(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
10 April 2025 (10.04.2025)

WIPO | PCT

(10) International Publication Number
WO 2025/073997 A1

(51) International Patent Classification:
A61K 9/14 (2006.01) *A61K 47/26* (2006.01)
A61K 31/00 (2006.01) *A61K 47/38* (2006.01)
A61K 47/12 (2006.01) *A61K 45/06* (2006.01)

(21) International Application Number:
PCT/EP2024/078139

(22) International Filing Date:
07 October 2024 (07.10.2024)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
23202117.0 06 October 2023 (06.10.2023) EP

(71) Applicant: **DSM IP ASSETS B.V.** [NL/NL]; Wilhelminasingel 39, 6221 BE MAASTRICHT (NL).

(72) Inventors: **KUENTZ, Martin Thomas**; University of Applied Sciences and, Arts Northwestern Switzerland, Hofackerstrasse 30, 4132 Muttenz (CH). **HERZIG, Susanne**; University of Applied Sciences and, Arts Northwestern Switzerland, Hofackerstrasse 30, 4132 Muttenz (CH). **ABREU-VILLELA, Renata**; DSM Nutritional Products Ltd., c/o Patent Department, Wurmisweg 576, 4303 Kaiseraugst (CH).

(74) Agent: **DSM-FIRMENICH IP**; DSM-Firmenich AG Wurmisweg 576, 4303 Kaiseraugst (CH).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CV, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IQ, IR, IS, IT, JM, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, MG, MK, MN, MU, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, WS, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, CV, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SC, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, ME, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:
— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*
— *of inventorship (Rule 4.17(iv))*

Published:
— *with international search report (Art. 21(3))*
— *in black and white; the international application as filed contained color or greyscale and is available for download from PATENTSCOPE*

(54) Title: CANNABINOID EXTRUDATE

(57) **Abstract:** The disclosed inventions pertain to solid extrudates for pharmaceutical use. The solid extrudates comprise at least one cannabinoid isolate and may be produced by hot melt extrusion. In an embodiment, a solid extrudate comprises 20-40 wt% of a cannabinoid isolate, 20-40 wt% of a hydroxypropyl methylcellulose, 5-15 wt% of a monounsaturated fatty acid, and 10-30 wt% of a surfactant.

WO 2025/073997 A1

CANNABINOID EXTRUDATE

Field

The disclosed inventions pertain to solid extrudates for human oral consumption, such as for pharmaceutical use. The solid extrudates comprise at least one cannabinoid isolate.

Background

Cannabinoid isolates are several structural classes of compounds found in the cannabis plant, primarily. They may exist as natural or synthetic compounds. At least 113 different cannabinoids have been isolated from the cannabis plant, some of which have been linked to beneficial pharmacological activity and others which are being investigated for pharmacological activity. Some health benefits associated with cannabinoids are lowering blood pressure, reducing inflammation, preventing relapse in drug and alcohol addiction, treating anxiety disorders, treating gastrointestinal (GI) disorders, and preventing seizures.

Cannabinoid isolates can be delivered in multiple ways, such as by inhalation, oral consumables, or sprays. A delivery format that is not pleasing to a consumer may affect use and compliance. For example, existing pharmaceutical products comprising cannabinoids are delivered in formats that require multiple steps or are otherwise displeasing to the patient.

For example, EPIDIOLEX®, the first and only FDA-approved prescription cannabidiol (CBD), requires dosing a liquid into a syringe. As the dose may vary, one or more administrations of varying syringe sizes or liquid amounts may be required. Once in the syringe, it must be inspected for air bubbles, the air bubbles removed, and the dose adjusted if needed. Care must be taken during administration to not spill the product and the product must be administered to the correct location of the patient's mouth. Lastly, the syringe must be washed, rinsed, and dried prior to the next dose. This method is cumbersome and may introduce errors in dosing.

Many of the existing drawbacks of cannabinoid isolate administration could be reduced or eliminated with a solid product that could be consumed orally, for example, as a tablet. However, solid products possess challenges in achieving sufficient stability and bioavailability of the cannabinoid. Improving the bioavailability of cannabinoid-containing products is challenging due to the poor water solubility of cannabinoids and the limited solubility of cannabinoids in various oils. The poor solubility leads to poor resorption to the body, followed by extensive first-pass metabolism and elimination.

A solid, orally consumable cannabinoid product with improved bioavailability would therefore be desirable. In addition, such product should preferably not exhibit discoloration.

Summary

The complicated process used to administer EPIDIOLEX® is essential because today a liquid formulation is required to deliver the CBD in a solubilized form to assure sufficient bioavailability. Excipients used for the liquid formulation are ethanol, sesame oil as well as benzyl alcohol. Bioavailability of crystalline CBD is known to be poor and administration of the solubilised CBD greatly improves bioavailability. However, ethanol is not desirable for all patients.

A common technical approach to increase bioavailability of poorly soluble compounds is to formulate them as amorphous solid dispersions (ASDs) to circumvent a slow dissolution rate and limiting solubility of an otherwise crystalline compound.

Thus, there is an ongoing need for solid compositions/ products and associated methods of manufacturing thereof comprising cannabinoid isolates in the form of ASDs containing high amounts of cannabinoid isolate(s) with improved bioavailability. In addition, such solid compositions/ product should preferably not exhibit extensive discoloration and provide good storage stability such as color stability and no crystallization of CBD over time.

The inventors have discovered solid extrudates, and compositions and methods for producing such solid extrudates, that evidence a surprising improvement in the bioavailability of a cannabinoid isolate that may be utilized in a desirable, orally consumable format. The solid extrudates may be produced by hot melt extrusion (HME), a solvent-free process with a low production footprint. Moreover, the disclosed compositions and methods may yield advantages for efficient process development and scale-up while enabling a continuous manufacturing process. Said compositions in addition did not show discoloration as well as (re-)crystallization of the cannabinoid isolate.

In an embodiment of the invention, a solid extrudate comprises:

a. 20-40 wt% of a cannabinoid isolate,
b. 20-40 wt% of a hydroxypropyl methylcellulose,
c. 5-15 wt% of a monounsaturated fatty acid, and
d. 10-30 wt% of a surfactant.

The solid extrudate may be manufactured by a hot melt extrusion process.

Potential advantages of the invention are higher bioavailability, improved patient compliance, easier or more efficient manufacturing, improved appearance (reduced discoloration), no crystallization of the cannabinoid isolate and improvements with respect to shipping and storage.

Brief Description of the Figures

Fig. 1 is a series of DSC measurements associated with Example 2-1.

Fig. 2 is a series of DSC measurements associated with Example 2-2.

Fig. 3 and 4 show extrudates associated with examples 10 and CE5

Detailed Description

The solid extrudate comprises a cannabinoid isolate.

Cannabinoids are chemical substances regardless of structure or origin, that join the cannabinoid receptors of the body and brain and that have similar effects to those produced by the cannabis plant. The two main cannabinoids found in the cannabis plant are delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD).

Cannabinoids found in the cannabis plant are generally referred to as cannabinoid isolates and are a unique family of terpeno-phenolic compounds.

Thus, it is well understood by a person skilled in the art, that the term cannabinoid isolate as used herein refers to cannabinoids found in the cannabis plant.

The cannabinoid isolate used according to the present invention may be natural (i.e. isolated from cannabis plant) or synthetic. In an embodiment, the cannabinoid isolate is synthetic, such as cannabinoid isolate produced by fermentation of recombinant yeast.

In an embodiment, the cannabinoid isolate comprises cannabigerolic acid (CBGA), cannbigerol (CBG), cannabidiolic acid (CBDA), cannabidiol (CBD), cannabidivarinic acid (CBDVA), or cannabidivarin (CBDV), cannabichromenic acid (CBCA), cannabichromene (CBC), cannabinolic acid (CBNA), cannabinol (CBN), cannabidivarinic acid, cannabichromevarinic acid (CVCVA), cannabichromevarin (CBCV), cannabigerovarinic acid (CBGVA), cannabigerovarin CBGV), cannabicyclolic acid (CBLA), cannabicyclol (CBL), cannabielsoinic acid (CBEA), cannabielsoin (CBE), cannabicitranic acid (CBTCA), or cannabicitran (CBTC) as well as any mixtures thereof. In an embodiment, the cannabinoid isolate comprises cannabigerolic acid (CBGA), cannbigerol (CBG), cannabidiolic acid (CBDA), or cannabidiol (CBD) as well as any mixtures thereof.

In a preferred embodiment, the cannabinoid isolate is cannabidiol (CBD). CBD [CAS NO: 13956-29-1] is a Biopharmaceutical Classification System (BCS) class II drug with low water solubility (0.0126 mg/ml) and high permeability (log P = 6.1). CBD is oxidation labile and has a molecular weight of 314.5 g/mol with a melting point between 66 and 67 °C.

CBD is e.g. commercially available from BSPG Laboratories Ltd (Kent, Great Britain).

Preferably in all embodiments of the present invention, CBD is extracted from industrial hemp (Cannabis sativa L.).

Preferably in all embodiments of the present invention, the CBD has a purity of at least 95%, more preferably of at least 96%, even more preferably of at least 97%, most preferably of at least 98% (HPLC). Even more preferably, the CBD does not contain any detectable (0.000006% limit of detection) tetrahydrocannabinol (THC) or any other controlled cannabinoid.

The solid extrudate or the melt used to form the solid extrudate comprises from 20-40 wt% of a cannabinoid isolate, preferably from 25-35 wt% of the cannabinoid isolate. In an embodiment the solid extrudate or the melt used to form the solid extrudate comprises from 25, 26, 27, 28, 29 or 30 wt% to 35, 34, 33, 32, 31, or 30 wt% of a cannabinoid isolate.

The solid extrudate comprises hydroxypropyl methylcellulose (HPMC), also known as hypromellose. Various grades of HPMC are commercially available. These grades can be split into pH sensitive grades and pH insensitive grades. Examples of pH sensitive HPMC grades are hydroxypropyl methylcellulose acetate succinate (HPMC-AS) and hydroxypropyl methylcellulose phthalate (HPMC-P). By pH sensitive it is meant that the release of the cannabinoid isolate from the solid extrudate will vary significantly based on the pH of the environment within the body. It is preferred that the hydroxypropyl methylcellulose is pH insensitive.

In an embodiment hydroxypropyl methylcellulose (HPMC) with a viscosity of 5 to 25 cP such as ~15 cP at 2% in water is used, which is e.g. commercially available as Methocel™ E15 Premium LV [CAS No: 9004-65-3].

In an embodiment, the Tg of the hydroxypropyl methylcellulose is from 130 to 200 °C as measured by DSC (Differential scanning calorimetry: sample amounts between 3 and 8 mg are filled in an aluminum pan with a pierced lid. The measurements are conducted at a heating rate of 10°C/min from 10 to 220°C. The measurement cell is purged with nitrogen at 200 mL/min).

The solid extrudate or the melt used to form the solid extrudate comprises from 20 to 40 wt% of a hydroxypropyl methylcellulose. In an embodiment, the solid extrudate or the melt used to form the solid extrudate comprises from 25 to 35 wt% of the hydroxypropyl methylcellulose. In an embodiment, the solid extrudate or the melt used to form the solid extrudate comprises from 20, 21, 22, 23, 24, 25, 26, 27, 28, or 29 wt% to 40, 39, 38, 37, 36, 35, 34, 33, 32, 31, or 30 wt% of the hydroxypropyl methylcellulose.

The solid extrudate comprises a monounsaturated fatty acid. In an embodiment, the monounsaturated fatty acid (MUFA) comprises palmitoleic acid, oleic acid, elaidic acid, vaccenic acid, gadoleic acid, eicosenoic acid, and erucic acid. In an embodiment, the monounsaturated fatty acid has from 16 to 18 carbons. In an embodiment, the monounsaturated fatty acid has 19 carbons. In a preferred embodiment, the monounsaturated fatty acid comprises oleic acid. In an embodiment, the monounsaturated fatty acid comprises at least 50 wt% of oleic acid, based on the total monounstaturated fatty acid content. In an embodiment, the monounsaturated fatty acid comprises at least 50, 60, 70, 80, 90, 95 or 100 wt% of oleic acid, based on the total monounstaturated fatty acid content.

In one embodiment, the solid extrudate comprises solely oleic acid as monounsaturated fatty acid, i.e. the extrudate comprises no (i.e. is free of) other mono-unsaturated fatty acid.

The solid extrudate or the melt used to form the solid extrudate comprises from 5 to 15 wt% of a monounsaturated fatty acid. In an embodiment, the solid extrudate or the melt used to form the solid extrudate comprises from 5, 6, 7, 8, 9, or 10 wt% to 15, 14, 13, 12, 11, or 10 wt% of monounsaturated fatty acid.

In an embodiment, the ratio of cannabinoid isolate to monounsaturated fatty acid, by weight, in the solid extrudate or the melt used to form the solid extrudate is from 4, 3.5, 3, or 2.5 to 1. In an embodiment, the ratio of cannabinoid isolate to monounsaturated fatty acid, by weight, in the solid extrudate or the melt used to form the solid extrudate is 4:1 to 2.5:1, more preferably from 3.5:1 to 2.5:1.

In one embodiment, the solid extrudate comprises oleic acid having a purity of at least 65 w.-% (assay), preferably from 65 to 88 % (assay) which is e.g. commercially available from PanReac AppliChem (ITW Reagents) / Assay Ph. Eur. (G.C.): 65.0 - 88.0 %. In another embodiment, the solid extrudate comprises oleic acid having a purity of at least 90%, more preferably of at least 95%, most preferably of at least 97% such as >99% (GC). Such oleic acid grades are e.g. commercially available at Sigma Aldrich or Hänseler AG.

In one embodiment, the solid extrudate does not comprise a natural oil comprising oleic acid such as in particular sesame oil or macadamia oil, as this leads to discoloration of the solid extrudate, in particular upon storage.

The solid extrudate or the melt used to form the solid extrudate comprises a surfactant. In an embodiment, the surfactant comprises sodium lauryl sulphate, lecithin, polyethylene glycol, a polyoxylethylene stearates, a polyoxyethylene glyceride, a poly(ethylene glycol)/poly(propylene glycol) block copolymer, such as a poly(ethylene glycol)-block-poly(propylene glycol)-block-poly(ethylene glycol) (i.e. HO-[CH_2-CH_2-O]$_a$-[$CH_2CH(CH_3)$-O]$_b$-[CH_2-CH_2-O]$_a$-H, or a polysorbate, for example polysorbate 20, 40, 60, or 80. Preferred is a polysorbate, more preferably polysorbate 80 (e.g. commercially available as Tween® 80 from Sigma Aldrich) or a poly(ethylene glycol)/poly(propylene glycol) block copolymer wherein a is selected in the range from 70-110 and b is selected in the range from 25 to 60 (e.g. commercially available as Lutrol F127 (a=101, b=56) or Lutrol F68 (a= 80, b = 27) from BASF) or a polyoxylethylene stearate such as PEG-32 stearate (e.g. commercially available as Gelucire 48/16 from Gattefossé) or a polyoxyethylene glyceride such as PEG-32 Hydrogenated palm glycerides (also known as stearoyl polyoxyl-32 glycerides, which is consists of mono, di- and triglycerides and PEG-32 (MW 1500) mono- and diesters of palmitic (C16) and stearic (C18) acids e.g. commercially available as Gelucire 50/13) as well as mixtures thereof. In an embodiment, at least 40 wt%, more preferably at least 50 wt%, more preferably at least 60 wt%, more preferably at least 70 wt%, more preferably at least 80 wt%, more preferably at least 90 wt%, more preferably 100 wt% of the surfactant comprises a polysorbate, based on the total

weight of the surfactant. Most preferred polysorbate 80 is used as the sole surfactant in the solid extrudate.

The solid extrudate or the melt used to form the solid extrudate comprises from 10-30 wt% of a surfactant, preferably from 15-25 wt% of a surfactant. In an embodiment the solid extrudate or the melt used to form the solid extrudate comprises from 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 wt% to 30, 29, 28, 27, 26, 25, 24, 23, 22, 21, or 20 wt% of a surfactant.

In an embodiment, the solid extrudate or the melt used to form the solid extrudate further comprises a porous inorganic carrier. Porous inorganic carriers decrease the density of the extrudate and may improve flowability and processability of the melt in the extrusion process. In an embodiment, the porous inorganic carrier comprises silica, calcium carbonate, calcium phosphate, polypropylene powders (Accurel®), porous calcium silicate (Florite®), or magnesium aluminometasilicate. A preferred porous inorganic carrier is a porous calcium silicate.

In an embodiment, the solid extrudate or the melt used to form the solid extrudate comprises from 5 to 25 wt%, more preferably from 5 to 20 wt%, more preferably from 8 to 15 wt% of a porous inorganic carrier. A preferred porous inorganic carrier is a calcium silicate, such as Florite® R. In an embodiment, the solid extrudate or the melt used to form the solid extrudate comprises from 5, 6, 7, 8, 9, 10, 11, or 12 wt% to 25, 24, 23, 22, 21, 20, 19, 18, 17, 16, 15, 14, 13, or 12 wt% of a porous inorganic carrier.

In an embodiment, the solid extrudate or the melt used to form the solid extrudate consists essentially of of a cannabinoid isolate, a hydroxypropyl methylcellulose, a monounsaturated fatty acid, and a surfactant with all the definitions and preferences as given herein.

In an embodiment, the solid extrudate or the melt used to form the solid extrudate consists essentially of a cannabinoid isolate, a hydroxypropyl methylcellulose, a monounsaturated fatty acid, a surfactant, and a porous inorganic carrier with all the definitions and preferences as given herein.

In an embodiment, the cannabinoid isolate is present as an amorphous solid within the solid extrudate, i.e. in the form of a so-called amorphous solid dispersion. Thus, in an embodiment, at least 90 wt%, based on the total weight of the cannabinoid isolate, of the cannabinoid isolate is in a non-crystalline form. Even more preferred, at least 95 wt%, based on the total weight of the cannabinoid isolate, of the cannabinoid isolate is in a non-crystalline form. Even more preferred, at least 98 wt%, based on the total weight of the cannabinoid isolate, of the cannabinoid isolate is in a non-crystalline form. Even more preferred, at least 99 wt%, based on the total weight of the cannabinoid isolate, of the cannabinoid isolate is in a non-crystalline form. Even more preferred, 100 wt%, based on the total weight of the cannabinoid isolate, of the cannabinoid isolate is in a non-crystalline form. The content of the

crystalline form of the cannabinoid isolate can be measured using commonly known methods, such as differential scanning calorimetry (DSC).

In the context of the present invention, DSC is used to determine the amount of crystalline form of the cannabinoid isolate. The DSC method to determine the crystallinity of the cannabinoid isolate is carried out as follows: Liquid or powder (solid) formulations (ca. 8–10 mg) are placed in aluminum pans and hermetically sealed. Empty pans are used as a reference samples. For the investigation of the cannabinoid bulk material (i.e. the non-formulated, crystalline cannabinoid), about 5-8 mg of sample is used. Each sample is heated from 10 °C at 10 °C/min to 90-220°C and then cooled down to 10 °C at 10 °C/min. Upon heating, for the non-formulated, crystalline cannabinoid a thermal transition peak is determined, which for CBD is approx. 68°C, which is attributed to the melting of cannabinoid crystals. By analyzing the DSC thermogram and measuring the peak area, the degree of crystallinity of a formulated sample can be determined, as the height of the DSC peak corresponds to the amount of heat released during crystallization/heat consumed during melting and is proportional to the degree of crystallinity of the sample. Accordingly, to determine the % of crystallinity, the peak areas of the samples are referenced against the peak area of the crystalline cannabinoid. The amount of crystalline cannabinoid present in a sample can be calculated, which is then used to determine the degree of crystallinity (%), based on known total amount of cannabinoid present in the sample. If no peak is observable in the range of the melting point of the cannabinoid (approx. 70°C), the cannabinoid in the formulated sample is in an amorphous, non-crystalline form.

In an embodiment, the solid extrudate or the melt used to form the solid extrudate further comprises one or more vitamins, such as vitamin A, vitamin B1, vitamin B2, vitamin B3, vitamin B7, vitamin B9, vitamin C, vitamin D, or vitamin E. In an embodiment, the solid extrudate or the melt used to form the solid extrudate further comprises vitamin B3.
In an embodiment, the solid extrudate or the melt used to form the solid extrudate further comprises a vitamin E. Vitamin E is a group of eight fat soluble compounds that include four tocopherols ((α)-tocopherol, (β)-tocopherol, (γ)-tocopherol and (δ)-tocopherol) and four tocotrienols ((α)-tocotrienol, (β)-tocotrienol, (γ)-tocotrienol and (δ)-tocotrienol).
Also mixtures of these compounds can be used such as (all-*rac*)-α-tocopherol. In the context of the present invention (all-*rac*)-α-tocopherol is preferred.

In an embodiment, the solid extrudate or the melt used to form the solid extrudate further comprises an emulsifier. In an embodiment, the emulsifier comprises a modified (food) starch, vitamin E TPGS, ascorbyl palmitate, pectin, alginate, carrageenan, furcellaran, dextrin derivatives, lignosulfonate, polysaccharide gums (such as gum acacia (= gum arabic), modified gum acacia, TIC gum, flaxseed gum, ghatti gum, tamarind gum and arabinogalactan), gelatine (bovine, fish, pork, poultry), plant proteins (such as are for example peas, soybeans, castor

beans, cotton, potatoes, sweet potatoes, manioc, rapeseed, sunflowers, sesame, linseed, safflower, lentils, nuts, wheat, rice, maize, barley, rye, oats, lupin and sorghum), animal proteins including milk or whey proteins, lecithin, polyglycerol ester of fatty acids, monoglycerides of fatty acids, diglycerides of fatty acids, sorbitan ester, and sugar ester (as well as derivatives thereof). Preferred emulsifiers are modified (food) starches, vitamin E TPGS, polysaccharide gums, gelatine (bovine, fish, pork, poultry), and plant proteins.

In an embodiment, the solid extrudate or the melt used to form the solid extrudate further comprises an auxiliary agent chosen from the group consisting of dyestuffs, thickeners (such as maltodextrin, glucose syrup), fillers, binders, flavours, antioxidants (other than vitamin E), a pH buffer, and mixtures thereof.

In an embodiment the solid extrudate according to the present invention is incorporated into dosage forms suitable for oral application such as a tablet (orally dispersible tablet, chewable tablet, film coated tablet, immediate release tablet, extended or sustained release tablet and similar), a capsule, an orally dispersible film, or a gummy.

The amount of the solid extrudate to be incorporated into such an oral dosage form is preferably selected in the range from 10 mg to 500 mg.

In an embodiment the invention relates to a pharmaceutical product comprising a solid extrudate as defined herein. Said pharmaceutical product is particularly suitable for oral administration of a cannabinoid isolate such as in particular CBD as it exhibits an improved bioavailability compared to a formulation comprising less than 5 wt.-% of a monounsaturated acid such as in particular oleic acid. Said pharmaceutical product preferably is in the form of a tablet (orally dispersible tablet, chewable tablet, film coated tablet, immediate release tablet, extended or sustained release tablet and similar), a capsule, an orally dispersible film, or a gummy

To prepare a solid dosage form or pharmaceutical product according to the present invention, the solid extrudate according to the present invention may be admixed with excipients known in the art such as

- diluents, like lactose, starch, microcrystalline cellulose, sorbitol, mannitol, dibasic calcium phosphate dihydrate, calcium sulfate dihydrate, sucrose-based diluents and mixtures thereof;
- binders, like acacia, cellulose derivatives, gelatin, glucose, polyvinylpyrollidone, starch, sucrose, sorbitol, tragacanth, sodium alginate and mixtures thereof;

- disintegrants, like microcrystalline cellulose and cellulose derivatives, starch and its derivatives, alginic acid and its derivatives, ion-exchange resins, cross-linked sodium carboxymethyl cellulose, sodium starch glycolate, cross-linked polyvinylpyrrolidone and formaldehyde-caseine;
- lubricants, antiadherents and glidants, like magnesium-, calcium- and sodium stearates, stearic acid, hydrogenated castor oil, talc, water, polyethylene glycol, sodium lauryl sulfate, magnesium lauryl sulfate and silica.

In a further embodiment the present invention relates to a method to improve the bioavailability of a cannabinoid isolate, preferably of CBD, said method comprising the step of formulating the cannabinoid isolate into an extrudate comprising from 5-15 wt% of a monounsaturated fatty acid, preferably oleic acid (compared to an extrudate comprising less than 5 wt% of the monounsaturated acid). Preferably the solid extrudate with the improved bioavailability comprises

a. 20-40 wt% of a cannabinoid isolate,
b. 20-40 wt% of a hydroxypropyl methylcellulose,
c. 5-15 wt% of a monounsaturated fatty acid, and
d. 10-30 wt% of a surfactant,

and with all the definitions and preferences as given herein.

Examples

Materials

- CBD was from BSPG Laboratories Ltd (Kent, Great Britain). BSPG's CBD is extracted from industrial hemp (Cannabis sativa L.) before being purified and crystallised to produce the final ingredient, which is highly pure (minimum purity of 98%) and does not contain any detectable (0.000006% limit of detection) tetrahydrocannabinol (THC) or any other controlled cannabinoid.
- HPMC (Hydroxyproply methylcellulose) was Methocel E15 Premium LV from Colorcon® (Kent, Great Britain).
- Croscarmellose was from Sigma Aldrich
- Oleic Acid and Sesame oil were from Hänseler AG.
- Tween® 80 (polysorbate 80) and glycerin monostearate were from Sigma Aldrich (Bruchs, Switzerland).
- Lutrol® F68 and F127 (Poly(ethylene glycol)-block-poly(propylene glycol)-block-poly(ethylene glycol)) were from BASF (Ludwigshafen, Germany).
- Gelucire® 48/16 and Gelucire® 50/13 were from Gattefossé plc. (Lucerne, Switzerland)
- Nicotinamide was from Sigma Aldrich (Bruchs, Switzerland)

- Florite® R (Calcium Silicate) was from Tomita Pharmaceuticals (Tokushima, Japan).
- Alpha-Tocopherol was from BASF (Ludwigshafen, Germany).

Example 1 – Hot Melt Extrusion Feasibility

Extrudates were prepared as follows to determine feasibility of extruding compositions comprising CBD. All extrudates were produced with the co-rotating twin-screw extruder ZE9 ECO from Three-Tec (Birren, Switzerland) equipped with a pair of screws with a diameter of 9 mm, a length of 180 mm. The three heating zones were heated 20 minutes before adding the powder mix to the extruder and the screw speed was set to 45 rpm. Prior to extrusion, all ingredients were pre-mixed with mortar and pestle and the blend (minimum 5g) was then given manually in small portions to the extruder. The extrudates were cooled to room temperature and stored in the fridge at 4°C. Performance in the hot melt extrusion process and a description of the resulting extrudate for various formulations is shown in Fig. 1.

It was demonstrated that numerous formulations according to the invention successfully form white or slightly yellow extrudates, also upon storage while the use of sesame oil or high amounts of oleic acid resulted in violet or strongly yellow/ brown extrudates.

No.	[wt%] CBD	[wt%] Polymer	[wt%] Oil	[wt%] Surfactant	[wt%] Inorganic Carrier	Comment on process and extrudate
1	30	30 HPMC	10 Oleic Acid	10 TWEEN 80 10 LUTROL F127	10 FLORITE R	White slightly yellow extrudate
2	30	30 HPMC	10 Oleic Acid	10 TWEEN 80 10 LUTROL	10 FLORITE R	White slightly yellow extrudate
3	30	25 HPMC 5 Croscarmellose	10 Oleic Acid	10 TWEEN 80 10 LUTROL	10 FLORITE R	White slightly yellow extrudate
4	30	30 HPMC	10 Oleic Acid	10 TWEEN 80	20 FLORITE R	White slightly yellow extrudate
5	40	30 HPMC	10 Oleic Acid	20 TWEEN 80		Slightly yellow extrudate
6	30	30 HPMC	10 Oleic Acid	20 LUTROL F127	10 FLORITE R	White slightly yellow extrudate
7	30	30 HPMC	10 Oleic Acid	20 LUTROL F68	10 FLORITE R	White slightly yellow extrudate
8	30	30 HPMC	10 Oleic Acid	20 GELUCIRE 50/13	10 FLORITE R	White slightly yellow extrudate
9	30	30 HPMC	15 Oleic Acid	15 Glycerin monostearate	10 FLORITE R	White slightly yellow extrudate
10	30	30 HPMC	10 Oleic acid	20 LUTROL F68	10 FLORITE R	White extrudate (Figure 3)
11	30	30 HPMC	Macadamia Oil (comprising 8% of Oleic Acid)	20 LUTROL F68	10 FLORITE R	White extrudate, slight color change after 2 weeks storage
CE1	30	15 HPMC	25 Oleic acid	20 LUTROL F68	10 FLORITE R	Strong yellow extrudate, color change to brown after 2 weeks
CE2	30	45 HPMC	5 Sesame Oil (comprising 1.95% Oleic Acid)	10 TWEEN 80	10 FLORITE R	White extrudate, color change to violet a few hours after processing
CE3	40	30 HPMC	10 Sesame Oil (comprising 3.8% Oleic Acid)	20 TWEEN 80		White extrudate, color change to violet a few hours after processing
CE4	30	30 HPMC	10 Sesame Oil (comprising 3.8% Oleic Acid)	20 LUTROL F68	10 FLORITE R	White extrudate, color change to violet a few hours after processing

No.	[wt%] CBD	[wt%] Polymer	[wt%] Oil	[wt%] Surfactant	[wt%] Inorganic Carrier	Comment on process and extrudate
CE5	30	30 HPMC	10 Sesame Oil (comprising 3.8% Oleic Acid)	20 LUTROL F68	10 FLORITE R	Violet extrudate (Figure 4)

Example 2 – Stability

An amorphous form of CBD is known to present better bioavailability. Samples were tested to determine whether CBD is present in an amorphous during storage.

Compositions were formed and extrudates obtained in the same manner of Example 1. Samples were tested either in the extrudate form or a milled form of the extrudate.

Milled samples of extrudates were produced as follows. The extrudates were cut into small pieces and grinded by a cryogenic grinder Freezer/Mill® from Spex SamplePrep (Metuchen, USA). The setting was 10 min precooling and a rate of 10 CPS for 2 cycles with 2 minutes. The resulting powder was purged with inert gas, packed airtight and stored in the fridge at 4°C.

The samples were stored according to storage conditions A, B, or C. Samples stored according to condition B were stored for four weeks in closed aluminum bags at 25 °C, 60% rH. Samples stored according to condition C were stored for four weeks in closed aluminum bags 40 °C, 75% rH for the stated amount of time. The storage conditions are summarized in Table 2.

Table 2 – Storage Conditions

Condition	Time	Temperature	Relative Humidity
A	0	N/A	N/A
B	4 weeks	25 °C	60%
C	4 weeks	40 °C	75%

The crystallization behavior of the extrudates or milled samples thereof was determined by using a differential scanning calorimeter DSC 3 (Mettler Toledo, Greifensee, Switzerland). The measurements were conducted at a heating rate of 10°C/min from 10 to 220°C. The measurement cell was purged with nitrogen at 200 mL/min. Sample amounts between 3 and 8 mg were filled in an aluminum pan with a pierced lid. Extrudates were cut into small pieces. The thermal events were analyzed with the STARe Evaluation-Software Version 16 (Mettler Toledo, Greifensee, Switzerland). For sample evaluation mainly the first heating curve was used.
As reference crystalline CBD was used (5-8mg). The crystalline CBD exhibited a thermal transition peak (melting point) at ca. 68°C.

Example 2-1

A set of samples have the compositions shown in Table 2-1. Compositions in the below table are expressed as parts by weight.

Table 2-1 – Example 2-1 Compositions

	2-1	CE 2-1
CBD	30	0
HPMC	30	30
Oleic Acid	10	10
TWEEN 80	20	20
FLORITE R	10	10
Total (parts by weight)	100	70

Results of the DSC are shown in Fig. 1. The notation used in Fig. 1 and 2 is composition/form/condition. For example, an extrudate of composition Comparative Example 2-1 stored according to condition C is notated as CE2-1/E/C. A milled powder of composition 2-1 stored according to condition A is notated as 2-1/P/A.

CBD has a melting point of approximately 70 °C. None of the samples show a peak at 70°C. Therefore, it was concluded that the CBD is amorphous throughout the experiment, whether in extrudate or powder form.

Example 2-2

A set of samples have the compositions shown in Table 2-2. Compositions in the below table are expressed as parts by weight.

Table 2-2 – Example 2-2 Compositions

	2-2	CE 2-2
CBD	30	0
HPMC	30	30
Oleic Acid	10	10
Lutrol 127	20	20
FLORITE R	10	10
Total (parts by weight)	100	70

Results of the DSC are shown in Fig. 2. None of the samples show a peak at 70 °C. Therefore, it was concluded that the CBD is amorphous throughout the experiment, whether in extrudate or powder form.

Example 3 – Cell Culture and Permeability Assay

Caco-2 ECACC 86010202 (European Collection of Cell Cultures, Salisbury, UK) were cultured at 37 °C, in atmosphere of 5% CO2 in DMEM medium supplemented with 4.5 g/L D-Glucose, 4 mM L-Glutamine, 1 mM Sodium Pyruvate, 1% MEM Non-Essential Amino Acids, 50 µg/mL Gentamicin (Life Technologies Europe B.V., Zug, Switzerland) and 10% heat-inactivated FBS (Sigma-Aldrich, Buchs, Switzerland). Sub-confluent cells were tryptinized using 0.25% Trypsin/EDTA (Life Technologies Europe B.V., Zug, Switzerland).

Cells were seeded at a density of 70,000 cells/well in 12-well cellQART® cell culture insert, PET membrane, 0.4 µM pore size, cell growth area 1.1 cm2/well (SABEU, Northeim, Germany). Media was changed every second to third day. After 21 days in culture, the barrier integrity of the differentiated cell monolayers grown on insert plates was confirmed by measuring transepithelial electrical resistance (TEER) using an EVOM2 Voltammeter (World Precision Instruments, Berlin) equipped with STX2-PLUS Electrodes. The TEER values correlate with the tightness of the confluent monolayer.

After 21 days the insert plates were washed 2 times with HBSS solution (HBSS pH 7.4 with Ca2+ and Mg2+, containing 5.5 mM D-(+)-glucose, Sodium Bicarbonate, and supplemented with 4 mM L-glutamine and 20 mM HEPES, Life Technologies Europe B.V., Zug, Switzerland) and incubated for 1 h at 37 °C in the CO_2 incubator. The different prototypes were prepared in HBSS solution at a concentration of 15 µM. The prototype solution was applied on the apical chamber (200 µL) and 1.5 mL of 4% BSA in HBSS solution were added to the basolateral chamber. The plate was then incubated for 3 h at 37 °C in the CO_2 incubator on an orbital shaker (80 rpm).

After incubation the buffer solutions from the basolateral (BL) and the apical (API) compartments were collected and diluted in acetonitrile for analysis. The cell layers (CL) were washed once with HBSS solution, then 500 µL acetonitrile were added to the apical part. The cells were scraped off from the membrane using a pipet tip, and then collected for analysis.

Cannabidiol was quantitated by a stable isotope dilution LC-MS method using an Agilent 1290 Infinity II UHPLC connected to a Bruker Impact II Q-TOF mass spectrometer. Eight cannabidiol calibration solutions covering a concentration range of 2.5 ng/ml to 2000 ng/ml were prepared in acetonitrile. A 500 ng/ml solution of deuterium labelled d3-Cannabidiol (CAS No. 1435783-16-6) in acetonitrile served as internal standard. Before injection, 250 ml of calibration solution was mixed with 25 ml of internal standard. Likewise, 250 ml of the centrifuged CaCo2 compartment samples were combined with 25 ml internal standard. The analytical column was a Raptor ARC C18 column (2.1 x 150 mm). The mobile phase was water/acetonitrile 24:76 (v/v) containing 5 mM ammonium formate and 0.1% v/v formic acid. The chromatogram was developed isocratically at a flow rate of 0.4 ml/min and a column temperature of 30°C. The injection volume was 1.5 ml. The column effluent was introduced into a VIP-HESI source (Bruker

Daltonik GmbH) operating in positive ionization mode. The mass spectrometer was operating in full-scan mode scanning the range m/z 100-1000 with a spectrum rate of 4 Hz. Extracted high-resolution chromatograms at m/z 315.2319 and m/z 318.2507 with 5 mDa width were used for quantitation. A calibration curve was established by least squares regression by plotting peak area ratios (area analyte versus area internal standard) against added concentrations. Regression and computation of quantitative data was performed with TASQ 1.4 software (Bruker Daltonik).

The amounts of CBD measured as a percent of the original CBD content from the apical compartment (API), basolateral (BL) compartment, and the cell layer (CL) are shown in Table 3. Cell permeability of CBD is determined by the sum of the amounts measured in the basolateral compartment and the cell layer (BL+CL). Higher recovery indicates higher cell permeability of CBD.

Table 3 – Cell Culture and Permeability Assay Data

							API		CL		BL		BL + CL
No.	**wt% CBD**	**[wt%] Polymer**	**[wt%] Oil**	**[wt%] Surfactant**	**[wt%] Coformer and Antioxidant**	**[wt%] FLORITE R**	**mean (%)**	**stdev (%)**	**mean (%)**	**stdev (%)**	**mean (%)**	**stdev (%)**	**(%)**
3-1	30	30 HPMC	10 Oleic Acid	20 TWEEN 80		10	40.5	8.2	11.8	1.5	47.7	4.9	**59.5**
3-2	30	30 HPMC	10 Oleic Acid	20 TWEEN 80		10	36	10	15.4	4.1	48.6	0.9	**64**
3-3	30	25 HPMC	10 Oleic Acid	20 TWEEN 80		15	31.8	1.8	11.9	0.6	56.3	2.7	**68.2**
3-4	30	25 HPMC 5 Croscarmellose	10 Oleic Acid	10 TWEEN 80 10 LUTROL F68		10	37.5	4.6	13.1	1.9	49.4	3.3	**62.5**
3-5	30	30 HPMC	10 Oleic Acid	10 TWEEN 80 10 GELUCIRE 48/16		10	39.5	3	10.8	3.6	49.7	5.7	**60.5**
3-6	30	30 HPMC	10 Oleic Acid	20 LUTROL F127		10	38.4	6.3	13.8	2.6	47.8	1.6	**61.6**
3-7	30	30 HPMC	10 Oleic Acid	20 LUTROL F68		10	38.2	0.6	9.6	1.8	52.2	7.9	**61.8**
3-8	30	30 HPMC	10 Oleic Acid	20 GELUCIRE 50/13		10	42.5	1.3	9.5	0.7	48	4.1	**57.5**
CE3-1		CBD in DMSO					31.6	1.7	18.6	1.4	49.7	0.9	**68.4**
CE3-2	30	30 HPMC	10 Sesame Oil (comprising 3.9% oleic acid)	20 TWEEN 80		10	49	7	13.3	1	37.7	5.5	**51**
CE3-3	30	30 HPMC	10 Sesame Oil (comprising 3.9% oleic acid)	20 LUTROL 127		10	47.6	15.4	9.8	2.1	42.6	1.9	**52.4**
CE3-4	30	30 HPMC		20 GELUCIRE 48/16	20 Nicotinamide		48.5	10.7	11.9	1.4	39.5	4.2	**51.5**
CE3-5	29	29 HPMC		19.5 GELUCIRE 48/16	19.5 Nicotinamide 3 alpha tocopherol		48.4	3.9	12.5	0.8	39.1	1.9	**51.6**

CE3-1 (CBD in DMSO) is included to determine the theoretical maximum recovery, being 68.4%. Several of the examples comprising HPMC, 10 wt% of oleic acid and surfactant reach nearly this maximum.

Sesame oil comprises about 39 wt% of monounsaturated fatty acid (oleic acid), about 41 wt% polyunsaturated fatty acid (linoleic acid), and about 13 wt% saturated fatty acids (palmitic acid and stearic acid). Surprisingly, recovery is substantially improved when increasing the monounsaturated fatty acid content by replacing 10 wt% sesame oil with 10 wt% oleic acid (compare 3-1, 3-2, 3-3, 3-4, 3-5, 3-6, 3-7, and 3-8 with CE3-2 and CE3-3).
Recovery for Examples 3-1 through 3-8 is also surprisingly improved over co-amorphous samples CE3-4 and CE3-5 not comprising any mono-unsaturated fatty acid.

Samples 3-1 and 3-2 have the same composition but Sample 3-2 uses a different extruder design than the other samples in Example 3. High recovery is demonstrated also with this alternative extruder design, indicated the robustness of the compositions.

Additional Description of Exemplary Embodiments

1. A solid extrudate or composition for forming an extrudate via a hot melt extrusion process comprising:
    a. 20-40 wt% of a cannabinoid isolate,
    b. 20-40 wt% of a hydroxypropyl methylcellulose,
    c. 5-15 wt% of a monounsaturated fatty acid, and
    d. 10-30 wt% of a surfactant.
2. The extrudate or composition according to the previous exemplary embodiment, wherein the cannabinoid isolate comprises cannabigerolic acid (CBGA), cannbigerol (CBG), cannabidiolic acid (CBDA), cannabidiol (CBD), cannabidivarinic acid (CBDVA), or cannabidivarin (CBDV), cannabichromenic acid (CBCA), cannabichromene (CBC), cannabinolic acid (CBNA), cannabinol (CBN), cannabidivarinic acid, cannabichromevarinic acid (CVCVA), cannabichromevarin (CBCV), cannabigerovarinic acid (CBGVA), cannabigerovarin CBGV), cannabicyclolic acid (CBLA), cannabicyclol (CBL), cannabielsoinic acid (CBEA), cannabielsoin (CBE), cannabicitranic acid (CBTCA), or cannabicitran (CBTC).
3. The extrudate or composition according to any one of the previous exemplary embodiments, wherein the cannabinoid isolate comprises cannabigerolic acid (CBGA), cannbigerol (CBG), cannabidiolic acid (CBDA), or cannabidiol (CBD).
4. The extrudate or composition according to any one of the previous exemplary embodiments, wherein the cannabinoid isolate comprises cannabidiol (CBD).
5. The extrudate or composition according to any one of the previous exemplary embodiments, wherein the cannabinoid isolate consists essentially of cannabidiol (CBD).

6. The extrudate or composition according to any one of the previous exemplary embodiments, wherein the cannabidiol (CBD) has a purity of at least 95%, more preferably of at least 96%, even more preferably of at least 97%, most preferably of at least 98%.
7. The extrudate or composition according to any one of the previous exemplary embodiments, wherein the extrudate or composition comprises from 20-40 wt% of a cannabinoid isolate, preferably from 25-35 wt% of the cannabinoid isolate.
8. The extrudate or composition according to any one of the previous exemplary embodiments, wherein the extrudate or composition comprises from 25, 26, 27, 28, 29 or 30 wt% to 35, 34, 33, 32, 31, or 30 wt% of a cannabinoid isolate.
9. The extrudate or composition according to any one of the previous exemplary embodiments, wherein the extrudate or composition comprises from 25 to 35 wt% of the hydroxypropyl methylcellulose.
10. The extrudate or composition according to any one of the previous exemplary embodiments, wherein the Tg of the hydroxypropyl methylcellulose is from 130 to 200 °C measured by DSC.
11. The extrudate or composition according to any one of the previous exemplary embodiments, wherein the extrudate or composition comprises from 20, 21, 22, 23, 24, 25, 26, 27, 28, or 29 wt% to 40, 39, 38, 37, 36, 35, 34, 33, 32, 31, or 30 wt% of the hydroxypropyl methylcellulose.
12. The extrudate or composition according to any one of the previous exemplary embodiments, wherein the hydroxypropyl methylcellulose is pH insensitive.
13. The extrudate or composition according to any one of the previous exemplary embodiments, wherein the monounsaturated fatty acid comprises palmitoleic acid, oleic, elaidic acid, vaccenic, gadoleic acid, eicosenoic acid, and erucic acid as well as any mixtures thereof.
14. The extrudate or composition according to any one of the previous exemplary embodiments, wherein the monounsaturated fatty acid is selected from the group consisting of palmitoleic acid, oleic, elaidic acid, vaccenic, gadoleic acid, eicosenoic acid, and erucic acid, and mixtures thereof.
15. The extrudate or composition according to any one of the previous exemplary embodiments, wherein the monounsaturated fatty acid is selected from the group consisting of palmitoleic acid, oleic, elaidic acid, vaccenic, gadoleic acid, eicosenoic acid, and erucic acid.
16. The extrudate or composition according to any one of the previous exemplary embodiments, wherein the monounsaturated fatty acid has from 16 to 18 carbons.
17. The extrudate or composition according to any one of the previous exemplary embodiments, wherein the monounsaturated fatty acid comprises oleic acid.

18. The extrudate or composition according to any one of the previous exemplary embodiments, wherein the monounsaturated fatty acid comprises at least 50 wt% of oleic acid, based on the total monounstaturated fatty acid content in the solid extrudate.
19. The extrudate or composition according to any one of the previous exemplary embodiments, wherein the monounsaturated fatty acid comprises at least 50, 60, 70, 80, 90, 95 or 100 wt% of oleic acid, based on the total monounstaturated fatty acid content.
20. The extrudate or composition according to any one of the previous exemplary embodiments, wherein the monounsaturated fatty acid consists essentially of oleic acid.
21. The extrudate or composition according to any one of the previous exemplary embodiments, wherein the extrudate or composition comprises from 5 to 15 wt% of a monounsaturated fatty acid.
22. The extrudate or composition according to any one of the previous exemplary embodiments, wherein the extrudate or composition comprises from 5, 6, 7, 8, 9, or 10 wt% to 15, 14, 13, 12, 11, or 10 wt% of monounsaturated fatty acid.
23. The extrudate or composition according to any one of the previous exemplary embodiments, wherein the extrudate or composition comprises solely oleic acid as monounsaturated fatty acid (i.e. does not comprise any other monounsaturated fatty acid).
24. The extrudate or composition according to any one of the previous exemplary embodiments, wherein the ratio of cannabinoid isolate to monounsaturated fatty acid in the extrudate or composition is from 4, 3.5, 3, or 2.5 to 1 by weight.
25. The extrudate or composition according to any one of the previous exemplary embodiments, wherein the ratio of cannabinoid isolate to monounsaturated fatty acid in the extrudate or composition is 4:1 to 2.5:1, more preferably from 3.5:1 to 2.5:1, by weight.
26. The extrudate or composition according to any one of the previous exemplary embodiments, wherein the surfactant comprises sodium lauryl sulphate, a poly(ethylene glycol)/poly(propylene glycol) block copolymer, lecithin, polyethylene glycol, or a polysorbate.
27. The extrudate or composition according to any one of the previous exemplary embodiments, wherein the surfactant comprises a poly(ethylene glycol)/poly(propylene glycol) block copolymer and/or a polysorbate.
28. The extrudate or composition according to any one of the previous exemplary embodiments, wherein the surfactant comprises a polysorbate.
29. The extrudate or composition according to any one of the previous exemplary embodiments, wherein the surfactant comprises polysorbate 20, 40, 60, or 80 preferably polysorbate 80.
30. The extrudate or composition according to any one of the previous exemplary embodiments, wherein the surfactant comprises a poly(ethylene glycol)/poly(propylene

glycol) block copolymer HO-[CH_2-CH_2-O]$_a$-[$CH_2CH(CH_3)$-O]$_b$-[CH_2-CH_2-O]$_a$-H wherein a is selected in the range from 70-110 and b is selected in the range from 25 to 60, preferably wherein a is 80 and b is 27 or a is 101 and b is 56.

31. The extrudate or composition according to any one of the previous exemplary embodiments, wherein the surfactant comprises a polyoxylethylene stearate, preferably PEG-32 stearate.
32. The extrudate or composition according to any one of the previous exemplary embodiments, wherein the surfactant comprises polyoxyethylene glycerides, preferably PEG-32 Hydrogenated palm glycerides.
33. The extrudate or composition according to any one of the previous exemplary embodiments, wherein the surfactant is selected from the group consisting of polysorbate 80, a poly(ethylene glycol)/poly(propylene glycol) block copolymer HO-[CH_2-CH_2-O]$_a$-[$CH_2CH(CH_3)$-O]$_b$-[CH_2-CH_2-O]$_a$-H wherein a is 80 and b is 27 or a is 101 and b is 56, PEG-32 stearate or PEG-32 Hydrogenated palm glycerides as well as mixtures thereof, preferably in the absence of any other surfactant.
34. The extrudate or composition according to any one of the previous exemplary embodiments, wherein at least 40 wt%, more preferably at least 50 wt%, more preferably at least 60 wt%, more preferably at least 70 wt%, more preferably at least 80 wt%, more preferably at least 90 wt%, more preferably 100 wt% of the surfactant comprises a polysorbate, based on the total weight of the surfactant.
35. The extrudate or composition according to any one of the previous exemplary embodiments, wherein the extrudate or composition comprises from 15-25 wt% of the surfactant.
36. The extrudate or composition according to any one of the previous exemplary embodiments, wherein the extrudate or composition comprises from 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 wt% to 30, 29, 28, 27, 26, 25, 24, 23, 22, 21, or 20 wt% of the surfactant.
37. The extrudate or composition according to any one of the previous exemplary embodiments, wherein the extrudate or composition further comprises a porous inorganic carrier.
38. The extrudate or composition according to any one of the previous exemplary embodiments, wherein the extrudate or composition further comprises a porous inorganic carrier comprising silica, calcium carbonate, calcium phosphate, polypropylene powders (Accurel®), porous calcium silicate (Florite®), or magnesium aluminometasilicate.
39. The extrudate or composition according to any one of the previous exemplary embodiments, wherein the extrudate or composition further comprises a porous inorganic carrier comprising a calcium silicate, preferably as sole porous inorganic carrier.

40. The extrudate or composition according to any one of the previous exemplary embodiments, comprising a porous inorganic carrier which is calcium silicate, preferably as sole porous inorganic carrier.
41. The extrudate or composition according to any one of the previous exemplary embodiments, wherein the extrudate or composition further comprises from 5 to 25 wt%, more preferably from 5 to 20 wt%, more preferably from 8 to 15 wt% of a porous inorganic carrier.
42. The extrudate or composition according to any one of the previous exemplary embodiments, wherein the extrudate or composition consists essentially of a cannabinoid isolate, a hydroxypropyl methylcellulose, a monounsaturated fatty acid, a surfactant, and optionally a porous inorganic carrier.
43. The extrudate or composition according to any one of the previous exemplary embodiments, wherein the extrudate comprises the cannabinoid isolate in the form of an amorphous solid dispersion.
44. The extrudate or composition according to any one of the previous exemplary embodiments, wherein at least 90, more preferably 95, more preferably 98, more preferably 99, more preferably 100 wt%, based on the total weight of the cannabinoid isolate, of the cannabinoid isolate is in a non-crystalline form.
45. The extrudate or composition according to any one of the previous exemplary embodiments, wherein at least 90, more preferably 95, more preferably 98, more preferably 99, more preferably 100 wt%, based on the total weight of the cannabinoid isolate, of the cannabinoid isolate is in an amorphous form.
46. The extrudate or composition according to any one of the previous exemplary embodiments, wherein the extrudate does not contain any sesame oil.
47. The extrudate or composition according to any one of the previous exemplary embodiments, wherein the extrudate does not contain any macadamia oil.
48. A solid dosage form suitable for oral application comprising a solid extrudate or composition according to any one of the previous exemplary embodiments, wherein the solid dosage form is in the form of a tablet (orally dispersible tablet, chewable tablet, film coated tablet, immediate release tablet, extended or sustained release tablet and similar), a capsule, an orally dispersible film, or a gummy.
49. A pharmaceutical product comprising a solid extrudate or composition according to any one of the previous exemplary embodiments, wherein the pharmaceutical product is preferably in the form of a tablet (orally dispersible tablet, chewable tablet, film coated tablet, immediate release tablet, extended or sustained release tablet and similar), a capsule, an orally dispersible film, or a gummy.
50. A method of forming a solid extrudate, comprising the steps of:

a. forming a melt comprising the composition of any one of the previous exemplary embodiments;
b. pushing the melt through a die,
c. hardening the melt to form a solid extrudate.

51. A pharmaceutical product comprising the solid extrudate of any one of the previous exemplary embodiments.
52. A pharmaceutical product comprising at least one solid extrudate formed from the method of any one of the previous exemplary embodiments.
53. A method to improve the bioavailability of a cannabinoid isolate, preferably of CBD, said method comprising the step of formulating the cannabinoid isolate into an extrudate comprising from 5-15 wt% of a monounsaturated fatty acid, preferably comprising from 5-15 wt% oleic acid.
54. A method to improve the bioavailability of a cannabinoid isolate, preferably of CBD, said method comprising the step of formulating the cannabinoid isolate into a solid extrudate or composition according to any one of the previous exemplary embodiments or a solid extrudate formed according to the exemplary embodiment 50.

The use of the terms “a” and “an” and “the” and similar referents in the context of describing the invention (especially in the context of the following claims) are to be construed to cover both the singular and the plural, unless otherwise indicated herein or clearly contradicted by context. The terms “comprising,” “having,” “including,” and “containing” are to be construed as open-ended terms (i.e., meaning “including, but not limited to,”) unless otherwise noted. Recitation of ranges of values herein are merely intended to serve as a shorthand method of referring individually to each separate value falling within the range, unless otherwise indicated herein, and each separate value is incorporated into the specification as if it were individually recited herein. The use of any and all examples, or exemplary language (e.g., “such as”) provided herein, is intended merely to better illuminate the invention and does not pose a limitation on the scope of the invention unless otherwise claimed. No language in the specification should be construed as indicating any non-claimed element as essential to the practice of the invention.

The term ‘consisting essentially of’ as used in the context of the invention means that the addition of the wt- percent of the ingredients add up to 100 wt.- percent. However, it cannot be excluded that small amounts of impurities may be present such as e.g. in amounts of less than 5 wt.- percent, preferably less than 3 wt.- percent which are introduced via the respective raw materials or processes used.

Preferred embodiments of this invention are described herein, including the best mode known to the inventors for carrying out the invention. Variations of those preferred

embodiments may become apparent to those of ordinary skill in the art upon reading the foregoing description. The inventors expect skilled artisans to employ such variations as appropriate, and the inventors intend for the invention to be practiced otherwise than as specifically described herein. Accordingly, this invention includes all modifications and equivalents of the subject matter recited in the claims appended hereto as permitted by applicable law. While certain optional features are described as embodiments of the invention, the description is meant to encompass and specifically disclose all combinations of these embodiments unless specifically indicated otherwise or physically impossible.

Claims

1. A solid extrudate comprising:
    a. 20-40 wt% of a cannabinoid isolate,
    b. 20-40 wt% of a hydroxypropyl methylcellulose,
    c. 5-15 wt% of a monounsaturated fatty acid, and
    d. 10-30 wt% of a surfactant.

2. The solid extrudate of claim 1, wherein the cannabinoid isolate is present as an amorphous solid.

3. The solid extrudate of any one of the previous claims, wherein the solid extrudate comprises:
    a. 25-35 wt% of a cannabinoid isolate,
    b. 25-35 wt% of a hydroxypropyl methylcellulose,
    c. 5-15 wt% of a monounsaturated fatty acid,
    d. 15-25 wt% of a surfactant.

4. The solid extrudate of any one of the previous claims, wherein the hydroxypropyl methylcellulose has a Tg of from 130 to 200 °C measured by DSC.

5. The solid extrudate of any one of the previous claims, wherein the monounsaturated fatty acid comprises oleic acid, preferably the monounsaturated acid consists essentially of oleic acid.

6. The solid extrudate of any one of the previous claims, wherein the monounsaturated fatty acid comprises at least 50 wt% of oleic acid, based on the total monounstaturated fatty acid content in the solid extrudate.

7. The solid extrudate of any one of the previous claims, wherein the surfactant comprises a polysorbate.

8. The solid extrudate of any one of the previous claims, wherein the surfactant comprises at least 60 wt% polysorbate, based on the total weight of the surfactant in the solid extrudate.

9. The solid extrudate of any one of the previous claims, wherein the hydroxypropyl methylcellulose is pH insensitive.

10. The solid extrudate of any one of the previous claims, further comprising a porous inorganic carrier, preferably in an amount of 5-20 wt%, based on the total amount of the solid extrudate.

11. The solid extrudate of any one of the previous claims, wherein the ratio of cannabinoid isolate to monounsaturated fatty acid is from 4:1 to 2.5:1 by weight.

12. The solid extrudate of any one of the previous claims, wherein the cannabinoid isolate is cannabidiol.

13. A pharmaceutical product comprising the solid extrudate of any one of the previous claims, wherein the pharmaceutical product is capable of oral administration.

14. A method of forming a solid extrudate, comprising the steps of:
    a. forming a melt comprising:
        i. 20-40 wt% of a cannabinoid isolate,
        ii. 20-40 wt% of a hydroxypropyl methylcellulose,
        iii. 5-15 wt% of a monounsaturated fatty acid, and
        iv. 10-30 wt% of a surfactant;
    b. pushing the melt through a die,
    c. hardening the melt to form a solid extrudate.

Fig. 1

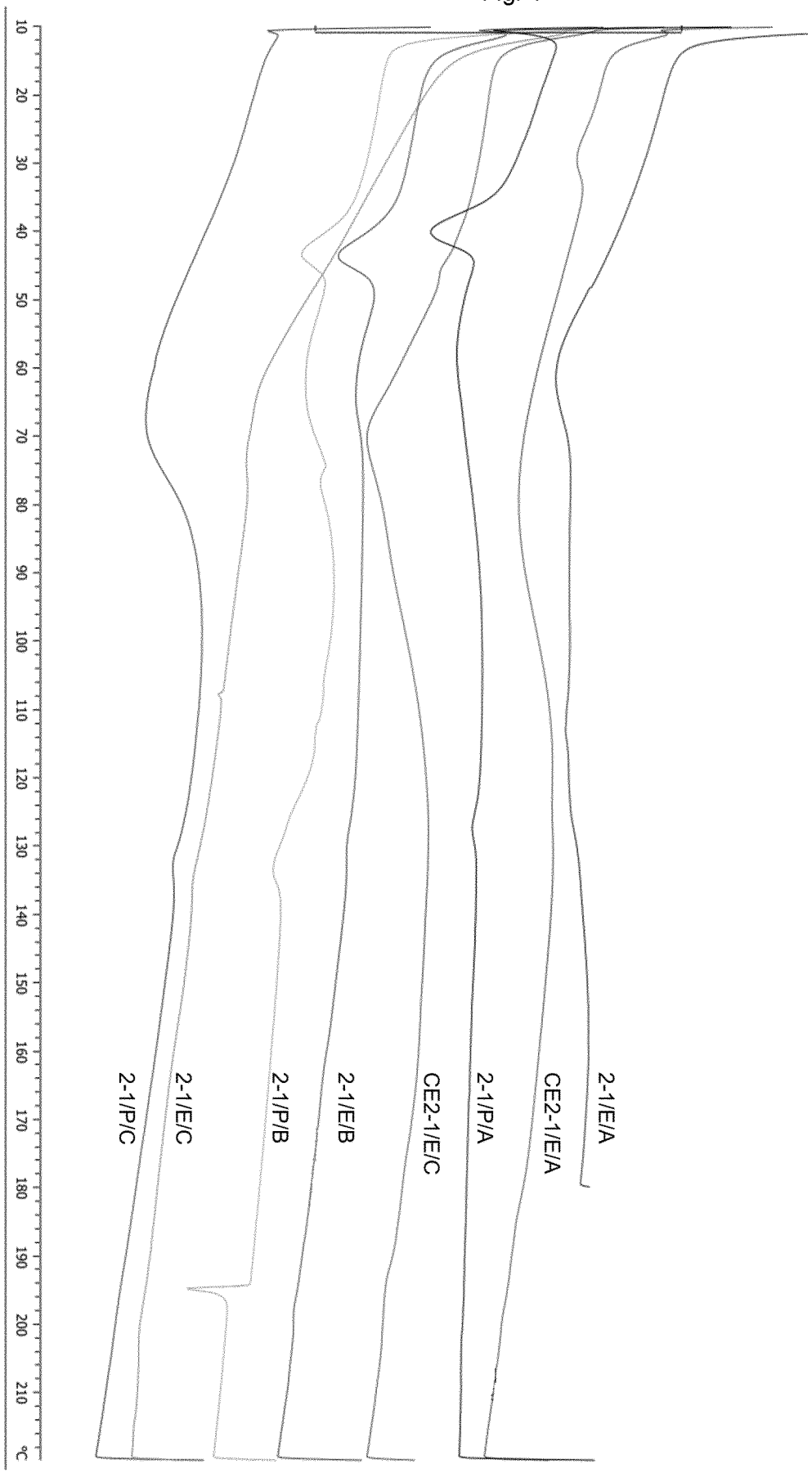

10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
°C
2-1/P/C
2-1/E/C
2-1/P/B
2-1/E/B
CE2-1/E/C
2-1/P/A
CE2-1/E/A
2-1/E/A

Fig. 2

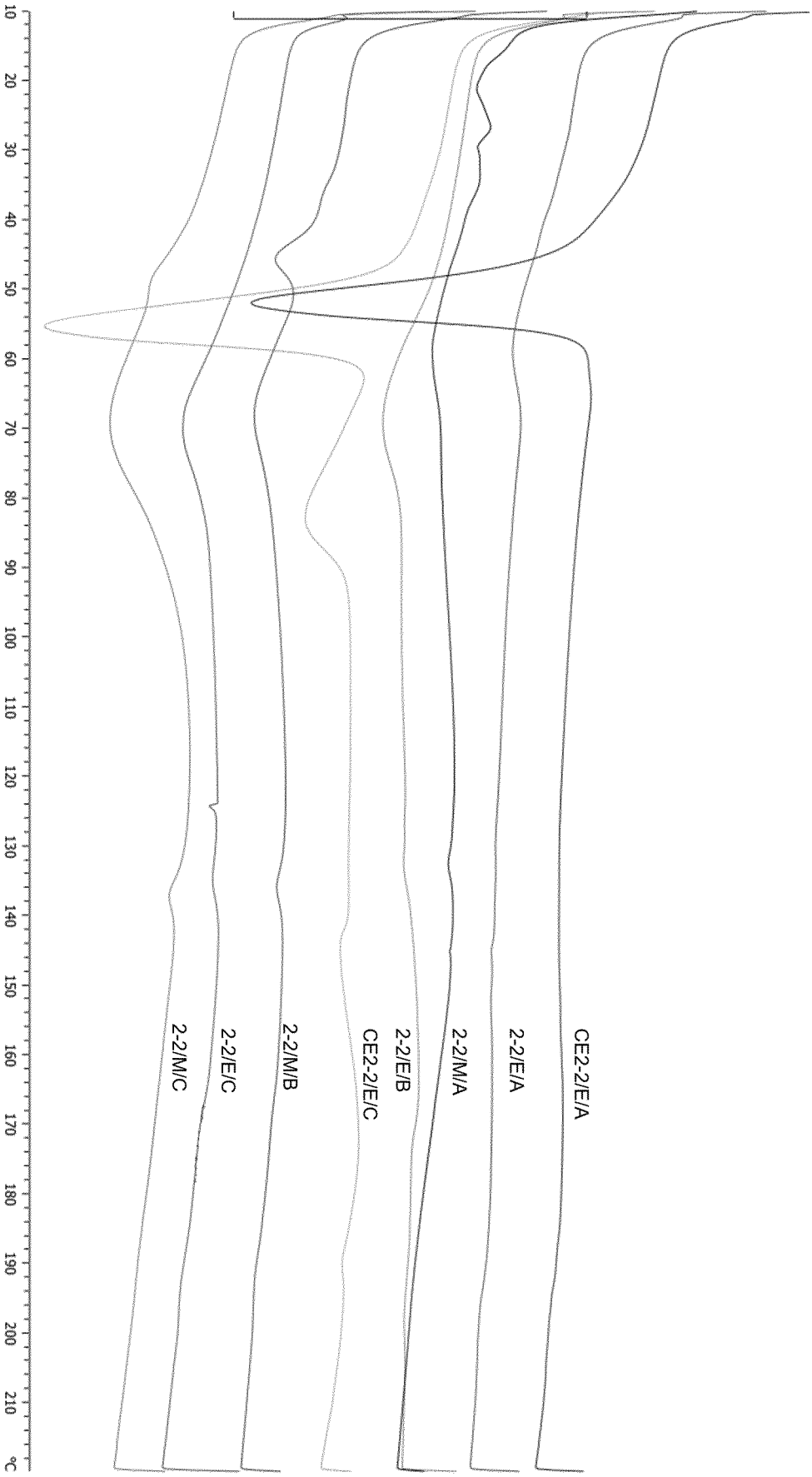

10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
°C
2-2/M/C
2-2/E/C
2-2/M/B
CE2-2/E/C
2-2/E/B
2-2/M/A
2-2/E/A
CE2-2/E/A

Fig. 3

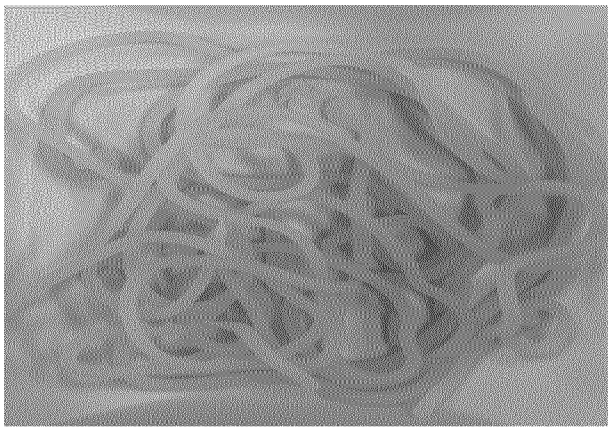
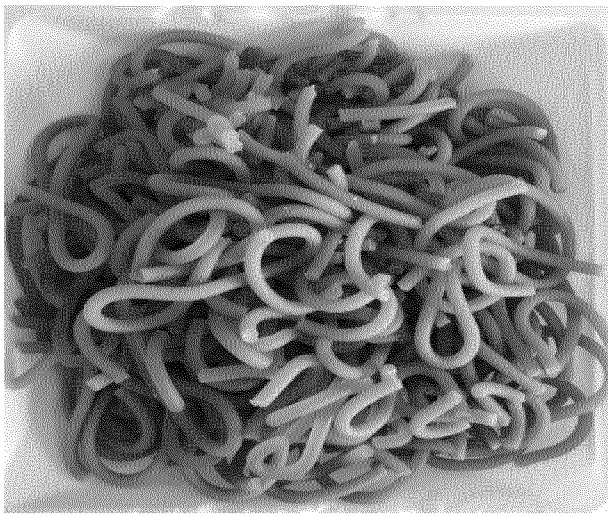


Fig. 4



INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2024/078139

A. CLASSIFICATION OF SUBJECT MATTER

INV. A61K9/14 A61K31/00 A61K47/12 A61K47/26 A61K47/38 A61K45/06

ADD.

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61K

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

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

EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2023/015378 A1 (CANNTAB THERAPEUTICS LTD [CA]) 16 February 2023 (2023-02-16) paragraphs [0084], [00114], [00123]; examples 1, 9	1-14
Y	WO 2021/119844 A1 (ORGANIGRAM INC [CA]) 24 June 2021 (2021-06-24) paragraph [0043]; claim 22; example 1	1-14
Y	WO 2023/055648 A1 (LATITUDE PHARMACEUTICALS INC [US]) 6 April 2023 (2023-04-06) paragraphs [0095], [0103], [0104]; claims 1, 8, 10-11	1-14
Y	US 2012/231083 A1 (CARLEY DAVID [US] ET AL) 13 September 2012 (2012-09-13) paragraphs [0135], [0272], [0302]; example 12; table 7	1-14

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance;; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance;; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
14 November 2024	22/11/2024

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Neumann, Robert

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2024/078139

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2023015378 A1	16-02-2023	NONE	
WO 2021119844 A1	24-06-2021	CA 3162516 A1	24-06-2021
		EP 4076487 A1	26-10-2022
		US 2023030491 A1	02-02-2023
		WO 2021119844 A1	24-06-2021
WO 2023055648 A1	06-04-2023	NONE	
US 2012231083 A1	13-09-2012	NONE	