued)

	Condition	Time	Appearance	Active VitE content (HPLC assay)
Spray congealed powder PEG 6000 with 5%w/w Vit E: large particle size (average d50 : 40 μm)		Initial	PASS	79.2
	5 °C	After 1 month	PASS	78.5
		After 3 month	PASS	88.3
	30 °C/75% RH	After 1 month	PASS	76.0
		After 3 month	PASS	66.0
Spray congealed powder PEG 6000 with 5%w/w Vit E: small particle size (average d50 : 16 μm)		Initial	PASS	80.2
	5 °C	After 1 month	PASS	78.6
		After 3 month	PASS	73.2
	30 °C/75% RH	After 1 month	PASS	77.2
		After 3 month	PASS	79.3

[0107] The spray congealed powders showed acceptable stability at 5°C. The samples with 1% Vitamin E seemed a little bit less stable than the other samples which have a higher Vitamin E content. At 30°C/75%RH, the loss of Vitamin E in the spray congealed powders was larger so that cold refrigeration is probably advisable.

[0108] Based on the above data it can be seen that the carrier system is not practical to manufacture (use of solvent, need for direct premixing to mitigate physical unstability/ demixing) and it is also chemically not stable (Vitamin E assay drops quite rapidly). Spray congealing in the meaning of the present invention highly facilitates the reliablemanufacture of powdered systems comprising little amounts of in particular liquids such as vitamin oils into a solid second component, and is looking more promising than the the absorption of Vitamin E on carriers.

Example 5

Blend uniformity (BU)

Powder blend composition 1:

[0109]

Tapentadol HCl 58.24 mg

Polyethylene Oxide WSR 303
Hydroxypropyl methylcellulose
Polyethylene glycol 6000

Spray congealed powder of Polyethylene glycol 6000 and alpha tocopherol (4.56 % of vitamin E in the spray congealed powder)	13.16 mg
Total weight of the powder	400 mg

Powder blend composition 2:

[0110]

Tapentadol HCl 291.20 mg

Polyethylene Oxide WSR 303
Hydroxypropyl methylcellulose
Polyethylene glycol 6000

Spray congealed powder of Polyethylene glycol 6000 and alpha tocopherol (4.56 % of vitamin E in the spray congealed powder)	15.35 mg
Total weight of the powder	700 mg

[0111] Of powder blend composition 1 and 2, batches of 240 kg were prepared.

[0112] The spray congealed powder was prepared according to an analoguous process as described in example 3. The individual components of the blend were delumped if necessary (screened using a Sweco separator with 20 mesh or following a passive manual method using a 20 mesh), then weighed and introduced in a 800L IBC bin. After 20 minutes blending on a Bohle blender at 6 rpm, the bin was opened to take samples from 10 different locations in the bin using a sample thief. The Vitamin E blend uniformity (BU) was determined by determining the active Vitamin E content of the collected samples by HPLC assay and calculating the % relative standard deviation which is a measure of the uniformity of the Vitamin E in the samples.

[0113] For blend 1, 3 batches of 240 kg were prepared and the % relative standard deviation for the Vitamin E content for the first batch was 1.5 %; for the second batch 2.3 % and the third batch 2.9 %.

[0114] For blend 2, 3 batches of 240 kg were prepared and the % relative standard deviation for the Vitamin E content for the first batch was 2.9 %; for the second batch 1.8 % and the third batch 1.7%.

[0115] These results show good BU.

Example 6

Tablet Content uniformity (CU)

Powder blend composition 3:

[0116]

Tapentadol HCl 58.24 mg

Polyethylene Oxide WSR 303
Hydroxypropyl methylcellulose
Polyethylene glycol 6000

Spray congealed powder of Polyethylene glycol 6000 and alpha tocopherol (4 % of vitamin E in the spray congealed powder)	15.00 mg
Total weight of the powder	400 mg

Powder blend composition 4:

[0117]

Tapentadol HCl 291.20 mg

Polyethylene Oxide WSR 303
Hydroxypropyl methylcellulose
Polyethylene glycol 6000

Spray congealed powder of Polyethylene glycol 6000 and alpha tocopherol (4 % of vitamin E in the spray congealed powder)	17.50 mg
Total weight of the powder	700 mg

[0118] Powder blends 3 and 4 were prepared as described in example 5. Tablets were prepared from powder blend compositions 3 and 4 as follows. The powder blends were extruded in a corotating twin-screw extruder; the resulting strands were cooled and cut into individual pieces which were compressed into tablets of 400 mg (containing 50 mg of tapentadol) respectively 700 mg (containing 250 mg of tapentadol). The collected tablets were film coated in a perforated pan film coater with a suspension consisting of 20% w/w pharmaceutical coating powder in purified water. The coating suspension was applied on the tablet cores to the level of 3% w/w, after which the tablets were dried, and the batch was sampled for analysis.

[0119] From 30 tablets prepared from each of the blends, the active Vitamin E content was determined by HPLC assay and the % relative standard deviations was calculated as a measure of content uniformity (CU) of the Vitamin E in the tablets.

[0120] The % relative standard deviation for the 400 mg tablets prepared from blend 3 was 4.96 % and the % relative standard deviation for the 700 mg tablets prepared from blend 4 was 3.87 %.

[0121] These results show good CU.

Claims

1. Process for preparing a powder comprising the steps of

   i) providing at least one first component, wherein the at least one first component comprises or represents vitamin oil, lecithine or simethicone,
   ii) providing at least one second component having a melting point or melting range above ambient temperature, wherein the at least one second component comprises or consists of polyalkylene glycol,
   iii) 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 range of said second component to 120 °C, wherein the homogeneous liquid mixture comprises from 92 wt % to 99.9 wt % of the at least one second component and from 0.1 wt % to 8 wt % of the at least one first component,
   iv) 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,
   v) spray congealing said mixture, and
   vi) isolating the powder obtained upon spray congealing.

2. The process according to claim 1, wherein the at least one first component comprises or consists of tocopherol and/or tocopherol derivatives.

3. The process according to any of the preceding claims, wherein the at least one second component comprises or consists of polyethylene glycol.

4. The process according to claim 3, wherein the polyethylene glycol is polyethylene glycol 6000 (PEG 6000).

5. The process according to any of the preceding claims, wherein said transfer unit comprises at least one feed line and at least one pump, wherein at least said feed line is adapted to be heatable.

6. The process according to any of the preceding claims, wherein the melting point or melting range of the second component is in the range from >40 °C to 120°C.

7. Powder obtainable by the process of any of the preceding claims.

8. The powder according to claim 7 comprising or consisting of from 92 wt % to 99.9 wt polyalkylene glycol as said at least one second component, and from 0.1 wt % to 8 wt % tocopherol as said at least one first component.

9. The powder according to claim 7 or 8 having a particle size distribution d_{50} in the range from 40 μm to 300 μm.

10. Use of a powder according to any of claims 7 to 9 for the preparation of a solid dosage form containing at least one pharmaceutically active ingredient.

11. Use according to claim 10, wherein said solid dosage form comprises at least one pharmaceutically active ingredient, at least one poly(alkylene oxide), at least one cellulose ether derivative, at least one polyalkylene glycol, and at least one vitamin oil.

12. Use according to claim 11, wherein said vitamin oil is present in an amount of less than 1 wt-%, based on the total weight of the solid dosage form.

13. Process for the preparation of a solid dosage form comprising the steps of

a) providing a powder according to the process of any of claims 1 to 6 (component a),
b) providing at least one pharmaceutically active ingredient (component b),
c) providing at least one third component (component c),
d) forming a mixture comprising components a, b and c,
e) transforming said mixture into a solid dosage form.

14. The process according to claim 13, wherein said at least one third component (component c) is selected from the group consisting of poly(alkylene oxide), poly(vinyl alcohol), hydroxymethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose and carboxy methylcellulose.

15. The process for the preparation of a tablet according to claim 13 or 14 comprising the steps of

a) providing the powder according to the process of any of claims 1 to 6 (component a),
b) providing at least one pharmaceutically active ingredient (component b),
c) providing at least one third component (component c),
d) forming a mixture comprising components a, b and c,
e) meltextruding said mixture,
f) collecting the extruded product, and
g) compressing the extruded product into a tablet.

Patentansprüche

1. Verfahren zur Herstellung eines Pulvers umfassend die Schritte

i) Zurverfügungstellen wenigstens einer ersten Komponente, wobei die wenigstens eine erste Komponente Vitaminöl, Lecithin oder Simeticon umfasst oder für diese Komponente steht,
ii) Zurverfügungstellen wenigstens einer zweiten Komponente, die einen Schmelzpunkt oder Schmelzbereich oberhalb Raumtemperatur aufweist, wobei die wenigstens eine zweite Komponente Polyalkylenglykol umfasst oder aus Polyalkylenglykol besteht,
iii) Bilden eines homogenen Flüssigkeitsgemisches umfassend die eine erste Komponente und die eine zweite Komponente durch Rühren und Erhitzen des Gemisches auf oder Halten des Gemisches bei einer Temperatur im Bereich von ab oberhalb des Schmelzpunktes oder des Schmelzbereichs der zweiten Komponente bis 120°C, wobei das homogene Flüssigkeitsgemisch ab 92 Gew.-% bis 99,9 Gew.-% wenigstens einer zweiten Komponente und von 0,1 Gew.-% bis 8 Gew.% wenigstens einer ersten Komponente umfasst,
iv) Übertragen des Flüssigkeitsgemisches in wenigstens eine Sprüherstarrungsvorrichtung durch wenigstens eine Transfervorrichtung, die daran angepasst ist, das Gemisch während seines Transportes in seiner flüssigen Form zu halten,
v) Sprüherstarren des Gemisches, und
vi) Isolieren des Pulvers, das durch Sprüherstarren erhalten wird.

2. Das Verfahren gemäß Anspruch 1, wobei die wenigstens eine erste Komponente Tocopherol und/oder Tocopherolderivate umfasst oder aus Tocopherol und/oder Tocopherolderivaten besteht.

3. Das Verfahren gemäß einem der vorhergehenden Ansprüche, wobei die wenigstens eine zweite Komponente Polyethylenglykol umfasst oder aus Polyethylenglykol besteht.

4. Das Verfahren gemäß Anspruch 3, wobei das Polyethylenglykol Polyethylenglykol 6000 (PEG 6000) ist.

5. Das Verfahren gemäß einem der vorhergehenden Ansprüche, wobei die Transfervorrichtung wenigstens eine Zuleitung und wenigstens eine Pumpe umfasst, wobei wenigstens die Zuleitung daran angepasst ist, beheizbar zu sein.

6. Das Verfahren gemäß einem der vorhergehenden Ansprüche, wobei der Schmelzpunkt oder der Schmelzbereich der zweiten Komponente im Bereich von >40°C bis 120°C ist.

7. Ein Pulver, das durch das Verfahren gemäß einem der vorhergehenden Ansprüche erhältlich ist.

8. Das Pulver gemäß Anspruch 7 umfassend oder bestehend aus ab 92 Gew.-% bis 99,9 Gew.-% Polyalkylenglykol als die wenigstens zweite Komponente und ab 0,1 Gew.-% bis 8 Gew.-% Tocopherol als die wenigstens erste Komponente.

9. Das Pulver gemäß Anspruch 7 oder 8, das eine Teilchengrößenverteilung d_{50} im Bereich ab 40 μm bis 300 μm aufweist.

10. Verwendung eines Pulvers gemäß einem der Ansprüche 7 bis 9 zur Herstellung einer festen Darreichungsform, die wenigstens einen pharmazeutisch wirksamen Bestandteil enthält.

11. Verwendung gemäß Anspruch 10, wobei die feste Darreichungsform wenigstens einen pharmazeutisch wirksamen Bestandteil, wenigstens ein Polyalkylenoxid, wenigstens ein Celluloseetherderivat, wenigstens ein Polyalkylenglykol und wenigstens ein Vitaminöl umfasst.

12. Verwendung gemäß Anspruch 11, wobei das Vitaminöl in einer Menge von weniger als 1 Gew.-% vorhanden ist, bezogen auf das Gesamtgewicht der festen Darreichungsform.

13. Verfahren zur Herstellung einer festen Darreichungsform umfassend die Schritte

a) Zurverfügungstellen eines Pulvers gemäß dem Verfahren einer der Ansprüche 1 bis 6 (Komponente a),
b) Zurverfügungstellen wenigstens eines pharmazeutisch wirksamen Bestandteils (Komponente b),
c) Zurverfügungstellen wenigstens einer dritten Komponente (Komponente c),
d) Bilden einer Mischung umfassend die Komponenten a, b und c,
e) Umwandeln der Mischung in eine feste Darreichungsform.

14. Das Verfahren gemäß Anspruch 13, wobei die wenigstens eine dritte Komponente (Komponente c) ausgewählt wird aus der Gruppe bestehend aus Polyalkylenoxid, Polyvinylalkohol, Hydroxymethylcellulose, Hydroxyethylcellulose, Hydroxypropylcellulose, Hydroxypropylmethylcellulose und Carboxymethylcellulose.

15. Das Verfahren zur Herstellung einer Tablette gemäß den Ansprüchen 13 oder 14 umfassend die Schritte

a) Zurverfügungstellen des Pulvers gemäß dem Verfahren einer der Ansprüche 1 bis 6 (Komponente a),
b) Zurverfügungstellen wenigstens eines pharmazeutisch wirksamen Bestandteils (Komponente b),
c) Zurverfügungstellen wenigstens einer dritten Komponente (Komponente c),
d) Bilden einer Mischung umfassend die Komponenten a, b und c,
e) Schmelzextrudieren der Mischung,
f) Sammeln des extrudierten Produkts, und
g) Komprimieren des extrudierten Produkts in eine Tablette.

Revendications

1. Procédé pour préparer une poudre comprenant les étapes consistant à

i) utiliser au moins un premier composant, ledit au moins un premier composant comprenant ou représentant

une huile de vitamine, de la lécithine ou de la siméthicone,
ii) utiliser au moins un deuxième composant, présentant un point de fusion ou une plage de fusion supérieur(e) à la température ambiante, ledit au moins un deuxième composant comprenant ou étant constitué par du polyalkylèneglycol,
iii) former un mélange liquide homogène comprenant ledit au moins un premier composant et ledit au moins un deuxième composant par agitation et par chauffage du mélange ou par maintien du mélange à une température dans la plage allant d'une température supérieure au point de fusion ou à la plage de fusion dudit au moins un deuxième composant jusqu'à 120°C, le mélange liquide homogène comprenant 92% en poids à 99,9% en poids dudit au moins un deuxième composant et 0,1% en poids à 8% en poids dudit au moins un premier composant,
iv) transférer le mélange liquide dans au moins une unité de solidification par pulvérisation à l'aide d'au moins une unité de transfert qui est conçue pour maintenir le mélange sous sa forme liquide pendant son transfert,
v) solidifier par pulvérisation ledit mélange et
vi) isoler la poudre obtenue après la solidification par pulvérisation.

2. Procédé selon la revendication 1, ledit au moins un premier composant comprenant ou étant constitué par du tocophérol et/ou des dérivés de tocophérol.

3. Procédé selon l'une quelconque des revendications précédentes, ledit au moins un deuxième composant comprenant ou étant constitué par du polyéthylèneglycol.

4. Procédé selon la revendication 3, le polyéthylèneglycol étant le polyéthylèneglycol 6000 (PEG 6000).

5. Procédé selon l'une quelconque des revendications précédentes, ladite unité de transfert comprenant au moins une conduite d'alimentation et au moins une pompe, ladite au moins une conduite d'alimentation étant conçue de manière à pouvoir être chauffée.

6. Procédé selon l'une quelconque des revendications précédentes, le point de fusion ou la plage de fusion du deuxième composant étant situé(e) dans la plage de >40°C à 120°C.

7. Poudre pouvant être obtenue par le procédé selon l'une quelconque des revendications précédentes.

8. Poudre selon la revendication 7, comprenant ou constituée par 92% en poids à 99,9% en poids de polyalkylèneglycol comme ledit au moins un deuxième composant et 0,1% en poids à 8% en poids de tocophérol comme ledit au moins un premier composant.

9. Poudre selon la revendication 7 ou 8, présentant une distribution des grosseurs de particule d_{50} dans la plage de 40 μm à 300 μm.

10. Utilisation d'une poudre selon l'une quelconque des revendications 7 à 9 pour la préparation d'une forme galénique solide contenant au moins un ingrédient pharmaceutiquement actif.

11. Utilisation selon la revendication 10, ladite forme galénique solide comprenant au moins un ingrédient pharmaceutiquement actif, au moins un poly(oxyde d'alkylène), au moins un dérivé d'éther de cellulose, au moins un polyalkylèneglycol et au moins une huile de vitamine.

12. Utilisation selon la revendication 11, ladite huile de vitamine étant présente en une quantité inférieure à 1% en poids, sur base du poids total de la forme galénique solide.

13. Procédé pour la préparation d'une forme galénique solide, comprenant les étapes consistant à

a) utiliser une poudre selon le procédé selon l'une quelconque des revendications 1 à 6 (composant a),
b) utiliser au moins un ingrédient pharmaceutiquement actif (composant b),
c) utiliser au moins un troisième composant (composant c),
d) former un mélange comprenant les composants a, b et c,
e) transformer ledit mélange en une forme galénique solide.

14. Procédé selon la revendication 13, ledit au moins un troisième composant (composant c) étant choisi dans le groupe

constitué par le poly(oxyde d'alkylène), le poly(alcool vinylique), l'hydroxyméthylcellulose, l'hydroxyéthylcellulose, l'hydroxypropylcellulose, l'hydroxypropylméthylcellulose et la carboxyméthylcellulose.

15. Procédé pour la préparation d'un comprimé selon la revendication 13 ou 14, comprenant les étapes consistant à

a) utiliser la poudre selon le procédé selon l'une quelconque des revendications 1 à 6 (composant a),
b) utiliser au moins un ingrédient pharmaceutiquement actif (composant b),
c) utiliser au moins un troisième composant (composant c),
d) former un mélange comprenant les composants a, b et c,
e) extruder à l'état fondu ledit mélange,
f) récupérer le produit extrudé et
g) comprimer le produit extrudé en un comprimé.

REFERENCES CITED IN THE DESCRIPTION

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