

(19) **DANMARK**

(10) **DK/EP 3424499 T3**



(12)

Oversættelse af
europæisk patentskrift

Patent- og
Varemærkestyrelsen

-
- (51) Int.Cl.: **A 61 K 31/164 (2006.01)** **A 61 K 31/215 (2006.01)** **A 61 K 31/352 (2006.01)**
A 61 P 25/00 (2006.01) **A 61 P 25/02 (2006.01)**
- (45) Oversættelsen bekendtgjort den: **2020-03-23**
- (80) Dato for Den Europæiske Patentmyndigheds bekendtgørelse om meddelelse af patentet: **2019-12-25**
- (86) Europæisk ansøgning nr.: **18162734.0**
- (86) Europæisk indleveringsdag: **2018-03-20**
- (87) Den europæiske ansøgnings publiceringsdag: **2019-01-09**
- (30) Prioritet: **2017-07-05 IN 201721023668**
- (84) Designerede stater: **AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HR HU IE IS IT LI LT LU LV MC MK MT NL NO PL PT RO RS SE SI SK SM TR**
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- (54) Benævnelse: **FARMACEUTISK SAMMENSÆTNING MOD NEUROPATISK SMERTE**
- (56) Fremdragne publikationer:
EP-A1- 1 849 773
WO-A1-2009/152025
WO-A1-2011/027373
WO-A1-2013/121449
WO-A2-2008/030752
EUN YEONG LIM ET AL: "Food-Derived Natural Compounds for Pain Relief in Neuropathic Pain", BIOMED RESEARCH INTERNATIONAL, vol. 2016, 1 January 2016 (2016-01-01), pages 1-12, XP55450350, ISSN: 2314-6133, DOI: 10.1155/2016/7917528

DESCRIPTION

TECHNICAL FIELD

[0001] The present disclosure relates to a pharmaceutical composition/formulation for use in controlling neuropathic pain. More particularly, the disclosure relates to a composition/formulation comprising a synergistic combination of Palmitoylethanolamide (PEA) and one or more natural ingredients.

BACKGROUND

[0002] Humans and animals suffering from chronic and severe pain require good clinical management. Multiple pharmacological agents are generally employed to treat diverse pathological pain states. Specifically, these pharmacological agents include opiates, nonsteroidal anti-inflammatory drugs, anticonvulsants, antidepressants, ketamine and others (Guindon *et al.*, 2007). However, adverse side effects from these pharmacological agents constrain therapeutic dosing ultimately limiting therapeutic efficacy.

[0003] Improvements have been made in understanding pathophysiological mechanisms underlying chronic pain states. In addition, efforts have been made in developing different analgesic mechanisms for chronic pain that are not only effective, but also nontoxic and devoid of unwanted central side effects. Further improvements in chronic pain management are still required.

[0004] Neuropathic pain (NP) is one such chronic pain which needs good clinical management. Neuropathic pain is defined as a pain that comes from problems with signals from the nerves. Neuropathic pain is different from the common type of pain caused by an injury, burn, pressure, etc. Indeed, neuropathic pain results from damage to or dysfunction of the peripheral or central nervous system, rather than stimulation of pain receptors. Diagnosis is suggested by out of proportion pain to tissue injury, dysesthesia (e.g., burning, tingling), and signs of nerve injury detected during neurologic examination. While different therapies have been suggested for treating and managing Neuropathic pain, one therapy in particular suggests employing Palmitoylethanolamide (PEA). PEA is an endogenous, fatty acid amide food component first discovered in the late 1950s when it was shown that the anti-allergic and anti-inflammatory activity exerted by egg yolk, peanut oil or soybean lecithin was due to a specific lipid fraction corresponding to PEA (Esposito and Cuzzocrea, 2013). PEA, was used many decades ago in some countries, but due to a lack of insight in its mechanism of action, interest waned. Since the 1990s, interest surged again due to the discovery of its effects in many different animal paradigms for pain and chronic inflammation (J Pain Res. 2012; 5: 437-442). PEA is synthesized and metabolized by different animal cell types and is also present in herbs or plants. It exerts a multitude of physiological functions related to metabolic and cellular homeostasis. It is a key element in the regulation of pathways linked to the inflammation process particularly in the down-regulation of the masto-cytes degranulation process, and processes underlying itching and pain.

[0005] Cannabinoid-based medicines have therapeutic potential for the treatment of pain. Augmentation of levels of endocannabinoids with inhibitors of fatty acid amide hydrolase (FAAH) is analgesic. FAAH is a membrane-bound serine hydrolase that belongs to the amidase signature family of hydrolases. FAAH enzyme breaks down fatty acid amides such as anandamide (N-arachidonylethanolamide), N-oleylethanolamide (N-OEA), PEA and oleamide. FAAH belongs to a large and diverse class of enzymes referred to as the amidase signature (AS) family.

[0006] FAAH Inhibitors are a class of molecules that inactivate the FAAH Enzymes by preventing the hydrolysis of anandamide, oleylethanolamide and PEA. It thereby increases endogenous levels. Known chemically synthesized FAAH inhibitors are BIA 10-2474, URB524, URB-597, URB694, URB937, etc. These inhibitors are disclosed in the article published by Colombano et al. titled, "O-(Triazolyl) methyl carbamates as a novel and potent class of fatty acid amide hydrolase (FAAH) inhibitors" and in the article published by Otrubova et al. titled, "The discovery and development of inhibitors of fatty acid amide hydrolase (FAAH)."

Related Prior Arts

[0007] US 5990170 discloses a method of synthesis of PEA.

[0008] US 5506224 refers to a method for treating diseases involving mast cell degranulation, as a consequence of a neurogenic and/or immunogenic hyper-stimulation, comprising the administration of an effective amount of a series of compounds included in a general formula, comprising also the PEA.

[0009] EP1082292 discloses a composition comprising anandamide and PEA.

[0010] WO 2001/010434 describes a pharmaceutical composition comprising PEA in micronized form having particle size less than 10 µm for use in the veterinary field.

[0011] WO 2001/024645 discloses a nutritional or therapeutic composition for oral administration, which comprises a naturally occurring precursor that is metabolized to a compound having anandamide activity for use as a medicament, in which such precursor is a long chain polyunsaturated fatty acid (LCPUFA) (e.g. arachidonic acid ARA or docosahexaenoic acid DHA) or a derivative thereof having a given general formula. According to an embodiment reported in such application, the composition also comprises an inhibitor of an anandamide inactivating enzyme (amidase), which is said to include PEA. However, no biological effects or further technical results of such hypothetical combination comprising PEA have been shown in such document.

[0012] WO 2002/080860 and WO 2005/046580 refers to a method of reducing food intake or reducing appetite in a mammal, said method comprising orally administering a fatty acid alkanolamide compound, derivative, homolog, or analog. PEA is reported to be one of such fatty acid alkanolamide compounds.

[0013] WO 2011/027373 A1 discloses a pharmaceutical composition containing an ultra-micronized form of PEA, in which more than 90% by weight of PEA has particle sizes lower than 6 microns (mm).

[0014] NL2011448 discloses a pharmaceutical composition comprising PEA particles and/or pharmaceutically acceptable esters or salts thereof, in which the PEA particles are substantially free of pharmaceutical excipients.

[0015] WO 2013/121449 discloses a use of chemically synthesized FAAH / NAAH inhibitor in association with oxazoline of PEA, for a combined, separate or sequential administration.

[0016] EP2444078 describes the activity of PEA and other Aliamides in the treatment of renal diseases. Silymarin is an extract of the plant *Silybum marianum*, also known as milk thistle, the activity of which in the treatment of liver diseases is known.

[0017] EP2944309 and WO 2016/185468 disclose a pharmaceutical composition comprising a combination of PEA and Opioid use for the treatment of pain.

[0018] WO 2016/063217 discloses a combination of PEA and Spirulina for the treatment of inflammatory states.

[0019] WO 2016/146453 discloses a pharmaceutical composition comprising a combination of PEA and a vitamin B.

[0020] WO 2016/183134 provides compositions comprising PEA, and an anti-inflammatory or anti-pain component.

[0021] WO 2016/193905 discloses a pharmaceutical composition comprising a combination of PEA and lycopene, and/or pharmaceutically acceptable salts and/or derivatives thereof.

[0022] EP3130336 relates to a food and/or nutraceutical composition comprising PEA. In particular, it relates to a food and/or nutraceutical composition comprising PEA in association with at least one component selected from a second active ingredient and an agent that modifies its release in the organism.

[0023] EP 1849773 relates to pyridyl non-aromatic nitrogen-containing heterocyclic-1-carboxylate derivative, which can be used in the treatment of diseases related to FAAH, such as urinary frequency and urinary incontinence, overactive bladder and/or a remedy for pain.

[0024] WO 2008/030752 relates to methods for determining effective doses a composition for inhibiting FAAH activity *in vivo*, and methods for optimizing therapeutic efficacy for treatment of disorders such as pain by altering the dose of FAAH inhibitor. WO 2008/030752 further discloses pharmaceutical compositions containing synthetic FAAH inhibitors that increase FAA level.

[0025] WO 2009/152025 relates to imidazole derivatives that can be used as FAAH inhibitors.

[0026] Lim, E. Y. et al. (Biomed Research Int. (2016), p. 1-12) relates to food-derived natural compounds for pain relief in neuropathic pain.

[0027] There are several patent applications (WO 2012/015704, WO 2013/028570, WO 2014/017936, WO 2015/07613, WO 2015/07615, WO 2015/012708, WO 2015/016728, WO 2015/157313), which disclose chemically synthesized different types of FAAH inhibitors which elevate PEA level. However, these chemically synthesized FAAH inhibitors may have side effects upon administration in human or animals. Several studies reveal the serious side-effects (including death) of chemically synthesized FAAH inhibitors. Some of them include Eddleston Michael et al; "Implications of the BIA-102474-101 study for review of first-into-human clinical trials", Br J Clin Pharmacol (2016) 81 582-586; Mallet et.al.; "FAAH inhibitors in the limelight, but regrettably", International Journal of Clinical Pharmacology and Therapeutics, Vol. 54 - No. 7/2016 (498-501); and Kaur et al." "What failed BIA 10-2474 Phase I clinical trial? Global speculations and recommendations for future Phase I trials", J Pharmacol Pharmacotherapy. 2016 Jul-Sep; 7(3): 120-126.

[0028] Current treatment options for neuropathic pain mainly focus on neuronal system suppressing GABA or other inhibitory receptors. Most of the drugs used for neuropathic pain cause drowsiness, dizziness, blurred vision, somnolence, peripheral edema, psychomotor slowing and paresthesia and many more. These side effects decrease the Quality of Life of patient and reduce active working life. Also these drugs require dosage adjustment in different disease conditions such as renal disease or liver disease etc. Moreover using these drugs for long term causes de-sensitisation of receptors. Therefore, the requirement of increase in the dose of these drugs is required to elicit the desired response and that leads to more number of side effects. In conclusion, the current treatment paradigm has some gaps and requires some new arsenal to fight against Neuropathic Pain.

[0029] The above mentioned documents disclosing use of FAAH inhibitors are chemically synthesized, and there can be side effects due to synthetic ingredients. Hence, there is a requirement to develop formulations which use natural ingredients, including natural FAAH inhibitors. Further, there is also requirement to provide a highly effective relief for neuropathic pain by PEA and its combination with other active ingredients without any side effects in humans or animals accompanied with good tolerability at an effective dose and good safety profile. Hence, there exists a need for combinations of PEA which are highly effective in a neuropathic pain, accompanied by acceptable safety profile and without any adverse effects.

SUMMARY

[0030] The present disclosure provides a pharmaceutical composition/formulation comprising a synergistic combination of Palmitoylethanolamide (PEA) and one or more naturally occurring Fatty Acid Amide Hydrolase (FAAH) Inhibitor. In a preferred aspect of the present disclosure, the present disclosure provides a composition or formulation comprising a synergistic combination of Palmitoylethanolamide and at least two naturally occurring FAAH inhibitors.

[0031] In another aspect of the present disclosure, the present disclosure provides a pharmaceutical composition/formulation comprising a synergistic combination of Palmitoylethanolamide (PEA) and one or more naturally occurring FAAH Inhibitors along with a pharmaceutically acceptable excipient.

[0032] In a further aspect of the present disclosure, the pharmaceutical composition/formulation of the present disclosure additionally comprises vitamins, coenzymes or a combination thereof.

[0033] In one aspect of the present disclosure, the natural FAAH Inhibitors in the present disclosure are selected from Myricetin, Isorhamnetin, Kaempferol, Pristimerin, Biochanin A, Genistein, Daidzein or a combination thereof.

[0034] In yet a further aspect of the present disclosure, in the composition/formulation of the present disclosure,

vitamins are selected from methylcobalamin, cyanocobalamin, benfotiamine or a combination thereof. The co-enzymes in the present disclosure are selected from ubidecarenone, thiamine pyrophosphate, Flavin adenine dinucleotide or a combination thereof.

[0035] In even another aspect of the present disclosure, the pharmaceutical composition/formulation of the present disclosure comprises a synergistic combination of PEA, Daidzein, Genistein and a pharmaceutically acceptable excipient.

[0036] In another aspect of the present disclosure, a process for the preparation of a composition/formulation is described. The process comprises (a) weighing and sieving the ingredients through a suitable sieve, (b) mixing the ingredients, (c) preparing a dough by adding a binder solution to the mixed ingredients and sieving to obtain granules, (d) drying the granules till the level of dryness (LOD) is reduced to less than 1.5 % w/w to obtain semi dried granules, and (e) sieving the semi dried granules through a suitable sieve to obtain the composition/formulation. The process further comprises adding lubricants or glidants to the semi dried granules and filling the granules in Hydroxypropylmethyl cellulose (HPMC) capsule shells and sealing.

[0037] In a preferred aspect of the present disclosure, the disclosure provides a process for preparing the composition/formulation of the present disclosure. The process comprises sifting previously weighed PEA, Natural FAAH Inhibitor(s), diluent(s), and disintegrating agent(s) separately through a sieve, mixing the contents to obtain a mixture, preparing a binder solution, and optionally adding second natural FAAH Inhibitor(s) in to the binder solution, adding the binder solution to the mixture obtained above and obtaining granules, drying the obtained granules to obtain semi dried granules and sifting the semi dried granules through a sieve, sifting previously weighed Lubricant(s) or glidant(s) separately through a sieve and mixing with the sifted semi dried granules to obtain a blend of the composition/formulation. The blend is further filled and sealed with HPMC capsule shells.

DETAILED DESCRIPTION

[0038] The invention is defined by the appended claims. Any embodiment not falling under the scope of the appended claims does not form part of the invention.

[0039] An objective of the present disclosure is to provide a composition/formulation comprising a synergistic combination of PEA and one or more natural ingredients.

[0040] In an embodiment of the present disclosure, the disclosure provides a composition/formulation comprising a synergistic combination of PEA with at least one of a naturally occurring FAAH Inhibitor. In one aspect of the present disclosure, the composition/formulation of the present disclosure may optionally comprise vitamins and co-enzymes. The composition/formulation of the present disclosure is able to provide a safe composition/formulation of PEA with one or more natural ingredients with enhanced or synergistic effects compared to PEA alone in the treatment of neuropathic pain.

[0041] Another object of the present disclosure is to provide a composition/formulation comprising a synergistic combination of PEA along with at least one of a naturally occurring FAAH Inhibitor to avoid side effects associated with synthetic FAAH inhibitors.

[0042] Another object of the present disclosure is to provide a composition/formulation comprising a synergistic combination of PEA along with at least one of a naturally occurring FAAH Inhibitor, and other active ingredients selected from vitamins, coenzymes or a combination thereof.

[0043] In one preferred embodiment of the present disclosure, a composition/formulation comprising PEA in micronized or non-micronized form is described. The composition/formulation includes at least one of a naturally occurring FAAH Inhibitor. The composition/formulation optionally includes vitamins or co-enzymes.

[0044] In a preferred aspect of the present disclosure, the present disclosure provides a pharmaceutical composition/formulation for treatment of neuropathic pain, wherein said composition/formulation comprises a synergistic

combination of PEA with at least one of a naturally occurring FAAH inhibitor and a pharmaceutically acceptable excipient. The said composition/formulation optionally comprises vitamins or co-enzymes.

[0045] In a preferred aspect of the present disclosure, the ratio of PEA:Natural FAAH Inhibitors is in a range of 99:1 to 50:50. In a more preferred aspect of the present disclosure, the ratio of PEA: FAAH Inhibitor is 84:15.

[0046] The pharmaceutical composition/formulation of the present disclosure comprises PEA in micronized or non-micronized form. The amount of PEA in the pharmaceutical composition/formulation of the present disclosure ranges from 35% by wt. to 80% by wt. of the composition/formulation. In an embodiment of the present disclosure the amount of PEA ranges from 45 to 80% by weight. In another embodiment of the present disclosure, the amount of PEA ranges from 50 to 80% by weight. In yet another embodiment of the present disclosure, the amount of PEA ranges from 60 to 80% by weight. In yet another embodiment of the present disclosure, the amount of PEA ranges from 65 to 80% by weight. In yet even another embodiment of the present disclosure, the amount of PEA ranges from 70 to 80% by weight. In yet a further embodiment of the present disclosure the amount of PEA ranges from 75 to 80% by weight.

[0047] In a preferred embodiment of the present disclosure, the pharmaceutical composition/formulation of the present disclosure comprises PEA in micronized or non-micronized form, wherein the amount of PEA in the pharmaceutical composition/formulation ranges from 150 mg to 2400 mg per unit dose.

[0048] The pharmaceutical composition/formulation of the present disclosure comprises at least one natural FAAH Inhibitor selected from Myricetin, Isorhamnetin, Kaempferol, Pristimerin, Biochanin A, Genistein, Daidzein. The amount of natural FAAH Inhibitor in the pharmaceutical composition/formulation of the present disclosure ranges from 0.5% by wt. to 40% by wt. of the composition/formulation. In an embodiment of the present disclosure, the amount of natural FAAH Inhibitor ranges from about 1 to 40% by weight. In an embodiment of the present disclosure, the amount of natural FAAH Inhibitor ranges from about 10 to 40% by weight. In an embodiment of the present disclosure, the amount of natural FAAH Inhibitor ranges from about 20 to 40% by weight. In a further embodiment of the present disclosure, the amount of natural FAAH Inhibitor ranges from about 30 to 40% by weight.

[0049] In a preferred embodiment of the present disclosure, the pharmaceutical composition/formulation of the disclosure comprises at least one natural FAAH Inhibitors selected from Myricetin, Isorhamnetin, Kaempferol, Pristimerin, Biochanin A, Genistein, Daidzein, wherein the amount of natural FAAH Inhibitor in the pharmaceutical composition/formulation ranges from 2 mg to 2722 mg per unit dose.

[0050] The pharmaceutical composition/formulation of the disclosure optionally comprises vitamins, co-enzymes or a combination thereof.

[0051] The vitamins are selected from methylcobalamin, cyanocobalamin, benfotiamine or a combination thereof. The amount of vitamins in the pharmaceutical composition/formulation of the present disclosure ranges from 0.01% by wt. to 30% by wt. of the composition/formulation. The amount of vitamins in the pharmaceutical composition/formulation of the present disclosure ranges from 0.1 mg to 200 mg per unit dose.

[0052] The co-enzymes are selected from ubidecarenone, thiamine pyrophosphate, flavin adenine dinucleotide or a combination thereof. The amount of co-enzymes in the pharmaceutical composition/formulation of the present disclosure ranges from 10 % by wt. to 40 % by wt. of the composition/formulation. The amount of co-enzymes in the pharmaceutical composition/formulation of the present disclosure ranges from 50 mg to 200 mg per unit dose.

[0053] The pharmaceutical composition/formulation of the present disclosure can be formulated as tablets, capsules, granules, powder, sachets, suspension, solution, modified release formulations, topical formulations, etc.

[0054] The formulations of the present disclosure comprise suitable excipients such as diluents, disintegrants, binders, solubilizing agent, lubricants, glidants, solvents etc.

[0055] The diluents are selected from microcrystalline cellulose, lactose (anhydrous / monohydrate / spray dried), starch, cellulose powder, silicified microcrystalline, ammonium alginate, calcium carbonate, calcium lactate, dibasic calcium phosphate (anhydrous/ dibasic dehydrate/ tribasic), calcium silicate, calcium sulfate, cellulose acetate, compressible sugar, confectioner's sugar, corn starch, pregelatinized starch, dextrates, dextrin, dextrose, erythritol,

ethylcellulose, fructose, fumaric acid, glyceryl palmitostearate, isomalt, kaolin, lactitol, magnesium carbonate, magnesium oxide, maltodextrin, maltose, mannitol, medium-chain triglycerides, polydextrose, polymethacrylates, simethicone, sodium alginate, sodium chloride, sorbitol, sterilizable maize, sucrose, sugar spheres, sulfobutylether β -cyclodextrin, talc, tragacanth, trehalose, xylitol or the like. The amount of diluent in the pharmaceutical composition/formulation of the present disclosure ranges from 5% by wt. to 50% by wt. of the composition/formulation.

[0056] The disintegrating agent is selected from croscarmellose sodium, crospovidone, carboxymethyl cellulose (sodium / calcium), sodium starch glycolate, alginic acid, calcium alginate, cellulose powdered, chitosan, colloidal silicon dioxide, corn starch, docusate sodium, glycine, guar gum, hydroxypropyl cellulose low-substituted, magnesium aluminum silicate, methylcellulose, microcrystalline cellulose, polacrillin potassium, povidone, sodium alginate, pregelatinized starch or the like. The amount of disintegrating agent in the pharmaceutical composition/formulation of the present disclosure ranges from 0.5% by wt. to 10% by wt. of the composition/formulation.

[0057] The binder is selected from hypromellose, starch, acacia, agar, alginic acid, calcium carbonate, calcium lactate, carbomers, carboxymethylcellulose sodium, carrageenan, cellulose acetate phthalate, ceratonia, chitosan, copovidone, corn starch, pregelatinized starch, cottonseed oil, dextrates, dextrin, dextrose, ethylcellulose, gelatin, glyceryl behenate, guar gum, hydrogenated vegetable oil type I, hydroxyethyl cellulose, hydroxyethylmethyl cellulose, hydroxypropyl cellulose, inulin, lactose, liquid glucose, low-substituted Hypromellose, magnesium aluminum silicate, maltodextrin, maltose, methylcellulose, microcrystalline cellulose, pectin, poloxamer, polycarbophil, polydextrose, polyethylene oxide, polymethacrylates, povidone, sodium alginate, stearic acid, sucrose, sunflower oil, tricaprillin, vitamin E polyethylene glycol succinate, zein or the like. The amount of binder in the pharmaceutical composition/formulation of the present disclosure ranges from 0.1% by wt. to 10% by wt. of the composition/formulation.

[0058] The solubilizing agent is selected from polysorbate 80, sodium lauryl sulfate, anionic emulsifying wax, nonionic emulsifying wax, glyceryl monooleate, phospholipids, polyoxyethylene alkyl ethers, polyoxyethylene castor oil derivatives, polyoxyethylene sorbitan fatty acid esters, polyoxyethylene stearates, polyoxylglycerides, sorbitan esters, triethyl citrate, vitamin E polyethylene glycol succinate, microcrystalline cellulose, carboxymethylcellulose sodium, diethanolamine, ethylene glycol palmitostearate, glycerin monostearate, hypromellose, hypromellose acetate succinate, lecithin, polyethylene alkyl ethers, aluminum oxide, poly(methylvinyl ether/maleic anhydride), calcium carbonate, crospovidone, cyclodextrins, fructose, hydroxypropyl betadex, oleyl alcohol, povidone, benzalkonium chloride, benzethonium chloride, benzyl alcohol, benzyl benzoate, cetylpyridinium chloride, inulin, meglumine, poloxamer, pyrrolidone, sodium bicarbonate, starch, stearic acid, sulfobutylether β -cyclodextrin, tricaprillin, triolein, docusate sodium, glycine, alcohol, self-emulsifying glyceryl monooleate, cationic benzethonium chloride, cetrimide, xanthan gum, lauric acid, myristyl alcohol, butylparaben, ethylparaben, methylparaben, propylparaben, sorbic acid or the like. The amount of Solubilizing Agent in the pharmaceutical composition/formulation of the present disclosure ranges from 0.25% by wt. to 15% by wt. of the composition/formulation.

[0059] The lubricant is selected from magnesium stearate, zinc stearate, calcium stearate, glycerin monostearate, glyceryl behenate, glyceryl palmitostearate, hydrogenated castor oil, hydrogenated vegetable oil type I, light mineral oil, magnesium lauryl sulfate, medium-chain triglycerides, mineral oil, myristic acid, palmitic acid, poloxamer, polyethylene glycol, sodium benzoate, sodium chloride, sodium lauryl sulfate, sodium stearyl fumarate, stearic acid, talc, potassium benzoate or the like. The amount of Lubricant in the pharmaceutical composition/formulation of the present disclosure ranges from 1% by wt. to 10% by wt. of the composition/formulation.

[0060] The glidant is selected from Colloidal silicon dioxide, talc, calcium phosphate tribasic, cellulose powdered, hydrophobic colloidal silica, magnesium oxide, magnesium silicate, magnesium trisilicate, silicon dioxide or the like. The amount of Glidant in the pharmaceutical composition/formulation of the present disclosure ranges from 1% by wt. to 10% by wt. of the composition/formulation.

[0061] The solvent is selected from water, alcohol, isopropyl alcohol, propylene glycol, almond oil, benzyl alcohol, benzyl benzoate, butylene glycol, carbon dioxide, castor oil, corn oil (maize), cottonseed oil, dibutyl phthalate, diethyl phthalate, dimethyl ether, albumin, dimethyl phthalate, dimethyl sulfoxide, dimethylacetamide, ethyl acetate, ethyl lactate, ethyl oleate, glycerin, glycofurol, isopropyl myristate, isopropyl palmitate, light mineral oil, medium-chain triglycerides, methyl lactate, mineral oil, monoethanolamine, octyldodecanol, olive oil, peanut oil, polyethylene glycol, polyoxyl 35 castor oil, propylene carbonate, pyrrolidone, safflower oil, sesame oil, soybean oil, sunflower oil, triacetin, tricaprillin, triethanolamine, triethyl citrate, triolein, water-miscible solvents or the like. The amount of solvent in the pharmaceutical

composition/formulation of the present disclosure is used in a quantity sufficient.

[0062] In a preferred embodiment of the present disclosure, the pharmaceutical composition/formulation is formulated for oral administration. Specifically, the solid pharmaceutical compositions, for example, can be in the form of tablets, capsules, pills, hard capsules filled with liquids or solids, soft capsules, sachets, powders, granules, suspensions, solutions or modified release formulations.

[0063] Developing pharmaceutical compositions or formulations wherein one or more ingredients are obtained from natural sources poses challenges for the formulator. Such challenges include providing a suitable size dosage form containing the effective amount of the active ingredients. Challenges also include providing stable formulations while retaining desirable pharmacokinetic properties. As currently understood, synthetic FAAH Inhibitors are not approved for therapeutic use in any country by any drug regulatory authority. The present disclosure provides stable and therapeutically effective compositions and formulations comprising PEA and one or more natural ingredients.

[0064] Some of the exemplary compositions /formulations of the present disclosure are described below:

Composition/Formulation 1:

S. No.	Ingredient	Amount (% w/w)
1.	PEA	35 to 80
2.	One Natural FAAH Inhibitor	0.5 to 40

Composition/Formulation 2:

S. No.	Ingredient	Amount (% w/w)
1.	PEA	35 to 80
2.	Two Natural FAAH Inhibitors	0.5 to 40

Composition/Formulation 3:

S. No.	Ingredient	Amount (% w/w)
1.	PEA	35 to 80
2.	Natural FAAH Inhibitor(s)	0.5 to 40
3.	Vitamin	0.01 to 30

Composition/Formulation 4:

S. No.	Ingredient	Amount (% w/w)
1.	PEA	35 to 80
2.	Natural FAAH Inhibitor(s)	0.5 to 40
3.	Co-enzyme	10 to 40

Composition/Formulation 5:

S. No.	Ingredient	Amount (% w/w)
1.	PEA	35 to 80
2.	Natural FAAH Inhibitor(s)	0.5 to 40
3.	Vitamin	0.01 to 30
4.	Co-enzyme	10 to 40

Composition/Formulation 6:

S. No.	Ingredient	Amount (% w/w)
1.	PEA	35 to 80
2.	Two Natural FAAH Inhibitors	0.5 to 40
3.	Vitamin	0.01 to 30
4.	Co-enzyme	10 to 40

General Process for preparation of the formulations of the present disclosure

[0065]

1. 1. Weigh accurately all the ingredients in separate containers.
2. 2. Sift previously weighed PEA, Natural FAAH Inhibitor(s), a diluent (s) and disintegrating agent(s) separately through sieve #40.
3. 3. Mix content of step 2 in rapid mixer granulator (RMG) with impeller of slow speed.
4. 4. Binder solution Preparation: In separate container, weigh a binding agent(s) and Solubilizing agent(s) and dissolve it into solvent(s) and add second natural FAAH Inhibitor(s) (if any) in to same solution.
5. 5. Add binder solution to step 3 in RMG at slow speed of impeller.
6. 6. Sift and dry the obtained granulated wet mass in a Fluid bed dryer at 50 °C±5 °C till the level of dryness (LOD) of the blend is reduced to less than 1.5 % w/w.
7. 7. Sift semi dried granules through sieve # 20 and sieve # 30.
8. 8. Sift previously weighed Lubricant(s) or Glidant(s) separately through sieve # 40 and mix with Step-7.
9. 9. Fill and seal the blend with HPMC capsule shells.
10. 10. Transfer the filled capsules into the hopper of polishing and visual inspection machine to remove the debris of powder sticking with the capsule shells.

Examples

[0066] Examples not falling under the scope of the appended claims do not form part of the invention.

Example 1**[0067]**

S. No	Ingredients	Std. Qty. mg/unit	% w/w
Intragranular Ingredients			
1	Micronized PEA	300	66.67
2	Natural FAAH Inhibitor (Daidzein)	50	11.11
3	MCC pH 101	45.5	10.11
4	Croscarmellose Sodium	15	3.33
Binder Solution			
5	PVP K-30	5	1.11
6	Polysorbate 80	10	2.22
7	IPA	QS	
8	Water	QS	
Extragranular Ingredients			
9	Magnesium Stearate	10	2.22
10	Talc	4	0.89
11	Zinc Stearate	6	1.33
12	Colloidal silicon dioxide	4.5	1.00
	Average Wt.	450	100.00

Example 2**[0068]**

S. No	Ingredients	Std. Qty. mg/unit	% w/w
Intragranular Ingredients			
1	Micronized PEA	300	60.00
2	Natural FAAH Inhibitor (Myricetin)	100	20.00
3	Lactose Monohydrate	45.5	9.10
4	Crospovidone	15	3.00
Binder Solution			
5	Hypromellose	5	1.00
6	Polysorbate 80	10	2.00
7	IPA	QS	
8	Water	QS	
Extragranular Ingredients			
9	Magnesium Stearate	10	2.00
10	Talc	4	0.80
11	Zinc Stearate	6	1.20
12	Colloidal silicon dioxide	4.5	0.90
Average Wt.		500	100.00

Example 3

[0069]

S. No	Ingredients	Std. Qty. mg/unit	% w/w
Intragranular Ingredients			
1	Micronized PEA	300	66.67
2	Natural FAAH Inhibitor (Isorhamnetin)	50	11.11
3	MCC pH 102	45.5	10.11
4	Croscarmellose Sodium	15	3.33
Binder Solution			
5	PVP K-30	5	1.11
6	Sodium Lauryl Sulfate	10	2.22
7	IPA	QS	
8	Water	QS	
Extragranular Ingredients			
9	Magnesium Stearate	10	2.22
10	Talc	4	0.89
11	Zinc Stearate	6	1.33
12	Colloidal silicon dioxide	4.5	1.00
Average Wt.		450	100.00

Example 4

[0070]

S. No	Ingredients	Std. Qty. mg/unit	% w/w
Intragranular Ingredients			
1	Micronized PEA	300	60.00
2	Natural FAAH Inhibitor (Kaempferol)	100	20.00
3	Mannitol	45.5	9.10
4	Sodium starch glycolate	15	3.00
Binder Solution			
5	PVP K-30	5	1.00
6	Polysorbate 80	10	2.00
7	IPA	QS	
8	Water	QS	
Extragranular Ingredients			
9	Magnesium Stearate	10	2.00
10	Talc	4	0.80
11	Zinc Stearate	6	1.20
12	Colloidal silicon dioxide	4.5	0.90
Average Wt.		500	100.00

Example 5

[0071]

S. No	Ingredients	Std. Qty. mg/unit	% w/w
Intragranular Ingredients			
1	Micronized PEA	300	46.15
2	Natural FAAH Inhibitor (Pristimerin)	250	38.46
3	MCC pH 102	45.5	7.00
4	Croscarmellose Sodium	15	2.31
Binder Solution			
5	Hypromellose	5	0.77
6	Polysorbate 80	10	1.54
7	IPA	QS	
8	Water	QS	
Extragranular Ingredients			
9	Magnesium Stearate	10	1.54
10	Talc	4	0.62
11	Zinc Stearate	6	0.92
12	Colloidal silicon dioxide	4.5	0.69
Average Wt.		650	100.00

Example 6

[0072]

S. No	Ingredients	Std. Qty. mg/unit	% w/w
Intragranular Ingredients			
1	Micronized PEA	300	60.00
2	Natural FAAH Inhibitor (Biochanin)	100	20.00
3	Lactose Monohydrate	45.5	9.10
4	Crospovidone	15	3.00
Binder Solution			
5	PVP K-30	5	1.00
6	Sodium lauryl sulfate	10	2.00
7	IPA	QS	
8	Water	QS	
Extragranular Ingredients			
9	Magnesium Stearate	10	2.00
10	Talc	4	0.80
11	Zinc Stearate	6	1.20
12	Colloidal silicon dioxide	4.5	0.90
Average Wt.		500	100.00

Example 7

[0073]

S. No	Ingredients	Std. Qty. mg/unit	% w/w
Intragranular Ingredients			
1	Micronized PEA	300	75.0
2	Natural FAAH Inhibitor (Genistein)	4	1.0
3	MCC pH 101	41.5	10.38
4	Croscarmellose Sodium	15	3.75
Binder Solution			
5	PVP K-30	5	1.25
6	Polysorbate 80	10	2.50
7	IPA	QS	
8	Water	QS	
Extragranular Ingredients			
9	Magnesium Stearate	10	2.50
10	Talc	4	1.0
11	Zinc Stearate	6	1.50
12	Colloidal silicon dioxide	4.5	1.13
Average Wt.		400	100.00

Example 8

[0074]

S. No	Ingredients	Std. Qty. mg/unit	% w/w
Intragranular Ingredients			
1	Micronized PEA	300	66.67
2	Natural FAAH Inhibitor (Daidzein)	50	11.11
3	MCC pH 101	41.5	9.22
4	Croscarmellose Sodium	15	3.33
Binder Solution			
5	PVP K-30	5	1.11
6	Polysorbate 80	10	2.22
7	Natural FAAH Inhibitor (Genistein)	4	0.89
8	IPA	QS	
9	Water	QS	
Extragranular Ingredients			
10	Magnesium Stearate	10	2.22
11	Talc	4	0.89
12	Zinc Stearate	6	1.33
13	Colloidal silicon dioxide	4.5	1.00
	Average Wt.	450	100.00

Example 9

[0075]

S. No	Ingredients	Std. Qty. mg/unit	% w/w
Intragranular Ingredients			
1	Micronized PEA	300	54.55
2	Natural FAAH Inhibitor (Myricetin)	100	18.18
3	Natural FAAH Inhibitor (Isorhamnetin)	50	9.09
4	Dicalcium Phosphate	45.5	8.27
5	Sodium starch glycolate	15	2.73
Binder Solution			
6	Hypromellose	5	0.91
7	Polysorbate 80	10	1.82
8	IPA	QS	
9	Water	QS	
Extragranular Ingredients			
10	Magnesium Stearate	10	1.82
11	Talc	4	0.73
12	Zinc Stearate	6	1.09
13	Colloidal silicon dioxide	4.5	0.82
	Average Wt.	550	100.00

Example 10

[0076]

S. No	Ingredients	Std. Qty. mg/unit	% w/w
Intragranular Ingredients			
1	Micronized PEA	300	54.55
2	Natural FAAH Inhibitor (Kaempferol)	100	18.18
3	Natural FAAH Inhibitor (Pristimerin)	50	9.09
4	Dicalcium Phosphate	45.5	8.27
5	Croscarmellose Sodium	15	2.73
Binder Solution			
6	PVP K-30	5	0.91
7	Polysorbate 80	10	1.82
8	IPA	QS	
9	Water	QS	
Extragranular Ingredients			
10	Magnesium Stearate	10	1.82
11	Talc	4	0.73
12	Zinc Stearate	6	1.09
13	Colloidal silicon dioxide	4.5	0.82
Average Wt.		550	100.00

Example 11

[0077]

S. No	Ingredients	Std. Qty. mg/unit	% w/w
Intragranular Ingredients			
1	Micronized PEA	300	60.0
2	Natural FAAH Inhibitor (Biochanin)	100	20.0
3	Natural FAAH Inhibitor (Genistein)	4	0.80
4	Mannitol	41.5	8.30
5	Sodium starch glycolate	15	3.0
Binder Solution			
6	PVP K-30	5	1.0
7	Sodium lauryl sulfate	10	2.0
8	IPA	QS	
9	Water	QS	
Extragranular Ingredients			
10	Magnesium Stearate	10	2.0
11	Talc	4	0.80
12	Zinc Stearate	6	1.20
13	Colloidal silicon dioxide	4.5	0.90
Average Wt.		500	100.00

Example 12

[0078]

S. No	Ingredients	Std. Qty. mg/unit	% w/w
Intragranular Ingredients			
1	Micronized PEA	300	66.67
2	Natural FAAH Inhibitor (Daidzein)	50	11.11
3	Mannitol	41.4	9.20
4	Croscarmellose Sodium	15	3.33
Binder Solution			
5	PVP K-30	5	1.11
6	Polysorbate 80	10	2.22
7	Natural FAAH Inhibitor (Genistein)	4	0.89
8	Vitamin (Methylcobalamin)	0.1	0.02
9	IPA	QS	
10	Water	QS	
Extragranular Ingredients			
11	Magnesium Stearate	10	2.22
12	Talc	4	0.89
13	Zinc Stearate	6	1.33
14	Colloidal silicon dioxide	4.5	1.00
Average Wt.		450	100.00

Example 13

[0079]

S. No	Ingredients	Std. Qty. mg/unit	% w/w
Intragranular Ingredients			
1	Micronized PEA	300	66.67
2	Natural FAAH Inhibitor (Daidzein)	50	11.11
3	MCC pH 101	37.5	8.33
4	Croscarmellose Sodium	15	3.33
Binder Solution			
5	Hypromellose	5	1.11
6	Polysorbate 80	10	2.22
7	Natural FAAH Inhibitor (Genistein)	4	0.89
8	Vitamin (Cyanocobalamin)	4	0.89
9	IPA	QS	
10	Water	QS	
Extragranular Ingredients			
11	Magnesium Stearate	10	2.22
12	Talc	4	0.89
13	Zinc Stearate	6	1.33
14	Colloidal silicon dioxide	4.5	1.00

Extragranular Ingredients			
	Average Wt.	450	100.00

Example 14

[0080]

S. No	Ingredients	Std. Qty. mg/unit	% w/w
Intragranular Ingredients			
1	Micronized PEA	300	60.00
2	Natural FAAH Inhibitor (Daidzein)	50	10.00
3	Coenzyme (Ubidecarenone)	50	10.00
4	Lactose Monohydrate	41.5	8.30
5	Sodium starch glycolate	15	3.00
Binder Solution			
6	PVP K-30	5	1.00
7	Polysorbate 80	10	2.00
8	Natural FAAH Inhibitor (Genistein)	4	0.80
9	IPA	QS	
10	Water	QS	
Extragranular Ingredients			
11	Magnesium Stearate	10	2.00
12	Talc	4	0.80
13	Zinc Stearate	6	1.20
14	Colloidal silicon dioxide	4.5	0.90
	Average Wt.	500	100.00

Example 15

[0081]

S. No	Ingredients	Std. Qty. mg/unit	% w/w
Intragranular Ingredients			
1	Micronized PEA	300	60.00
2	Natural FAAH Inhibitor (Daidzein)	50	10.00
3	Coenzyme (Thiamine Pyrophosphate)	50	10.00
4	MCC pH 101	41.5	8.30
5	Croscarmellose Sodium	15	3.00
Binder Solution			
6	PVP K-30	5	1.00
7	Polysorbate 80	10	2.00
8	Natural FAAH Inhibitor (Genistein)	4	0.80
9	IPA	QS	
10	Water	QS	

Extragranular Ingredients			
11	Magnesium Stearate	10	2.00
12	Talc	4	0.80
13	Zinc Stearate	6	1.20
14	Colloidal silicon dioxide	4.5	0.90
Average Wt.		500	100.00

Example 16

[0082]

S. No	Ingredients	Std. Qty. mg/unit	% w/w
Intragranular Ingredients			
1	Micronized PEA	600	80
2	Natural FAAH Inhibitor (Daidzein)	50	6.67
3	MCC pH 101	46.5	6.20
4	Croscarmellose Sodium	10	1.33
Binder Solution			
5	Natural FAAH Inhibitor (Genistein)	4	0.53
6	PVP K-30	5	0.67
7	Polysorbate 80	10	1.33
8	IPA	QS	
9	Water	QS	
Extragranular Ingredients			
10	Magnesium Stearate	10	1.33
11	Talc	4	0.53
12	Zinc Stearate	6	0.80
13	Colloidal silicon dioxide	4.5	0.60
Average Wt.		750	100.00

Example 17

[0083]

S. No	Ingredients	Std. Qty. mg/unit	% w/w
Intragranular Ingredients			
1	Micronized PEA	150	35.71
2	Natural FAAH Inhibitor (Daidzein)	75	17.86
3	MCC pH 101	70.5	16.79
4	Croscarmellose Sodium	10	2.38
Binder Solution			
5	Natural FAAH Inhibitor (Genistein)	75	17.86
6	PVP K-30	5	1.19
7	Polysorbate 80	10	2.38

Binder Solution			
8	IPA	QS	
9	Water	QS	
Extragranular Ingredients			
11	Magnesium Stearate	10	2.38
12	Talc	4	0.95
13	Zinc Stearate	6	1.43
14	Colloidal silicon dioxide	4.5	1.07
Average Wt.		420	100

Stability Study

Example 18 - Stability and dissolution study of formulation of Example 1 Stability Condition: ACCELERATED STABILITY TESTING: 40°C, 75% RH

[0084]

S. No	Duration of Study		Initial	1 Month	3 Months	6 Months
	TEST	Specification				
1.0	Description	White to off white colored granular powder filled in hard HPMC base capsule having red caps and red body.	Complies	Complies	Complies	Complies
2.0	Average weight of capsules	550 ± 7.5 %	551.2 mg	559.3 mg	551.4 mg	552.6 mg
3.0	Net fill content	450 ± 7.5 %	447.3 mg	448.1 mg	450.9 mg	481.7 mg
4.0	Disintegration time	Not More Than 30 minutes	2 - 4 minutes	4 - 5 minutes	4 - 5 minutes	4 - 5 minutes
5.0	Assay					
5.1	Assay of PEA	Between 90.0 % and 110.0 % of LC	99.1 %	100.7 %	101.3 %	99.5 %
5.2	Assay of Daidzein	Between 90.0 % and 110.0 % of LC	101.5 %	101.3 %	100.1 %	98.6 %
6.0	Dissolution (60 minutes)					
6.1	Dissolution of PEA	Not Less than 70 % in 60 minutes	92.1 %	95.1 %	93.3 %	91.3 %
6.2	Dissolution of Daidzein	Not Less than 70 % in 60 minutes	89.6 %	90.6 %	89.1 %	92.2 %

Example 19 - Stability and dissolution study of formulation of Example 7 Stability Condition: ACCELERATED STABILITY TESTING: 40°C, 75% RH

[0085]

S. No	Duration of Study		Initial	1 Month	3 Months	6 Months
	TEST	Specification				
1.0	Description	White to off white colored granular powder filled in hard HPMC base capsule having red caps and red body.	Complies	Complies	Complies	Complies
2.0	Average weight of capsules	$500 \pm 7.5 \%$	503.5 mg	505.8 mg	504.9 mg	500.9 mg
3.0	Net fill content	$400 \pm 7.5 \%$	401.9 mg	403.8 mg	404.5 mg	400.5 mg
4.0	Disintegration time	Not More Than 30 minutes	1 - 2 minutes	2 - 3 minutes	2 - 3 minutes	2 - 3 minutes
5.0	Assay					
5.1	Assay of PEA	Between 90.0 % and 110.0 % of LC	99.2 %	99.6 %	100.3 %	100.9 %
5.3	Assay of Genistein	Between 90.0 % and 110.0 % of LC	95.9%	98.9%	98.3 %	99.9 %
6.0	Dissolution (60 minutes)					
6.1	Dissolution of PEA	Not Less than 70 % in 60 minutes	95.9 %	96.3 %	92.3 %	94.3 %
6.3	Dissolution of Genistein	Not Less than 70 % in 60 minutes	88.1 %	89.9 %	92.3 %	87.6 %

Example 20 - Stability and dissolution study of formulation of Example 8 Stability Condition: ACCELERATED STABILITY TESTING: 40°C, 75% RH

[0086]

S. No	Duration of Study		Initial	1 Months	3 Months	6 Months
	TEST	Specification				
1.0	Description	White to off white colored granular powder filled in hard HPMC base capsule having red caps and red body.	Complies	Complies	Complies	Complies
2.0	Average weight of capsules	$550 \pm 7.5 \%$	555.8 mg	559.6 mg	555.3 mg	552.1 mg
3.0	Net fill content	$450 \pm 7.5 \%$	458.0 mg	452.4 mg	459.4 mg	455.8 mg
4.0	Disintegration time	Not More Than 30 minutes	3 - 4 minutes	3-4 minutes	3 - 4 minutes	4 - 6 minutes
5.0	Assay					
5.1	Assay of PEA	Between 90.0 % and 110.0 % of LC	106.9%	107.3 %	106.2 %	108.2%
5.2	Assay of Daidzein	Between 90.0 % and 110.0 % of LC	100.8 %	100.4 %	98.9 %	99.0 %
5.3	Assay of Genistein	Between 90.0 % and 110.0 % of LC	95.6 %	96.8 %	94.6 %	96.9 %
6.0	Dissolution (60 minutes)					
6.1	Dissolution of PEA	Not Less than 70 % in 60 minutes	99.0 %	91.8 %	100.7 %	100.2 %

S. No	Duration of Study		Initial	1 Months	3 Months	6 Months
	TEST	Specification				
6.2	Dissolution of Daidzein	Not Less than 70 % in 60 minutes	88.8 %	85.4 %	94.0 %	94.8 %
6.3	Dissolution of Genistein	Not Less than 70 % in 60 minutes	80.1 %	88.5 %	89.6 %	95.9 %

Example 21 - Animal Study - Screening effect of synergistic combination or composition/formulation comprising PEA and other natural ingredients against Oxaliplatin induced peripheral neuropathy in rat.

TEST SYSTEM AND ANIMAL HUSBANDRY

[0087] Species: Rat (*Rattus norvegicus*);

Strain: Wistar; Sex: Male / Female

No. of animals: 54 Animals (n=6 per group)

Animal House conditions:

[0088] Lighting: 12/ 12 hour light-dark cycle

Temperature: 25 ± 2 °C

Relative Humidity: 30 to 70%

Temperature and relative humidity were recorded Thrice daily.

[0089] During Experiments, Standard certified rat pellet feed (Manufactured by Keval Sales Corporation, Vadodara) and drinking water treated by reverse osmosis) were provided ad libitum to all animals.

[0090] EXPERIMENTAL PROCEDURE: In study fifty-four (54) rats, were divided into total nine (09) groups. Group 1 served as the normal control, Group 2 served as the disease control, Group 3, Group 4 and Group 5 served as component (A, B and C), Group 6, Group 7 and Group 8 served as formulation of test drug, while Group 9 served as the Reference standard group. For these studies, the following combinations were used.

Table 1: represents various treatments to respective groups.

[0091]

Table 1

S. No.	Group	No. of Animals	Test Drug
1	G1	6	Normal Control
2	G2	6	Disease Control
3	G3	6	PEA (60 mg/kg, P.O.)
4	G4	6	DAIDZEIN (10 mg/kg, P.O.)
5	G5	6	GENISTEIN (0.8 mg/kg, P.O.)
6	G6	6	PEA (60 mg/kg, P.O.) + DAIDZEIN (10 mg/kg, P.O.) (Example 1)
7	G7	6	PEA (60 mg/kg, P.O.) + GENISTEIN (0.8 mg/kg, P.O.) (Example 7)
8	G8	6	PEA (60 mg/kg, P.O.) + DAIDZEIN (10 mg/kg, P.O.) + GENISTEIN (0.8 mg/kg, P.O.) (Example 8)
9	G9	6	Pregabalin (20 mg/kg, P.O.)

[0092] Group-1 received vehicle (0.25% w/v Sodium CMC) orally (p.o.) for three consecutive days (Day 1, 2 & 3). Group-2 to Group-8 received test drugs, while Group 9 received Pregabalin orally (p.o.) on Day-1, Day-2 and Day-3. All treatment groups (Group 2 to 9) were administered with oxaliplatin (12 mg/kg, i.p.) on Day-3 prior to 2 hrs of test drug administration. After 24 hrs of oxaliplatin administration, treated groups as well as the normal control group were assessed using the Cold hyperalgesia method.

[0093] Cold Hyperalgesia method (Tail Immersion Test): In the Tail-immersion test, water was maintained at low (0 to 4°C) temperature. The tail of the rat was immersed in cold water and the duration (time in seconds) of tail immersion was recorded, until the tail was withdrawn from water. The cut-off time of 20 seconds was used. The decrease in tail contact time with cold water was indicative pain whereas prolonged contact time was noted as anti-allodynic effect.

Table 2: Effect of administration of 'Test Composition/formulation' on Oxaliplatin induced peripheral neuropathy in rats (Cold Hyperalgesia Method).

Groups	1	2	3	4	5	6	7	8	9
Animal Mark	Normal Control	Disease Control	PEA (60 mg/kg)	Daidzein (10 mg/kg)	Genistein (0.8 mg/kg)	PEA (60 mg/kg) + Daidzein (10 mg/kg)	PEA (60 mg/kg) + Genistein (0.8 mg/kg)	PEA (60 mg/kg) + Daidzein (10 mg/kg) + Genistein (0.8 mg/kg)	Pregabalin (20 mg/kg)
1	20.00	16.00	11.32	8.55	7.68	17.13	16.93	18.87	17.20
2	20.00	14.81	11.55	8.00	7.15	17.13	16.93	18.87	20.00
3	20.00	6.19	10.85	8.98	7.23	17.13	16.93	18.87	20.00
4	20.00	5.66	10.97	7.95	7.68	17.13	16.93	18.87	19.95
5	20.00	4.05	11.44	8.12	7.68	17.13	16.93	18.87	18.37
6	20.00	3.78	10.75	8.05	7.68	17.13	16.93	18.87	20.00
AVG (seconds)	20.00	8.42	11.15	8.28	7.52	17.13	16.93	18.87	19.25
%			55.73	41.38	37.58	85.65	84.65	94.35	96.27

Table 3: Effect of administration of 'Test Composition/formulation' on Oxaliplatin induced peripheral neuropathy in rat

Groups	1	2	3	4	5	6	7	8	9
Group Name (Human Effective Dose / Day)	Normal Control	Disease Control	PEA (600 mg)	Daidzein (100 mg)	Genistein (8 mg)	PEA (600 mg) + Daidzein (100 mg)	PEA (600 mg) + Genistein (8 mg)	PEA (600 mg) + Daidzein (100 mg) + Genistein (8 mg)	Pregabalin (200 mg)
Day 0	20.00	20.00	20.00	20.00	20.00	20.00	20.00	20.00	20.00
Day 4	20.00	8.42	11.15	8.28	7.52	17.13	16.93	18.87	19.25
%			55.73	41.38	37.58	85.65	84.65	94.35	96.27

[0094] RESULT & DISCUSSION: In this study, Oxaliplatin (12 mg/kg) was administered via intraperitoneal injection in rats. After intraperitoneal injection of Oxaliplatin, there was a significant reduction in tail withdrawal latency in the disease control group. In all treatment groups, either alone or in combination, tail withdrawal latency periods were significantly increased compared to the disease control group. This indicates that treatments were effective against peripheral neuralgia induced by oxaliplatin injection. The effect of treatment groups 6-8 was comparable with that of the standard drug pregabalin as shown in Table 2-3.

[0095] CONCLUSION: Based on the above experiments, when rats were treated only with PEA, Daidzein, or Genistein (i.e., Groups 3-5), in comparison to PEA+Daidzein, PEA+Genistein, and PEA+Daidzein+Genistein (i.e., Groups 6-8), the latter was found to be more effective in treating Oxaliplatin induced neuropathic pain in rats at defined dose levels

REFERENCES CITED IN THE DESCRIPTION

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- **KAUR et al.**What failed BIA 10-2474 Phase I clinical trial? Global speculations and recommendations for future Phase I trialsJ Pharmacol Pharmacotherapy, 2016, vol. 7, 3120-126 [\[0027\]](#)

FARMACEUTISK SAMMENSÆTNING MOD NEUROPATISK SMERTE**Patentkrav:**

1. Farmaceutisk sammensætning, der består af: Palmitoylethanolamid (PEA) og én eller flere naturligt forekommende fedtsyreamidhydrolaseinhibitorer (FAAH-inhibitorer), hvor den naturligt forekommende FAAH-inhibitor er valgt blandt myricetin, isorhamnetin, kaempferol, pristimerin, biochanin A, genistein, daidzein eller en kombination deraf.
2. Farmaceutisk sammensætning ifølge krav 1, hvor mængden af PEA ligger mellem 35 og 80 vægtprocent af sammensætningen.
3. Farmaceutisk sammensætning ifølge krav 1, hvor mængden af naturligt forekommende FAAH-inhibitor ligger mellem 0,5 og 40 vægtprocent af sammensætningen.
4. Farmaceutisk sammensætning ifølge krav 1, hvor den naturligt forekommende FAAH-inhibitor er valgt blandt daidzein, genistein eller en kombination deraf.
5. Farmaceutisk sammensætning ifølge et hvilket som helst af de foregående krav, der endvidere omfatter vitaminer, coenzymmer eller en kombination deraf.
6. Farmaceutisk sammensætning ifølge krav 5, hvor vitaminerne er valgt blandt methylcobalamin, cyanocobalamin, benfotiamin eller en kombination heraf, og hvor coenzymmerne er valgt blandt ubidecarenon, thiaminpyrophosphat, flavinadenindinukleotid eller en kombination deraf.
7. Farmaceutisk sammensætning ifølge krav 5, hvor mængden af vitaminer ligger mellem 0,01 og 30 vægtprocent af sammensætningen.
8. Farmaceutisk sammensætning ifølge krav 5, hvor mængden af coenzymmer ligger mellem 10 og 40 vægtprocent af sammensætningen.
9. Farmaceutisk sammensætning ifølge et hvilket som helst af de foregående krav, der endvidere omfatter farmaceutisk acceptable excipienser.
10. Farmaceutisk sammensætning ifølge krav 9, hvor den farmaceutisk acceptable

excipiens er valgt blandt en diluent, et sprængmiddel, et bindingsmiddel, et solubiliseringsmiddel, et smøremiddel, et glidemiddel eller et opløsningsmiddel.

11. Farmaceutisk sammensætning ifølge krav 10, hvor mængden af diluent ligger mellem 5 og 50 vægtprocent af sammensætningen, sprængmiddel ligger mellem 0,5 og 10 vægtprocent af sammensætningen, bindingsmiddel ligger mellem 0,1 og 10 vægtprocent af sammensætningen, solubiliseringsmiddel ligger mellem 0,25 og 15 vægtprocent af sammensætningen, smøremiddel ligger mellem 1,0 og 10 vægtprocent af sammensætningen, glidemiddel ligger mellem 1,0 og 10 vægtprocent af sammensætningen, eller hvor mængden af opløsningsmiddel er mængdetilstrækkelig.

12. Farmaceutisk sammensætning ifølge krav 1, hvor sammensætningen er i form af en tablet, en kapsel, et omslag, en pille, en hård kapsel fyldt med væske eller faststof, en blød kapsel, et pulver, et granulat, en suspensionsopløsning eller formuleret med modificeret frigivelse.

13. Fremgangsmåde til fremstilling af en farmaceutisk sammensætning ifølge krav 1, hvor fremgangsmåden består af:

- a. nøjagtig afvejning af alle bestanddelene i separate beholdere,
- b. separat sigtning af tidligere afvejte PEA, naturlig(-e) FAAH-inhibitor(-er), diluent(-er) og et eller flere sprængmidler,
- c. blanding af indholdet fra trin b,
- d. fremstilling af bindingsmiddelsopløsning i en separat beholder og tilsætning af dette til trin c og sigtning af dejen for at opnå granulater,
- e. tørring af de opnåede granulater indtil tørhedsniveauet (LOD) er reduceret til mindre end 1,5 vægtprocent/vægt,
- f. sigtning af halvtørrede granulater gennem en egnet sigte,
- g. separat sigtning af tidligere afvejte smøremiddel/smøremidler eller glidemiddel/glidemidler gennem en egnet sigte og tilsætning til trin f.