Pharmaceutical or neutraceutical composition comprising palmitoylethanolamide particles.

The present invention relates to a pharmaceutical composition comprising palmitoylethanolamide particles and/or pharmaceutically acceptable esters or salts thereof, in which the palmitoylethanolamide particles are substantially free of pharmaceutical excipients. The present invention relates further to a method for preparing such palmitoylethanolamide particles, to the particles obtainable with said method and to pharmaceutical compositions comprising said particles.
PHARMACEUTICAL OR NEUTRACEUTICAL COMPOSITION COMPRISING
PALMITOYLETHANOLAMIDE PARTICLES

FIELD OF THE INVENTION

The present invention relates to a pharmaceutical and/or neutraceutical composition for human and/or veterinary use, comprising N-palmitoylthanolamide (also referred to as palmidrol or N-(2-Hydroxyethyl)hexadecanamide). The present invention relates particularly to a pharmaceutical or neutraceutical composition for human and/or veterinary use, comprising a therapeutically efficient amount of palmitoylthanolamide in micronized particles without pharmaceutical excipients in such a way to enable filling capsules with the said micronized compound.

BACKGROUND OF THE INVENTION

In recent years more attention has been given to the clinical potential of palmitoylthanolamide. It has been used to treat a wide range of diseases and disorders. However, due to its lipophilic nature, pharmaceutical excipients have been used in considerable amounts to prepare suitable pharmaceutical formulations from it. Some of these excipients may decrease the efficacy of palmitoylthanolamide and lead to unwanted side effects. Furthermore, laborious and sophisticated techniques among which micronization techniques have been used to prepare suitable pharmaceutical compositions comprising palmitoylthanolamide in such a way to enable filling tablets or sachets for human or veterinary use with the said compound and leading to a commercially viable product.

In the United States Patent Application 20110171313 it is stated that palmitoylthanolamide, a substance of lipophilic and lipidic nature, is hard to subject to micronization methods, due to the easiness with which the fatty compound palmitoylthanolamide tends to generate aggregates. Further, it is stated in this patent that the micronization in mechanical energy mills tends to heat the particles and thus promotes an aggregation phenomenon, in practice being in contrast with the desired object to transform the composition into fine particle sizes in order to enhance surface-content ratio and the absorption.

These considerations lead to the various formulation-technology processes, as described in United States Patent Application 20110171313 and in United States Patent 6548550. In these patents a procedure has been developed and has been described to formulate palmitoylthanolamide in a micronized-and in an ultra-micronized formulation.
These formulations have been developed based on the philosophy of the inventors, as stated in the patents mentioned above, and it is stated that palmitoylethanolamide tends to generate waxy agglomerates, also due to the rise in temperature when the product particles spend prolonged periods of time in the described classical micronization chamber.

In United States Patent Application 20110171313 the inventors stated related to the procedures of micronization of palmitoylethanolamide:

"In the tests that were initially carried out, in fact, a trend of the product to generate waxy agglomerates had been noticed, also due to the temperature rise for prolonged dwelling times of the product particles in the micronization chamber, which are necessary to obtain a more efficient micronization."


Any crude oils throughout the world contain significant quantities of wax, which can crystallize during production and/or transportation of the oil; this may cause major difficulties and stagnation in pipeline transportation. The same holds true for the procedures of filling capsules or creating tablets or sachets with fatty or oily ingredients: agglomerates may be formed, especially when heated, so that the industrial filling of capsules becomes impossible. Although the said patents define specific micronization and ultramicronization techniques to enable the industrial production of presentations (such as tablets, capsules or sachets), the procedure described does not prevent the said waxy agglomerates in the final marketed formulations. In Figure 1 these waxy agglomerates, indicated with ‘C’ for 'conglomerates’, can be easily observed.

This micronization however does not lead to a final finely powdered product as filled in commercially available sachets. On the contrary the waxy agglomerates ‘C’ are easy to identify and in Figure 1 these can be compared to the finely milled palmitoylethanolamide flakes, indicated with ‘F’, according to this invention; palmitoylethanolamide free of excipients, sweeteners and other chemical additives; the white powder.

Figure 1: Conglomerates of palmitoylethanolamide (labeled with 'C'), ultramicronized as described in the most recent patent 'Composition containing ultra-micronized palmitoyl – ethanolamide; EP 2475352 A1’. Finely milled palmitoylethanolamide flakes, indicated with ‘F’, according to this invention; the white powder.
In the international patent application WO01/10434 (D1) a pharmaceutical composition is referred to and we quote:

“The present invention relates to pharmaceutical compositions containing N-palmitoylthanolamide (palmidrol) for use in the veterinary field, particularly for the treatment of the eosinophilic skin condition in felines which is normally known as Eosinophilic Granuloma Complex, and of tendinous keloids in horses.” In that patent it is clear that the said pharmaceutical composition is based on the said micronization method, by air jet spray, and not on the procedures we describe in this embodiment. All examples presented in the international patent application WO01/10434 (D1) are based on the micronization method by air jet spray.

This is explicitly defined in the section “PREPARATION OF N-PALMITOYLETHANOLAMIDE (PEA)” where the inventors state:

"PEA is a known compound and can be prepared in accordance with the synthesis method described in EP 0 550 008 which is incorporated herein by reference. The micronization of PEA and its co-micronization with excipients were performed with compressed-air turbine micronizing apparatus. It should be noted that this result of the micronization method obtained with PEA is surprising since it is unusual for a molecule of a lipid nature to produce particles with a mean fineness much less than 10 μ. The extreme fineness of the particles can be translated into improved absorption of the drug.”

In the above mentioned patent or in the related patents micronization without excipients leading to a commercial viable formulation has not been referred to; the inventors did not present any mention in any of their patents to alternative micronization methods using milling devices as described in this embodiment, leading to excipient free and commercially viable formulations. The only method of micronization method described was: The micronization of PEA and its co-micronization with excipients were performed with compressed-air turbine micronizing apparatus.

In the subsequent experiments and scale up experiments described in this embodiment, various procedures were found, described in this invention, to fill capsules with pure pamitoylthanololamide without facing any of the rheological problems specified in the patents discussed above, leading to waxy agglomerates being formed.

Although in United States Patent Application 20110171313 it was recommended to micronize palmitoylthanolamide to very small particles, no clear clinical proof was given to support the usefulness of micronization or ultra-micronization of palmitoylthanolamide in such small particles (diameter below 10 microns). On the contrary, as we will point out in this patent, such small particles give rise to unwanted metabolites of palmitoylthanolamide.

Furthermore, as we presented above, the latest commercial product according to the ultramicronization technique contains a substantial number of fatty-agglomerated particles.
Furthermore, evidence from the clinical trials conducted before 2002, as well as animal data, support the fact that biological and clinical relevant effects can be obtained with palmitoylethanolamide without any of these sophisticated micronization or ultra-micronization techniques.

The technology described in the family of patents discussed, is complicated in nature and specific excipients are needed in order to compress tablets and prepare ultra-micronized particles for sublingual use. Furthermore, these formulations of palmitoylethanolamide have numerous drawbacks, as will be pointed out subsequently, and illustrated in examples 7 and 8.

First of all, the ultra-micronized form of palmitoylethanolamide, of which about 99.9% by weight has particle sizes below 6 microns, gives rise to high plasma levels of a metabolite of palmitoylethanolamide, 2-arachidonoylglycerol (2-AG), which is non-essential for treatment purposes. In this regard it is stated in United States Patent Application 20110171313 that the administration per os of palmitoylethanolamide in the ultra-micronized form generates a quick and huge increase of 2-AG in blood (‘which increase is higher than 400% compared to the basal levels’).

The inventors of United States Patent Application 20110171313 misjudged this as a positive finding, because at that time the inventors thought 2-AG was an endocannabinoid of great importance in the modulation of the activation of cells capable of expressing the cannabinoid CB2 receptor. However, later this was found not to be correct, as 2-arachidonoylglycerol (2-AG) appears to have affinity for several receptors in addition to CB2 (Stella N, Schweitzer P, Piomelli D (August 1997). "A second endogenous cannabinoid that modulates long-term potentiation". Nature 388 (6644): 773–8.; Sugiuira T, Kodaka T, Nakane S, et al (January 1999). Evidence that the cannabinoid CB1 receptor is a 2-arachidonoylglycerol receptor. Structure-activity relationship of 2-arachidonoylglycerol, ether-linked analogues, and related compounds. The Journal of Biological Chemistry 274 (5): 2794–801.).

2-AG is present at relatively high levels in the central nervous system and it has been demonstrated that 2-AG has a different pharmacological profile compared to its mother compound, palmitoylethanolamide, a profile which potentially could give rise to unwanted side effects. The key mechanism of action for palmitoylethanolamide is via the nuclear peroxisome proliferator-activated receptor type A. Palmitoylethanolamide has no affinity for the CB1 or for the CB2 receptor and should therefore not be regarded as an endocannabinoid. (O'Sullivan, S. E.; Kendall, D. A. (2010). "Cannabinoid activation of peroxisome proliferator-activated receptors: Potential for modulation of inflammatory disease". Immunobiology 215 (8): 611–616.). The pharmacologically desired action is not via 2-AG, but via this nuclear receptor.
A second drawback of the palmitoylethanolamide formulations according to the family of patents discussed and known in the state of the art, is the presence of a number of excipients, which might compromise its desired clinical effects and lead to unwanted side effects.

Firstly, the excipients used in the available formulations of palmitoylethanolamide impair a smooth passage into the blood, due to complex pharmaceutical interactions between the active ingredient, i.e. palmitoylethanolamide, and these excipients. For example, excipients, such as magnesium stearate (up to 12% of total weight are present in the micronized commercially available palmitoylethanolamide products) and povidone, can decrease absorption of lipophilic molecules (see below).

The primary role of magnesium stearate in supplements is to act as a lubricant and thus to prevent tablet and/or capsule contents from sticking to the machinery that processes them. However, it has been pointed out that the effect of magnesium stearate is to increase the time it takes for tablets and capsules to dissolve, due to the film it forms on capsule and/or tablet ingredients, as will be pointed out in some detail in this patent. Magnesium stearate coats a good portion of the molecules in a tablet or capsule, requiring digestive enzymes to break down the magnesium stearate coating and thus complicating the absorption of the natural molecule, palmitoylethanolamide, which can also be found in food, such as peanut oil, egg yolk, soybean lecithin and dairy products (KUEHL F.A., JACOB T.A., GANLEY O.H., ORMOND R.E., MEISINGER M.A.P. The identification of N-(2-hydroxyethyl)-palmitamide as a naturally occurring anti-inflammatory agent. J. Am. Chem. Soc. 1957;79:5577–5578.).

The negative influence of magnesium stearate on the dissolution of lipophilic molecules is widely known (Tay T, Morton DA, Gegenbach TR, Stewart PJ. Dissolution of a poorly water-soluble drug dry coated with magnesium and sodium stearate. Eur J Pharm Biopharm. 2012 Feb;80(2):443-52. Epub 2011 Oct 20.). These authors were particularly concerned about individuals suffering from impaired digestion, because they may have more difficulty in absorbing nutrients (and palmitoylethanolamide is a nutrient) coated with magnesium stearate. Moreover, as many users of palmitoylethanolamide suffer from diabetes, and diabetes can be a cause of impaired digestion, the drawback of this excipient needs to be taken seriously.

Meanwhile, it is widely known by those skilled in the art that magnesium stearate is capable of forming films on other tablet excipients during prolonged mixing, leading to a prolonged drug liberation time, a decrease in hardness and an increase in disintegration time (Uzunović A, Vranic E. Effect of magnesium stearate concentration on dissolution properties of ranitidine hydrochloride coated tablets. Bosn J Basic Med Sci. 2007 Aug;7(3):279-83).

Chowhan et al (Chowhan ZT, Chi LH. Drug-excipient interactions resulting from powder mixing. IV: Role of lubricants and their effects on in vitro dissolution (J Pharm Sci. 1986 Jun;
75(6):542-5)) compared magnesium stearate to sodium stearyl fumarate under identical mixing conditions to study their roles in drug-excipient interactions. After prolonged mixing sodium stearyl fumarate did not interact with the drug or excipients, as a result the disintegration time and drug dissolution rate from hand-filled, uncompacted capsules were not adversely affected. On the other hand, magnesium stearate did exhibit drug-excipient interactions, which resulted in lamination and subsequent adhesion of the lubricant to the drug-crospovidone agglomerates. These interactions adversely affected the disintegration time and drug dissolution rate from hand-filled, uncompacted capsules. This is already sufficient to support the development of a magnesium-stearate free formulation. The other negative aspect described was the adhesion of the magnesium stearate flakes to the drug-crospovidone agglomerates, which also resulted in a decrease in the drug dissolution rate. Thus, also a povidone-free formulation might be superior in its physico-chemical properties. The combination of povidone as a binder and stearic acid as a lubricant has frequently been reported to increase dissolution problems (Desai D, Kothari S, Huang M. Solid-state interaction of stearic acid with povidone and its effect on dissolution stability of capsules. Int J Pharm. 2008 Apr 16;354(1-2):77-81. Epub 2007 Nov 29.).

In this study the authors clearly state: “based on the observed solid-state interaction, a combination of stearic and povidone should be avoided for immediate release formulations”.

Furthermore, the origin of magnesium stearate is bovine-based, and many users of palmitoylethanolamidamide ask for formulations which are 100% non-animal, which is a reason to select a formulation free of magnesium stearate and filled in vegetable capsules. We will provide a description of such a non-animal formulation in example 2 described below.

An additional drawback of the palmitoylethanolamidamide formulation known in the state of the art is that considerable amounts of sorbitol are used in the formulation. The amounts used can generate adverse effects, such as diarrhea and gastrointestinal discomfort in sensitive individuals and in diabetic patients. (Fernández-Bañares F, Esteve M, Viver JM. Fructose-sorbitol malabsorption. Curr Gastroenterol Rep. 2009 Oct;11(5):368-74; Payne ML, Craig WJ, Williams AC. Sorbitol is a possible risk factor for diarrhea in young children. J Am Diet Assoc. 1997 May;97(5):532-4.).

As Gould et al pointed out: diabetic patients are more likely to have associated diseases that are accompanied with diarrhea. Ingested sugar-free foods that may contain sorbitol or other agents can thus easily provoke diarrhea in diabetic patients (Gould M, Sellin JH Diabetic diarrhea. Curr Gastroenterol Rep. 2009 Oct;11(5):354-9.). Even chewing gum containing sorbitol can give rise to diarrhea and weight loss (Bauditz J, Norman K, Biering H, Lochs H, Pirlich M. Severe weight loss caused by chewing gum. BMJ. 2008 Jan 12;336(7635):96-7.). Furthermore, in animal models sorbitol is not always toxicologically clean, as it can for instance retard bone resorption (Mattila PT, Svanberg MJ, Mäkinen KK, Knuuttila ML. Dietary

Due to the issues mentioned above and as diabetic patients suffering from neuropathic pains often use palmitoylethanolamide, the presence of sorbitol in a palmitoylethanolamide formulation is suboptimal.

Furthermore, the presence of sorbitol in a palmitoylethanolamide formulation designed for sublingual use has an extra drawback, as sorbitol compromises the bioavailability of palmitoylethanolamide. If patients use the formulation with sorbitol sublingually, the sweetness of the product leads to production of large quantities of saliva in the mouth. This will reduce sublingual resorption and induce swallowing reflexes. Swallowing is contra-productive if sublingual resorption is intended.

In view of the statements mentioned above a need exists to provide a stable palmitoylethanolamide formulation that overcomes all the problems mentioned above.

Particularly, a need exists for a stable palmitoylethanolamide formulation, in which the excipients and sweeteners mentioned above, such as magnesium stearate, povidone and sorbitol, are not used. However, up to now this was thought not to be feasible.

SUMMARY OF THE INVENTION

The inventors of the present invention found that the current state of the art ideas in the field of how to come to optimally stable palmitoylethanolamide formulations, in particular to a fine palmitoylethanolamide powder, are not correct and are based on prejudice.

A first aspect of the present invention relates to a pharmaceutical composition comprising particles of palmitoylethanolamide and/or pharmaceutically acceptable esters or salts thereof, in which the palmitoylethanolamide particles are substantially free of pharmaceutical excipients, such that said palmitoylethanolamide particles do not form agglomerates.

A second aspect of the present invention relates to a method to prepare palmitoylethanolamide particles, in which the particles are substantially free of pharmaceutical excipients, comprising the following steps:

i) providing palmitoylethanolamide flakes;

ii) micronizing the palmitoylethanolamide flakes into palmitoylethanolamide particles in the absence of pharmaceutical excipients, so that the particles obtained have a particle size distribution, in which:
- at least 99% of the particles have a diameter between 1 µm and 850 µm;
- at least 40% of the particles have a diameter smaller than 425 µm.

A third aspect of the present invention relates to the above mentioned pharmaceutical composition of palmitoylethanolamide particles for use in the treatment or prevention of various diseases and disorders.

The present invention proves that it is possible to prepare a fine powder with sufficient flow (defined as optimal rheological properties of the palmitoylethanolamide particles in order to fill capsules with finely milled palmitoylethanolamide without the emergence of waxy agglomerates) of palmitoylethanolamide, if micronization is carried out at room temperature on laboratory scale in batches up to several hundred grams.

This invention also proves that it is possible to prepare a fine powder, with optimal rheological properties, at an industrial size with batches reaching from several kilograms up to more than a thousand kilograms.

Furthermore, the particles according to the present invention do not comprise pharmaceutical excipients, such as magnesium stearate, povidone or sorbitol. As will be explained below this has a favorable effect on production costs, but more importantly adverse effects due to the use of these excipients is avoided, while the bioavailability of palmitoylethanolamide might be optimized.

In the prior art, at the time of the filing date of this patent, it was not recognized that it is possible to prepare the desired palmitoylethanolamide particles without using pharmaceutical excipients.

Furthermore, the micronized palmitoylethanolamide according to this invention is suited to be dissolved in topical formulations, particularly in a cream base consisting of cetomacrogol, cetostearyl-alcohol, cetiol and sorbitol (cremor cetomacrogolis) alone, or in the presence of L-theanine, bismaltolato-oxovanadium, or co-analgesics such as baclofen, amitriptyline and ketamine, as illustrated in example 12.

DEFINITIONS

The term 'pharmaceutical excipient' or 'excipient' as used here has its normal scientific meaning and refers to inert carriers used in pharmaceutical and neutraceutical compositions. A non-exhaustive list of excipients is provided in Rowe et al, Handbook of Pharmaceutical Excipients, fifth edition, 2006.
The term ‘micronization’ as used here has its normal scientific meaning and refers to the process of reducing the size of particles, such as flakes. The term comprises at least grinding, milling, cutting and bashing.

The term ‘diameter’ as used here has its normal scientific meaning and refers to a volumetric measurement based on the presumed spherical shape of the palmitoylethanolamide particles.

The term ‘pharmaceutical composition’ as used here has its normal scientific meaning and refers to a composition comprising one or more pharmaceutically or neutraceutically active constituents which may be administered to mammals, including humans.

The term ‘pharmaceutical composition’ as used here encompasses the term ‘nutritional compositions’ as well as ‘food for medical purposes’.

DETAILED DESCRIPTION OF THE INVENTION

A first aspect of the present invention relates to a pharmaceutical or neutraceutical composition (further referred to as ‘pharmaceutical’) comprising palmitoylethanolamide particles and/or pharmaceutically acceptable esters or salts thereof, in which the palmitoylethanolamide particles are free of pharmaceutical excipients, such that said palmitoylethanolamide particles do not form agglomerates.

The palmitoylethanolamide particles as such are thus present as a free drug, i.e. that in the solid particles the palmitoylethanolamide is not intimately embedded in an excipient. However, the particles as such, may form a part of a pharmaceutical composition, which composition may comprise one or more pharmaceutically acceptable excipients or diluents.

In this regard ‘free of pharmaceutical excipients’ thus means that the palmitoylethanolamide particles as such comprise less than 0.1%, preferably less than 0.01%, more preferably less than 0.001% on a dry weight basis of pharmaceutical excipients, such as magnesium stearate or povidone.

Preferably, the complete pharmaceutical composition is free from pharmaceutical excipients, however, besides the palmitoylethanolamide particles small amounts of excipients may be used to prepare the composition. Also in such a composition, the palmitoylethanolamide particles as such are substantially free of pharmaceutical excipients.

In a preferred embodiment of the present invention the palmitoylethanolamide particles have a size distribution in which:
- at least 99% of the particles have a diameter between 1 μm and 850 μm; and
- at least 40% of the particles have a diameter smaller than 425 μm.

The palmitoylethanolamide particles as such as well as the pharmaceutical composition are preferably free from magnesium stearate, povidone, sorbitol and/or other pharmaceutical excipients, i.e. that these comprise less than 0.1%, preferably less than 0.01%, more preferably less than 0.001% on a dry weight basis of pharmaceutical excipients.

In another preferred embodiment of this invention the pharmaceutical composition comprises a second or further pharmaceutically active ingredient. Preferably, the second or further pharmaceutically active ingredient based on synergies with the mechanism of action of palmitoylethanolamide, such as l-theanine, vitamin D, glucosamine, Boswellia serrate extracts, vanadium salts such as bis (maltolato)oxovanadium and/or picamilon. These compounds are all classified as supplements, and are selected based on their mechanism of action, which works synergistically to that of palmitoylethanolamide. Some examples from the clinic of the synergistic effects of palmitoylethanolamide when administered together with the above mentioned supplements, have been given in example 11.

l-theanine has been selected because l-theanine induces pharmacological stabilization of mast cells and inhibits pro-inflammatory cytokines, such as TNF-α, IL-1β, IL-6, and IL-8, as described in Kim NH, Jeong HJ, Kim HM. Theanine is a candidate amino acid for pharmacological stabilization of mast cells. (Amino Acids. 2012 May;42(5):1609-18. doi: 10.1007/s00726-011-0847-9. Epub 2011 Feb 23).

Vitamin D has been selected for its synergistical effects on palmitoylethanolamide, related to the effect of supplementation: a significant reduction of the proinflammatory cytokine IL6. Furthermore, treatment of T cells with vitamin D or analogs inhibits the secretion of proinflammatory Th1 of the proinflammatory compounds such as IL2, interferon and TNF-alpha, and promotes the production of more anti-inflammatory Th2 cytokines (IL3, IL4, IL5, IL10), recently pointed out by Prietl et al (Prietl B, Treiber G, Pieber TR, Amrein K. Vitamin d and immune function. Nutrients. 2013 Jul 5;5(7):2502-21. doi: 10.3390/nu5072502.)

Glucosamine has been selected not only for its supposed analgesic effect in artrotic pains, but specifically because Glucosamine has been shown to have additional immunosuppressive properties. Recently it has been shown that the production of Th2 cytokines, such as IL-4 and IL-5, was significantly decreased after in vitro administration of glucosamine. The authors therefore suggested that glucosamine might be a useful immunomodulatory agent for the treatment of human atopic eczema. (Kim CH, Cheong KA, Park CD, Lee AY. Glucosamine improved atopic dermatitis-like skin lesions in NC/Nga mice by inhibition of Th2 cell development. Scand J Immunol. 2011 Jun;73(6):536-45. doi: 10.1111/j.1365-3083.2011.02526.x.)
Palmitoylthanolamide also has been described as a useful anti-inflammatory compound for the same disease, which was the base of selecting glucosamine as an adjunct in palmitoylthanolamide preparations described in this embodiment. (Kircik L. A nonsteroidal lamellar matrix cream containing palmitoylthanolamide for the treatment of atopic dermatitis. J Drugs Dermatol. 2010 Apr;9(4):334-8.

Vanadium salts have been selected based on the findings of Oliver et al (2007), where these salts significantly reduced clinical arthritis and inhibited pro-inflammatory cascades relevant for the pathogenesis of arthritis and osteoarthritis: synovial mRNA expression of collagenase, stromelysin, and IL-la. (Oliver SJ, Firestein GS, Arsenault L, Cruz TF, Cheng TP, Banquerigo ML, Boyle DL, Brahn E. Vanadate, an inhibitor of stromelysin and collagenase expression, suppresses collagen induced arthritis. J Rheumatol. 2007 Sep;34(9):1802-9. Epub 2007 Aug 1.) Extract of Boswellia serata has been selected due to its positive therapeutic effects on the levels of inflammatory cytokine-patterns. (Bowden RG, J Moreillon J, Deike E, Griggs J, Wilson R, Shelmadine B, Cooke M, Beaujean A. The use of an anti-inflammatory supplement in patients with chronic kidney disease. J Complement Integr Med. 2013 Jul 1;10(1):1-10.). Boswellia serata extracts down regulate of TNF-alpha and decreases many other inflammatory cytokines, such as IL-1, IL-2, IL-4, IL-6 and IFN-gamma. Furthermore, Boswellia has comparable effects to palmitoylthanolamide in models for neuro-inflammatory, such as stroke (Moussaieff A, Yu J, Zhu H, Gattoni-Celli S, Shohami E, Kindy MS. Protective effects of incensole acetate on cerebral ischemic injury. Brain Res. 2012 Mar 14;1443:89-97.). Picamilon has been selected, because this molecule has been proven to have neuroprotective properties, among which positive effects in diabetic neuropathy, one of the key indications of palmitoylthanolamide. [Kuchmerovskaia TM, Parkhometks PK, Donchenko GV, Obrosova IG, Klimenko AP, Kuchmerovskii NA, Pakirbaeva LV, Efimov AS. Correction of diabetic neuropathies using aldose reductase inhibitors and pikamilon]. Vopr Med Khim. 1998 Nov-Dec;44(6):559-64.)

Furthermore, it is preferred to present the composition in a capsule or in a sachet for sublingual use.

Preferably, the pharmaceutical composition according to the present invention is for use in the treatment or in the prevention of so-called silent inflammations and neuroinflammations, such as Alzheimer's disease, Parkinson's disease, diabetes mellitus, and atherosclerosis.

Furthermore, the pharmaceutical composition according to the present invention may also be used in the treatment or in the prevention of aseptic inflammations and autoimmune induced inflammations, such as colitis ulcerosa, amyotrophic lateral sclerosis (morbus
Charcot), morbus Crohn, ankylitis spondylopoetica, reumatoid arthritis, chronic otitis media, cochleotis, tinnitus, pancreatitis, autoimmune nephritis, chronic hepatitis, steatosis, vitiligo, psoriasis, allergic dermatitis, pruritis, prostatitis, interstitial cystitis, vaginitis, vulvovestibulitis, depression, asthmatic disorders, morbus Sjoegren, keratoconjunctivitis sicca, multiple sclerosis, diabetic nephropathy, diabetic retinopathy, chronic hepatitis, critical illness polyneuropathy and the syndrome of Guillain-Barre-Landry-Srohl.

The pharmaceutical composition according to the present invention may also be used to prevent or to reduce reperfusion-ischemia injury and thus can be used to treat disorders such as spinal cord injury, brain injury, stroke, nerve crush syndromes, retinitis diabeticca, myocardial infarction, renal reperfusion injury during and after renal transplantation, macular edema, laminitis (in horse and in cattle), liver ischemia and reperfusion injury after stenting or after Dotter procedures.

The pharmaceutical composition according to the present invention can also be used to counteract or to prevent neurotoxicity induced by neurotoxic drugs or chemotherapeutic drugs, such as thalidomide, bortezomib, cisplatin, carboplatin, oxilaplatin, taxotere, taxane-derivatives (such as paclitaxel and docetaxel), vinca-alkaloids, vincristine, capesitabine, and 5-fluorouracil.

The pharmaceutical composition according to the present invention can also be used to treat neurotoxicity induced by hypervitaminosis B6, paraneoplastic and irradiation pains. Furthermore, it is to be preferred to use the pharmaceutical composition according to the present invention to reduce or to prevent pain in a variety of chronic pain states, such as neuropathic pain syndromes, chronic regional pain syndrome type I and type II, diabetic pain, joint pains, artrosis pains, pain in the syndrome of Costen, fibromyalgia pain, herpes zoster pain, cancer pains, pain in central cord lesions, syringomyelia, spinal cord tumors and hydromyelia, migraine, atypical facial pains, and neuralgias.

Furthermore, it is to be preferred to use the pharmaceutical composition according to this invention in the treatment or in the prevention of whooping cough (infection with Bordetella pertussis) and its late sequellae, post-Lyme syndrome, myalgic encephalomyelitis (ME), prolonged reconvalescence after severe disorders and infectious diseases, the chronic fatigue syndrome (CFS) and the post viral fatigue syndrome (PVFS).

The pharmaceutical composition according to the present invention can also be used to treat inflammations of the skin, such as erythrasma, psoriasis and atopic eczema.

A second aspect of the present invention relates to a method to prepare particles of palmitoylthanolamide, in which the particles are free of pharmaceutically acceptable excipients, comprising the following steps:

i) providing palmitoylthanolamide flakes;
ii) micronizing the palmitoylethanolamide flakes into palmitoylethanolamide particles in the absence of pharmaceutical excipients, in such a way that the particles obtained have a particle size distribution, in which:

- at least 99% of the particles have a diameter between 1 μm and 850 μm,
- at least 40% of the particles is smaller than 425 μm.

By applying the method of this invention one is able to obtain palmitoylethanolamide particles and pharmaceutical compositions thereof without having to use excipients. This has a positive effect on production costs. More importantly, palmitoylethanolamide particles and compositions are obtained that do not cause adverse effects or reduce the bioavailability of palmitoylethanolamide, due to the presence of excipients. The latter will not only be important for the human species, but also for canine species and other carnivorous species, as the digestive tract of these animals is shorter and it is likely that fatty compounds such as magnesium stearate might compromise the bioavailability of palmitoylethanolamide even more than that it does in humans.

The flakes used for preparing the palmitoylethanolamide particles according to the present invention have a particle size of 200 to 20,000 μm, preferably 1000 to 20,000 μm.

It is to be preferred to carry out micronization of the palmitoylethanolamide flakes at a temperature between minus 20 to minus 200°C, preferably minus 100°C to minus 200°C, more preferably minus 190°C to minus 200°C, most preferably at about minus 196°C Celsius.

In a preferred embodiment of the present invention the micronization of the palmitoylethanolamide flakes is carried out in the presence of liquid nitrogen. For example the micronization can take place by adding liquid nitrogen to create a cryogenic micronization procedure. During micronization, as in grinding, for instance in grinding mills known in the field, as for instance in a Retsch grinding device, 1-20 ml. fluid nitrogen could be added per minute.

Furthermore, in order to prevent clustering of palmitoylethanolamide particles during encapsulation (as smearing effects), the encapsulation of the particles in capsules may also take place under cryogen conditions, i.e. at the above mentioned temperatures, such as for example about minus 196 degrees Celsius.

This procedure is generally known to be used in cryogenic micronization, as in grinding, of materials defined as tough, soft or elastic. As materials defined as tough, soft or elastic are difficult, if not impossible, to micronize at room temperature, because these materials bend instead of break into small pieces, cooling to a temperature of about minus 196 degrees Celsius, using liquid nitrogen, makes the structure brittle, thus making micronization easy. To micronize fatty compounds, such as palmitoylethanolamide, this cooling technology has never been applied: there is no prior art. We have discovered that the principle of cryogenic...
micronization, as grinding, is also applicable to palmitoylethanolamide. Moreover, we also found that the cryogenic procedure helps to prevent waxy agglomerates from being generated and to improve the flow of palmitoylethanolamide during the process of encapsulating palmitoylethanolamide. Micronizing palmitoylethanolamide in seconds becomes possible by using this technique, without any tendency of palmitoylethanolamide to form waxy agglomerates.

For encapsulation any encapsulation machine can be used, for instance a Capsugel 8. However, also during the process of encapsulation temperature influences generation of waxy agglomerates in such a way that smooth filling of capsules becomes impossible. It was found that cryogenic filling of capsules makes smooth filling possible. By dripping 1-20 ml of liquid nitrogen per minute and preferably by dripping 5 ml per minute into the entry opening of the encapsulation machine the generation of waxy agglomerates is prevented. Cryogenic filling of capsules with palmitoylethanolamide is not known in the prior art.

Surprisingly, in a follow-up experiment, in which batches were scaled up to generate 1 kg of palmitoylethanolamide powder, using an oscillating and rotating sieve mill, such as one of the mills of the OscilloWitt series, suited for the size reduction of heat-sensitive products and products that are difficult to process, finely grained palmitoylethanolamide could be prepared without the necessity of cryomilling, which demonstrated that the assumptions of the patent of United States Patent Application 20110171313 are incorrect. Furthermore, even grinding in a cross beater mill and a hammer mill (TA 0202; Freewitt) resulted in finely grained palmitoylethanolamide, without waxy agglomerates being generated, which could be used to fill capsules as the powder had optimal rheological properties. Furthermore, subsequent filling procedures of capsules in a Capsugel machine could also be achieved without cooling; fine powder without the tendency to generate waxy agglomerates was produced and could be filled in capsules without technical problems. All this has led to an improved production process compared to the current state of the art.

A third aspect of this invention relates to palmitoylethanolamide particles obtained by applying the methods mentioned above, and their use in a pharmaceutical composition.

A fourth aspect of this invention relates to palmitoylethanolamide particles alone or combined with the above mentioned supplements such as l-theanine, Boswellia serrata, vitamin D, BMOV and/or accepted co-analgesics such as baclofen, amitriptyline, ketamine and clonidine, and their use in a pharmaceutical composition for topical use. Surprisingly we found that palmitoylethanolamide, as well as l-theanine, BMOV, Boswellia serrata and the mentioned co-analgesics all dissolve in a cream based on cetomacrogol, cetostearyl-alcohol, cetiol and sorbitol (cremor cetomacrogolis), as explained in example 14.
Now aspects of the invention will be described more elaborately by means of some non-limiting examples.

Example 1

The palmitoylethanolamide was formulated according to one of the methods described in this invention, where palmitoylethanolamide flakes were milled to a fine powder in an oscillating and rotating sieve mill, at room temperature. This generated palmitoylethanolamide particles as described with the above mentioned characteristics: at least 99% of the particles have a diameter between 1 μm and 850 μm; and at least 40% of the particles have a diameter smaller than 425 μm. The palmitoylethanolamide powder after the milling had rheological properties that allowed easy filling of capsules, using in this case a Macofar filling machine at room temperature.

For the first clinical experiments a batch of 1000 capsules was produced; these capsules were used in the clinical experiment in a human patient; for the experiment in a dog the milled palmitoylethanolamide was applied to food, without the capsule.

Example 1

A quantity of 100 grams of pure palmitoylethanolamide (99.8% purity) flakes (particle between 1 mm. to 2 cm.) was inserted into a high speed Magimix 4200 XL. The high speed blade reduced the particle size of the flakes to a particle size in a range of μm 50 μm. to 800 μm. Surprisingly, waxy agglomerates were not formed. The fine palmitoylethanolamide particles formed a fine aerosol, settling after about 1 to 2 minutes after the cutting process of the flakes. The powder had a sufficient flow. This experiment proved that waxy agglomerates were not formed, whereas one of the key characteristics for encapsulation, flow, was good according to professionals in the state of pharmaceutical art.

Example 2

A vegetable capsule or a gelatine based capsule filled with 300, 400 or 600 mg. of micronized palmitoylethanolamide according to this invention.

Example 3
A sachet for sublingual use, filled with 600 or 800 mg. of micronized palmitoylethanolamide.

Example 4

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Food mix for horses and cattle containing:

10 grams of lupine feed or any other acceptable fodder containing 3 grams of micronized palmitoylethanolamide (measuring cup supplied).

Example 5

Containers for dogs and cats containing 150 mg of micronized palmitoylethanolamide per serving, mixed with freeze-dried meat powder (measuring cup supplied).

Example 6

The following experiment is devised to show the creation of a second unique formulation of the present invention: a soft gel or capsule, in which the amount of palmitoylethanolamide is dissolved in or mixed with a polyunsaturated oil, such as soybean oil, rice bran oil, fish oil, olive oil or any other polyunsaturated oil. Below we will describe the formulation based on rice bran oil.

25 The preferred softgel capsule or any other capsule formulation of the present invention is prepared in accordance with the following sequence of ingredients and procedure.

Rice bran oil, a carrier suspension agent for soft gel formulation useful for the absorption of lipophilic ingredients, such as palmitoylethanolamide, and in itself a therapeutic oil containing various polyunsaturated fatty acids, is heated to a temperature of about 95-100° C. Then palmitoylethanolamide is added. This temperature is around the melting point of palmitoylethanolamide. The palmitoylethanolamide and the oil is mixed until a uniform mixture has been formed.

35 In the experiment 10 grams of palmitoylethanolamide was dissolved in 10 grams of rice bran oil at a temperature of about 95-100° C. The finely powdered palmitoylethanolamide dissolved
in the oil and a homogenous fatty soft substance emerged. Consequently, this demonstrates that a softgel capsule or any other capsule can be filled with a mixture of oil and palmitoylethanolamide.

Example 7:

First clinical tests with powdered, micronized palmitoylethanolamide.

In the example described here, palmitoylethanolamide was formulated according to the method described in this invention, where palmitoylethanolamide flakes were milled to a fine powder in an oscillating and rotating sieve mill, at room temperature. This generated the described palmitoylethanolamide particles with the above mentioned characteristics: at least 99% of the particles have a diameter between 1 µm and 850 µm; and at least 40% of the particles have a diameter smaller than 425 µm. The palmitoylethanolamide powder after the milling had rheological properties that allowed easy used to filling of capsules, using in this case a Macofar filling machine.

Tapering off Normast, substituting Normast for finely milled palmitoylethanolamide according to this invention.

In the clinical experiments described below Normast ultramicronized tablets were compared to the palmitoylethanolamide formulated according to this invention. The composition of Normast consist of tablets of palmitoylethanolamide (ultra-micronized), and in each tablet the following excipients are used: microcrystalline cellulose, croscarmellose, povidone, magnesium stearate, colloidal silicon, polysorbate 80. In this ultra-micronized form of palmitoylethanolamide 90% of all particles have a size smaller than 6 microns, as described in United States Patent Application 20110171313. The palmitoylethanolamide according to this invention consisted of capsules of finely milled palmitoylethanolamide, as described above, without any excipient added.

In the first clinical experiment, an eleven-year-old Cavalier King Charles spaniel was a full responder on 300 mg. of Normast a day. Normast has been successfully used in this breed of dogs (http://www.neuropathie.nu/research-development/syringomyelia-in-cavalier-spaniels-treated-successfully-with-no.html).

35
Symptoms of syringomyelia started at an age of 9.5 years. The dog was treated for one year, all his clinical signs (air scratching, inactivity, paresis, lacrimation and inflammation of the eyes) disappeared. The dog was then tapered off Normast treatment. Within a period of 2-4 days the symptoms of syringomyelia re-appeared: inactivity, air scratching, locomotor problems, paresis and clear signs of conjunctivitis/eye inflammation (excessive lacrimation and redness).

After a week the symptoms grew worse and the dog became increasingly immobile and lethargic. Normast was reintroduced and within 4 days the symptoms started to decrease. The symptoms of eye inflammation did not fully resolve.

After some time a new period of tapering off was started. The same relapse occurred as described above. Palmitoylethanolamide, 300 mg. a day, produced according to the present invention, free of excipients, was introduced. Within 3 days the symptoms started disappearing, the dog became more active, and all signs of eye inflammation disappeared. After using palmitoylethanolamide for a week the clinical picture had improved further and there were even clear indications the dog had reached an improved state compared to the earlier state using Normast. He was more playful, willing to run and barked much more frequently in response to playful situations, which had previously been extremely rare; the eyes were both clear without signs of inflammation. His owner interpreted the reactions of the dog on the formulation used according to this invention as “significantly better” compared to Normast. The dog was also able to move around quicker and for longer periods of time. The improvements on the formulation described in this patent were observed over a period of 8 months. Clinically, the state of health of the dog was also clearly superior compared to that while treated with Normast. After this clinical experiment, demonstrating the clinical effects of palmitoylethanolamide, formulated according to this invention a series of Cavalier King Charles Spaniels, all previous responders to Normast treatment, were tapered off Normast and switched to palmitoylethanolamide, formulated according to this invention. The owners of the dogs informed us without exception, that the dogs were livelier under the present formulation and its clinical effects were more robust.

These substitution experiments demonstrated at least equal biological activity of the palmitoylethanolamide produced according to the present invention compared to Normast. The advantages of palmitoylethanolamide according to the present invention compared to Normast were:
1. Easy administration of finely milled palmitoylethanolamide powder via food to the dog, compared to crushing a tablet or applying a 300 mg tablet into the food of the dog.

2. Better clinical response, both the syringomyelia symptoms as well as the inflammation of the eye responded more favourably on treatment with palmitoylethanolamide according to this invention than on Normast.

In the second clinical experiment, a 62-year-old lady suffering from chronic artrosis and joint pains during 20 years, was treated conventionally but this did not result in a satisfactory response. She started treatment with Normast and she responded favourably. She experienced less pain and improved mobility. After several months she stopped taking palmitoylethanolamide, and within 4 days her symptoms re-emerged. She restarted Normast and noticed improvement within 5 days. During a holiday period she stopped again, and this again resulted in a relapse. She restarted treatment, after 1 week without palmitoylethanolamide treatment. The symptoms decreased and she felt much better. This defined her as a full responder on palmitoylethanolamide using Normast. She then stopped Normast at the end of August 2012 and started treatment with the palmitoylethanolamide according to this invention. Her situation remained stable, and her symptoms improved further within 7 days. She could even play golf again for 4 hours, without being exhausted, which was not possible at all while being treated with Normast. Hence, the clinical results with the palmitoylethanolamide composition according to the present invention were significantly better. The clinical improvements were unaltered during a further observation period of 4 months. Furthermore, according to verbal information from the patient, the palmitoylethanolamide capsules according to this invention were much easier to swallow compared to the Normast 600 mg tablets.

Both patients described above were clear Normast responders and their symptoms relapsed after stopping Normast treatment. Re-initiating treatment with palmitoylethanolamide formulated according to this invention improved both patients, and in both cases there were clear indications of an even better response compared to treatment with Normast, in line with our conviction presented in this invention.

Example 8

Superiority of Palmitoylethanolamide micronized according to this invention over Normast; treatment effects for a 62-year-old women with chronic pain due to chronic idiopathic axonal polyneuropathy.
This patient suffered already for 3 years from severe pains, unresponsive to classic analgesics and physiotherapy. We prescribed Normast, which gave partial relief, around 30% reduction compared to baseline pain scores. 30% pain reduction is regarded as clinical relevant, but it is only a partial effect. After 6 weeks we therefore switched to a comparable formulation, but with an additional anti-oxidant, a resveratrol (brand name Pelvilen). This enhanced the analgesic effects and the pain reduction was around 50%. After some months we substituted Pelvilen for the same dose but administered according to the present invention. Pain reduction remained stable around 50% compared to baseline.

Example 9

Therapeutic utility of palmitolethanamide formulized according to the present invention as a non-sweetened formulation administered sublingually for the treatment of Sudeck’s dystrophy.

This case description concerns a 72-year-old woman who has had CRPS (Chronic Regional Pain Syndrome) type 1 or Sudeck’s Dystrophy since 13 years. This syndrome developed after she fell off a short flight of stairs and bruised her ankle. Initially, pain and swelling developed only on her left foot. After some time however, the symptoms spread also to her right foot.

Both feet were swollen, the skin felt hot and was shiny, the toenails dystrophic. All these confirm a typical case of CRPS type 1.

She experienced severe, burning pain that made sleeping difficult. The bed sheets caused contact pain and this woman had to cool her feet during the night. As part of the treatment her pain was assessed on a scale of 1 to 10, where 10 is the most severe pain imaginable. Her pain had very severe peaks, but averaged 6-8 when she came in for treatment. Her quality of life had also suffered significantly; she rated this herself as a 4, again on a 10-point scale (where 1 is terrible and 10 excellent).

From the beginning 13 years ago, many treatments and painkillers were tried to treat her CRPS. Treatments to open the blood vessels wider (vasodilatating drugs) had counter-productive effects, increasing the pain and swelling. DSMO cream applied locally on the feet also did not help. Only the drug amitriptyline had positive-, but limited effects. Pain remained present at a score of 6-8 and quality of life at 4 (i.e. poor) when we first saw her.
As all usual methods had been tried, we started her straight away on PEA combined with a topical cream of 10% ketamine in the base described in this invention. Palmitoylethanolamide was prescribed as the formulation according to the present invention, to be taken 3 times per day. The dose form was a capsule of 400mg.

After ten days she returned to our clinic. She came in walking and the swelling of her feet was significantly less. After one month of treatment the swelling and the pain were reduced by more than 50%. After 2 months of treatment according to the present invention she was able to ride the bicycle again for 20-km/ day and could again wear socks and shoes, which was not possible before treatment.

Example 10.

Palmitoylethanolamide sublingually and orally for the treatment of whooping cough.

Whooping cough is a respiratory infection due to Bordetella pertussis. Whooping cough is an increasing problem and often misdiagnosed. Long periods of extreme coughing wear out patients and in some cases the coughing goes on for months, long after the initial infectious period. This is due to a disturbance of the immune system, triggered by a toxin of the Bordetella bacteria. Palmitoylethanolamide can correct this disbalance, shorten the period of cough and improve the quality of life.

A husband and a wife both were infected by Bordetella pertussis and developed whooping cough, serologically proven. The husband also suffered from polyneuropathy pains. The male patient was treated first, and the treatment focus was on polyneuropathy pain. Coincidently and much to our surprise, he reported a decrease of whooping cough symptoms after about 2 weeks of treatment with palmitoylethanolamide. His wife also suffered from whooping cough and did not notice a decrease in that period for her own symptoms. So she started the treatment with palmitoylethanolamide 2 weeks after her husband, and noticed the same positive influence.

Both were treated with palmitoylethanolamide, 3 weeks three times daily sublingually and for a further 2 months oral palmitoylethanolamide, 3 times 400 mg was given. After 10 days the whooping cough symptoms started to diminish, and the general condition of the patients started to improve. Tiredness decreased, and in the husband, pain decreased by more than 50%.

Example 11.
Palmitoylethanolamide combined with l-theanine, vitamin D, glucosamine, vanadium salts such as bis (maltolato)oxovanadium and/or picamilon.

Patient suffering from diabetic pain for many years, treatment refractory to amitriptyline was treated with palmitoylethanolamide according to this invention, dose 1200 mg daily. Her baseline pain score decreased around 30%. Patient was further treated adding 3 times 100 mg of l-theanine daily; this further reduced the pain scores to around 50% and markedly reduced stress based on the chronic pain state.

Patient suffering from chronic idiopathic axonal polyneuropathy, diagnosed via EMG. Patient suffered from neuropathic pain and was initially treated with pregabalin 75 mg twice daily, which remained without analgesic effects and induced intolerable side effects. Treatment was started with palmitoylethanolamide according to this invention, dose 1200 mg daily. Pain scores decreased 30% related to baseline scores. Vitamine D3 was added, after finding a suboptimal blood level of vitamin D (35 microgr/ml). Painscores decreased further after the combination.

Patient suffering from osteoarthritis and painscores of 8 over 10. Treatment was started with palmitoylethanolamide according to this invention, dose 1200 mg daily. Painscores decreased to 5. After adding picamilon 50 mg thrice daily pain was reduced to 3 and patient felt much less stressed.

Example 12

A topical formulation based on a cream or ointment containing palmitoylethanolamide, micronized according to this invention, alone or in combination with l-theanine, Bismalotlatoxovanadium (BMOV), vitamin D or calcipotriol, Boswellia extracts and/or co-analgesics such as bacefen, amitriptyline, ketamine or clonidine.

Surprisingly we found a base for a topical formulation, a cream consisting of cetomacrogol, cetocteyl-alcohol, cetiol and sorbitol in which palmitoylethanolamide 1 to 5% could be dissolved alone or in combination with 0.1-5% l-theanine, 0.1-1.5% bismaltolatoexovanadium, 5-50 micrograms calcipotriol/g and 0.1-3% Boswellia extract. Although the lipophilic nature of these compounds is highly different, the selected base surprisingly remained stable after adding palmitoylethanolamide, alone or in combination with the above-mentioned compounds.
12.1 A cream consisting of cetomacrogol, cetostearyl-alcohol, cetiol and sorbitol. 0.1, 1, 2.5, 5 and 10 g palmitoylethanolamide were dissolved in 100 g of the above-mentioned cream base at 90 degrees Celsius for 3 minutes. All micronized palmitoylethanolamide powder dissolved rapidly. Tubes of 100 g were filled with liquid cream. After reaching room temperature the cream was tested on physical characteristics of the thus formulated creams. Physical Properties of the cream: up to and including 5% creamy white, homogeneous mixture, soft consistency, smoothness, easily spreadable. 10% cream was not acceptable in its physical characteristics due to impossibility to spread the cream and presence of palmitoylethanolamide clusters.

12.2. A cream consisting of co-analgesics and palmitoylethanolamide. In a base of 1.5% palmitoylethanolamide 2-10% amitriptyline or 1-10 % racemic ketamine could be easily dissolved

12.3 A cream was compounded consisting of 2 % palmitoylethanolamide, 1% Boswellia extract, 0.5% l-theanine and 0.5% bismaltolatoexovanadium (BMOV). After preparing the base cream of cetomacrogolis with 2% palmitoylethanolamide, we added the other compounds in the melted cetamacrogolis cream. All added compound surprisingly dissolved rapidly, without any unwanted reactions. After cooling off the cream had good physical characteristics: homogeneous mixture, soft consistency, smoothness and easily spreadable.

12.4. The pilot cream of example 12.3 was prescribed in a case of severe treatment-refractory neuropathic diabetic pain in both feet (painscore 7 over 10 on the numeric rating scale). After applying the cream the painscores decreased by 2 points and the patient felt much relief.
CONCLUSIES

1. Farmaceutische samenstelling omvattende palmitoylethanolamide deeltjes en/of farmaceutisch acceptabele esters of zouten daarvan, waarin de palmitoylethanolamide deeltjes vrij zijn van farmaceutische excipiënten, zodat de palmitoylethanolamide deeltjes geen agglomeraten vormen.

2. Farmaceutische samenstelling volgens conclusie 1, waarin de palmitoylethanolamide deeltjes een deeltjesgrootteverdeling hebben waarbij:
   - ten minste 99% van de deeltjes een diameter heeft tussen 1 μm en 850 μm; en
   - ten minste 40% van de deeltjes een diameter heeft die kleiner is dan 425 μm.

3. Farmaceutische samenstelling volgens conclusie 1 of 2, waarin de palmitoylethanolamide deeltjes vrij zijn van magnesiumstearaat, povidon, sorbitol and/of andere farmaceutische excipiënten.

4. Farmaceutische samenstelling volgens een van de conclusies 1-3, waarin de samenstelling een tweede of verdere farmaceutisch actief ingrediënt omvat voor het verminderen van pijn en/of ontsteking.

5. Farmaceutische samenstelling volgens conclusie 4, waarin het tweede of verdere farmaceutisch actieve ingrediënt theanine, vitamine D, glucosamine, Boswellia extracten, vanadium zouten zoals bis(maltolato)oxovanadium (BMOV), of picamilon is.

6. Farmaceutische samenstelling volgens één van de voorgaande conclusies, waarin de samenstelling wordt verschaft in capsule of sachet.

7. Farmaceutische samenstelling volgens één van de voorgaande conclusies voor gebruik in de behandeling of voor gebruik in de preventie van immuun of chronische ontstekingsaandoeningen, neuro-ontstekingen of chronische pijn aandoeningen in zoogdieren, bijvoorkeur mensen.
8. Werkwijze voor het vervaardigen van palmitoylethanolamide deeltjes, waarin de deeltjes vrij zijn van farmaceutisch acceptabele excipiënten, omvattende de volgende stappen:
   i) verschaffen van palmitoylethanolamide vlokken;
   ii) verkleinen, snijden of malen van de palmitoylethanolamide vlokken in palmitoylethanolamide deeltjes in de afwezigheid van farmaceutische excipiënten, op een dusdanige manier dat de deeltjes die zijn verkregen een deeltjesgrootteverdeling hebben waarin:
      - ten minste 99% van de deeltjes een diameter heeft tussen 1 µm en 850 µm,
      - ten minste 40% van de deeltjes een diameter heeft die kleiner is dan 425 µm.

9. Werkwijze volgens conclusie 8, waarbij het verkleinen van de palmitoylethanolamide vlokken wordt uitgevoerd bij een temperatuur van min 20 tot min 200°C, bijvoorkeur min 100 tot min 200°C, meest bijvoorkeur min 190 tot min 200°C.

10. Werkwijze volgens conclusie 9, waarin het verkleinen van de palmitoylethanolamide vlokken wordt uitgevoerd in de aanwezigheid van vloeibare stikstof.

11. Werkwijze volgens een van de conclusies 8-10, waarin het verkleinen van de palmitoylethanolamide vlokken wordt uitgevoerd in een oscillerende en roterende zeefmolen of hamermolen, of enig ander daarvoor geschikte molen, bij kamertemperatuur.

12. Palmitoylethanolamide deeltjes verkrijgbaar met de werkwijze zoals beschreven in één van de conclusies 8-11.

14. Farmaceutische samenstelling omvattende palmitoylethanolamide zoals beschreven in één van de conclusies 8-13, opgelost in een basis voor crème bestaande uit alleen cetomacrogol, cetostearyl-alcohol, cetiol en sorbitol (cremor cetomacrogolis), of in combinatie met l-theanine, bis(maltolato)oxovanadium (BMOV), Boswellia serrata extracten en/of co-
analgesica zoals amitriptyline, baclofen en ketamine.