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(54) Title: COMPOSITION COMPRISING AT LEAST ONE PROTOBERBERINE ALKALOID AND ITS PRODUCTION PROCESS

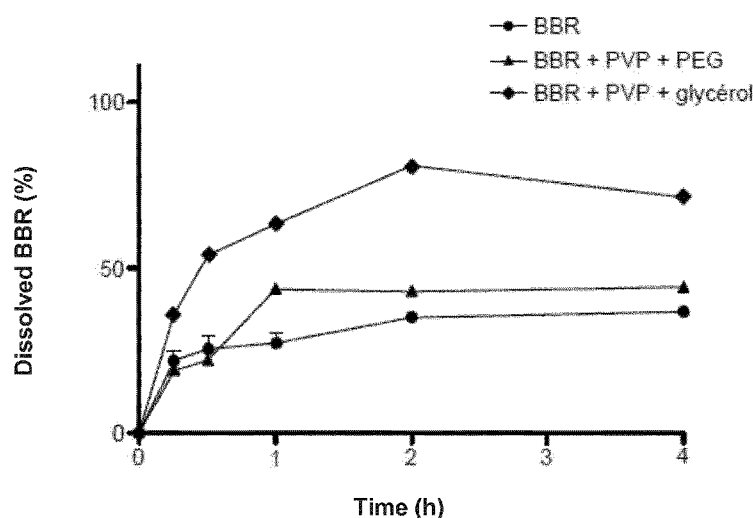


FIG. 1

(57) Abstract: Composition comprising at least one protoberberine alkaloid and its production process This invention concerns a composition in the form of an extrudate containing at least one protoberberine alkaloid as active substance together with at least one polymer, said protoberberine alkaloid consisting of at least a first amorphous phase and possibly a second crystalline phase. This invention also concerns the process for producing such a composition and its use.

**Composition comprising at least one protoberberine alkaloid and its
production process**

This invention concerns a composition comprising at least one
5 protoberberine alkaloid, its production process and its use.

In the sense of this invention, the term "protoberberine
alkaloid" designates not only naturally-occurring and/or plant-derived
protoberberine alkaloids and synthetic protoberberine alkaloids but also all
protoberberine alkaloid derivatives, e.g. salts of protoberberine alkaloids. By
10 way of example, the term "berberine" that designates a protoberberine
alkaloid covers all berberine derivatives such as berberine salts, e.g.
berberine hydrochloride or berberine sulphate.

Protoberberine alkaloids are basic, nitrogen-containing,
heterocyclic organic compounds, mostly derived from plants, with well-known
15 and widely exploited therapeutic properties.

Protoberberine alkaloids belong to the family of isoquinolines.
According to the article of Da-Cunha et al. (The Alkaloids: Chemistry and
Biology. Protoberberine Alkaloids. Elsevier, 2005, vol. 62, pages 1-75),
protoberberine alkaloids can be classified between ten different types based
20 on chemical structure, as summarised in Table 1 below.

The Type III protoberberine alkaloids include berberine with
the chemical structure shown; this is of special interest.

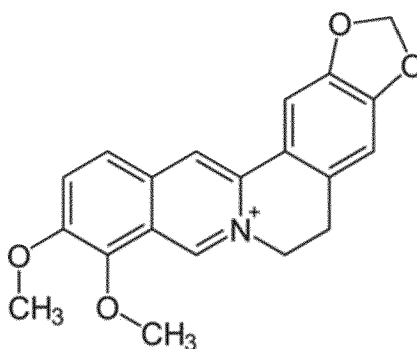
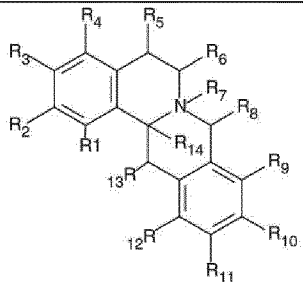
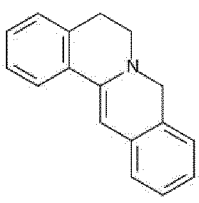
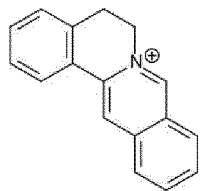
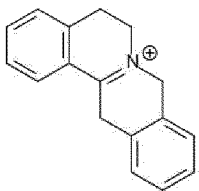
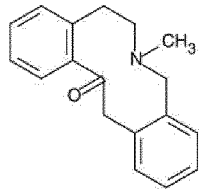
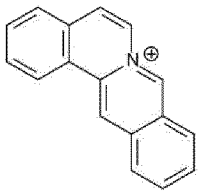
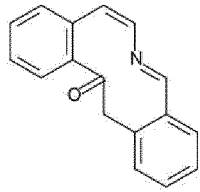
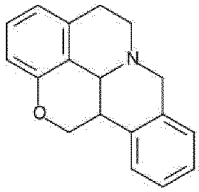
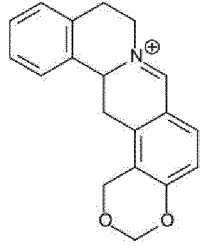
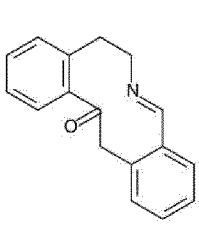


Table 1: different types of protoberberine alkaloid

 <p>Type I</p>	 <p>Type II</p>
 <p>Type III</p>	 <p>Type IV</p>
 <p>Type V</p>	 <p>Type VI</p>
 <p>Type VII</p>	 <p>Type VIII</p>
 <p>Type IX</p>	 <p>Type X</p>

Hierarchically, berberine (2,3-methylenedioxy-9,10-dimethoxy-protoberberine) can therefore be classified as follows: alkaloids

5 > isoquinolines > protoberberine alkaloids > berberine. It is a protoberberine alkaloid with many therapeutic powers that therefore belongs to the group of isoquinolines which are naturally-occurring compounds found in salt form in certain plant species.

Most protoberberine alkaloids, including berberine, are heat-sensitive compounds that are both lipophobic and hydrophobic which results in them being insoluble/immiscible in water as well as in lipids and lipid derivatives.

5 It is noted that scientific studies have shown that the bioavailability of berberine is very low, under 5%, and even only about 0.68% in the laboratory rats experimented upon. Moreover, it has been shown that efflux pumps, e.g. P-glycoprotein (P-gp) in the gut and liver, seem to reduce this alkaloid's bioavailability. P-gp is a cell membrane transporter that
10 pumps molecules absorbed by cells out into the gut lumen. For berberine, most of the compound that is absorbed is rapidly expelled into the gut lumen by this glycoprotein.

Nevertheless, despite its low bioavailability (i.e. despite the smallness of the amount of the dose administered that actually reaches the
15 bloodstream in unchanged form) and also despite its low solubility in the gut environment, berberine's positive effects against many pathologies makes it a compound of interest. This is why many different methods and processes have been developed to formulate berberine for administration to humans and/or for veterinary use. Most of the formulations considered
20 have been lipid-based but, because of the low solubility/miscibility of berberine in lipid and lipid derivatives, the amount incorporated into such lipid phases remains very low with respect to the dose that it would be convenient to administer. Moreover, the amount of berberine that is released from such formulations is small which makes the bioavailability of
25 this compound very low.

Document WO2015/097642 describes another preparation process for a berberine-containing formulation based on a step in which a predetermined quantity of berberine is mixed with a predetermined quantity of polyethylene glycol in an aqueous ethanol solution, in order to obtain a
30 viscous precipitate which is then harvested, sieved and dried to yield granules that can be packed in capsules. Although the incorporation of

berberine seems to be better than in lipid formulations, according to document WO2015/097642, this process is nevertheless rather demanding and difficult to operate. In practice, several successive steps have to be conducted and sieving viscous material can give rise to clogging
5 problems slowing down production of the formulation.

Other processes are used to generate formulations in the form of spherical particles, pellets or granules. In particular, to produce a powder form, extrusion techniques can be used, e.g. the techniques of extrusion-spheronisation, Tween Screw Granulation (TSG) and Hot Melt
10 Extrusion (HME).

The extrusion-spheronisation technique generates round particles of uniform size from a wet mass (containing an active substance with at least one additive) which is passed through a grill with a predetermined mesh-size before drying of the resultant particles. More
15 particularly, this process to produce a powder form consists of the following steps: mixture of an active substance with at least one additive, wet granulation (compaction) of the resultant mixture, extrusion of the compacted mixture to produce an extrudate, spheronisation of the extrudate to produce spherical particles/granules, and drying of the
20 resultant spherical particles/granules.

Tween Screw Granulation generates intermediate products for the preparation of tablets and capsules. This technique involves the granulation (compaction) of powdered substances in an extruder to give rise to granule formation at the machine's outlet.

25 Hot Melt Extrusion allows molecular dispersion of an active substance through a polymer matrix to create a solid dispersion. Solid dispersion is made possible by the input of heat coupled with the stress induced by the movement of screws through the material in the extruder. Finally, Hot Melt Extrusion gives rise to the formation at the outlet of an
30 extrudate in the form of a ring which can then be ground up or turned into pellets.

Although the techniques of extrusion-spheronisation and Tween Screw Granulation do not involve any heat input and typically require a liquid phase (usually aqueous) to generate spherical particles and/or granules, Hot Melt Extrusion can be carried out without any such liquid phase but depends on heating.

In addition, although the techniques of extrusion-spheronisation and Tween Screw Granulation both involve aggregation of a powder while attempting to preserve the powder's constituents' original properties as intact as is possible, the technique of Hot Melt Extrusion, in contrast, produces a glassy structure as a result of the action of heat and the powder particles are not all still present in their initial (native) crystalline form at the end of the hot melt extrusion process.

Document CN104997735 describes the preparation of micro pills containing berberine hydrochloride with an additive (MCC, starch, sucrose or dextrin), using an extrusion-granulation process. Document JPH0959159 too describes the preparation of compositions (in tablet or granule form) containing quinine or berberine, a polymer and lactose, using an extrusion-granulation process. In all cases, the active substance (berberine hydrochloride or quinine or berberine) and certain additives are mixed and compacted (granulation) to generate granules at the outlet of the extruder, without changing the properties of the original (native) crystalline particles of active substance and excipient. However, it turns out that, for each of the compositions according to Documents CN104997735 and JPH0959159, that only very small quantities of berberine are released from the micro pills, granules and tablets because the berberine they contain is minimally soluble.

Unfortunately therefore, it would seem that current formulations containing a protoberberine alkaloid, in particular berberine, are inappropriate not only because of the low dissolution of the protoberberine alkaloid but also because little of the alkaloid is released out of these formulations. This ultimately manifests as low bioavailability of

the alkaloid (compound) of interest. Moreover, it seems that the production processes for these current formulations are demanding and difficult to operate.

The purpose of the invention is to overcome disadvantages of the background art by providing (1) a composition containing a more soluble protoberberine alkaloid, e.g. berberine, so that its bioavailability is significantly enhanced, and (2) a production process for such a composition that, as well as being easy to operate, flexible and economically viable, ensures that the protoberberine alkaloid is present and evenly distributed throughout the resultant final composition. In addition, the invention intends to provide a composition that is stable over time, i.e. one which conserves its properties in terms of dissolution of the protoberberine alkaloid as well as the level of release of the alkaloid over time.

To resolve at least some of these problems, the invention provides for a composition in the form of an extrudate containing at least one protoberberine alkaloid as active substance together with at least one polymer, said protoberberine alkaloid consisting of at least a first amorphous phase and possibly a second crystalline phase.

In the sense of this invention, the term "consisting of at least a first amorphous phase and possibly a second crystalline phase" means that said protoberberine alkaloid may comprise either 100% amorphous phase by mass, or it may consist of both a first amorphous phase and a second crystalline phase, the sum of the percentage masses of said first and second phases amounting in this case to 100. In other words, the composition according to the invention may contain said at least one protoberberine alkaloid (1) entirely in an amorphous form, or (2) partially in an amorphous form (phase) and partially in a crystalline form (phase).

Note that a phase is said to be amorphous when its constituent molecules have no order at either medium- or long-distance scale; this differentiates it from a so-called crystalline phase.

In the sense of this invention, the word "extrudate" means a material that comes out of an extruder, in particular out of the die of an extruder.

The composition according to the invention therefore presents
5 in the form of an extrudate in which a protoberberine alkaloid (the active substance) consists of at least a first amorphous phase and possibly a second crystalline phase, said phase(s) being dispersed through at least one polymer.

Unexpectedly, it has been determined in the framework of this
10 invention that, in such a composition—in the form of an extrudate containing at least one protoberberine alkaloid as active substance together with at least one polymer and in which said protoberberine alkaloid consists of at least a first amorphous phase and possibly a second crystalline phase—the protoberberine alkaloid is markedly more soluble (especially in the
15 environment of the gut). In addition, it has been shown that, in such a composition according to the invention, the protoberberine alkaloid is significantly more bioavailable than has been observed with current compositions.

Surprisingly, it has also been shown in the framework of this
20 invention that, even if the protoberberine alkaloid is heat-sensitive, it is not broken down even in a production process based on hot melt extrusion of the composition that nevertheless involves subjecting the protoberberine alkaloid to high temperatures, as will be explained later. In a composition according to the invention, the active substance, i.e. a protoberberine alkaloid
25 consisting of at least a first amorphous phase and possibly a second crystalline phase, is dispersed through a polymer matrix with both active substance and polymer being melted in the course of the production process implemented according to the invention as described below.

In addition, a composition according to the invention can be
30 stored for several months without any compromise of its properties. In particular, it has been shown that a composition according to the invention

conserves its properties in terms of dissolution of the protoberberine alkaloid as well as the level of release of the alkaloid over time.

Advantageously according to the invention, said protoberberine alkaloid predominantly consists of a first amorphous phase.

- 5 In the sense of this invention, the term "predominantly consists of a first amorphous phase" means that said protoberberine alkaloid consists of 50-100% by mass of an amorphous phase, and 0-50% of a crystalline phase, more particularly that said protoberberine alkaloid consists of 51-100% by mass of an amorphous phase, and 0-49% of a crystalline phase.

- 10 Preferably according to the invention, said protoberberine alkaloid is selected from the group comprising alborine, anibacanine, anisocycline, artavenustine, berberastine, berberine, berberubine, berlambine, canadine, capaurimine, capaurine, caseadine, caseamine, cavidine, cerasodine, cerasonine, cheilanthifoline, clarkeanidine, columbamine, constrictosine, coptisine, coreximine, corybulbine, corycavamine, corycavine, corydaldizine, corydalmine, corymotine, corynoxidine, corypalmine, corysamine, corytenchine, coulteropine, cryptopine, cyclanoline, dauricoside, discretamine, fississaine, govanine, groenlancidine, gusanlung-A, gusanlung-B, gusanlung-D, hunnemanine, jatrorrhizine, lambertine, lienkonine, malacitanine, manibacanine, mecambridine, muramine, orientalidine, pallimamine, palmatine, pessoine, phellodendrine, prechilenine, protopine, schefferine, scoulerine, sinactine, spiduxine, spinosine, stephabinamine, stephamine, stepharanine, stepholidine, stylopine, tetrahydropalmatine, thaicanine, thaipetaline, thalictricavine, thalidastine, thalifendine, xilopinine, yuanaamide, dihydroberberine, dehydrocorydalmine, palmatrubine, dehydrodiscretamine, dehydrocheilanthifoline, demethylenberberine, epiberberine, pseudocoptisine, pseudopalmatine, pseudojatrorrhizine, pseudoepiberberine, pseudocolumbamine, dehydrodiscretine, dehydrocoreximine, thalifaurine, corysamine, dehydrothalictrifoline, dehydrothalictricavine, dehydrocorydaline, dehydroapocavidine,
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lincagenine, dehydrocapaurimine, 13-methyl-pseudoepiberberine, mequinine, as well as derivatives, salts and mixtures thereof.

Preferably according to the invention, said polymer in a composition according to the invention is selected from the group comprising

5 copolymers of ammonium methacrylate, hydroxypropylcellulose (HPC), polyvinyl acetate, ethylcellulose, hydroxypropylmethylcellulose phthalate, polyvinylpyrrolidone (PVP), hydroxypropymethylcellulose (HPMC), hydroxypropymethylcellulose acetosuccinate, cellulose acetobutyrate, cellulose acetophthalate, polyvinylpyrrolidone-co-vinyl acetate,

10 polyethylene-co-vinyl acetate, co-methacrylic acid polyvinyl acetate, polyethylene oxide, polylactide-co-glycolide, polyvinyl alcohol, pectin, polycarbophile, polycaprolactone, carnauba wax, ethylene-vinyl acetate copolymer, lecithin, castor and hydrogenated soy oil, waxes (microcrystalline waxes, etc.), natural or synthetic starch (cornstarch, pregelatinised starch,

15 potato starch, etc.), maltodextrin, isomalt, chitosan, gums (xanthan gum, etc.), agar, lactose, soluble or insoluble natural or synthetic fibers such as inulin, β -glucan and Konjac fibers, as well as derivatives and mixtures thereof.

Preferably according to the invention, said protoberberine

20 alkaloid is a naturally-occurring and/or plant-derived protoberberine alkaloid. It is of course understood that synthetic protoberberine alkaloids are also envisaged as active substances in the sense of this invention. Similarly, all derivatives of protoberberine alkaloids including their salts are also envisaged as active substances in the sense of this invention.

Advantageously, the composition according to the invention

25 includes at least one plasticising agent. Addition of a plasticising agent to a composition according to the invention is advantageous and further enhances the alkaloid's (the active substance's) solubility and bioavailability. Moreover, the inclusion of a plasticising agent allows the production of a

30 composition according to the invention in a process in which temperatures below the melting points of either protoberberine alkaloid or polymer can be

used to induce melting of both these compounds and dispersion of the protoberberine alkaloid through the polymer matrix. For example, if the protoberberine alkaloid in a composition according to the invention is berberine, the melting point of which is of the order of 142-145°C, and the polymer is hydroxypropylcellulose, the melting point of which is of the order of 130-140°C, the inclusion of glycerol as plasticising agent ensures that the berberine and the hydroxypropylcellulose melt and the protoberberine alkaloid will disperse through the polymer at a temperature of the order of 80-90°C. Reducing the temperature that needs to be applied means that the protoberberine alkaloid is not subjected to heat-induced breakdown and therefore its properties are better preserved. In addition, reducing the temperatures required makes the production process cheaper and faster.

Preferably according to the invention, said plasticising agent is selected from the group comprising polyols, lipids, lecithins, sucrose esters, triethyl citrate, polyethylene glycol, glycerol, dibutyl sebate, butyl stearate, glycerol monostearate, diethyl phthalate, and mixtures thereof.

According to the invention, preferred plasticising agents are glycerol, polyethylene glycol and triethyl citrate.

Preferably, the composition according to the invention also contains at least one additive selected from the group constituted of lubricants, surfactants, antioxidants, chelating agents and mixtures thereof.

By way of example, the following compounds could be used in a composition according to the invention—alone or mixed together—as a lubricant: glycerol dibehenate, talc, silica, stearic acid, boric acid, starches, waxes, sodium oleate, sodium acetate, magnesium stearate, calcium stearate, sodium stearate, sodium benzoate, sodium laurylsulfate, glycerol distearate, glycerol palmitostearate, microcrystalline cellulose or polyoxyl-8-glycerides.

By way of example, the following compounds could be used in a composition according to the invention—alone or mixed together—as a

surfactant: Pluronic®, Span®, Cremophor®, polysorbates (Tween®, etc.), Vitamin E TPGS and sodium ducosate.

By way of example, the following compounds could be used in a composition according to the invention—alone or mixed together—as an
5 oxidising and/or chelating agent: butylated hydroxytoluene, butylated hydroxyanisole, EDTA, citric acid and Vitamin E.

Advantageously, the composition according to the invention also contains at least one first additional active polyphenol-type substance selected from the group constituted of phenolic acids, stilbenes, phenolic
10 alcohols, lignanes, flavonoids and mixtures thereof. In particular, glycosylated and aglycone forms of polyphenols are envisaged as the additional active substance according to this invention. More particularly in the sense of this invention, the word "polyphenol" covers polyphenols from natural sources, synthetic polyphenols and all polyphenol derivatives.

15 By way of example in the sense of this invention, phenolic acids could be derivatives of hydroxybenzoic acid (gallic acid, tannic acid, etc.) or derivatives of hydroxycinnamic acid (curcumin, coumaric acid, caffeic acid, ferulic acid, etc.).

By way of example in the sense of this invention, the stilbene
20 could be resveratrol, sirtinol, piceatannol or polydatine.

By way of example in the sense of this invention, flavonoids could be flavanols (quercetine, myricetine, kaempferol, isorhamnetine, morine, rutine, tiliroside, trihydroxyethylrutine, fisetine, etc.), flavones (apigenine, luteoline, baicaleine, chrysin, diosmine, nobiletine, tangeretine,
25 wogonine, aminogenisteine, etc.), flavanones (bavachine, 8-isopentenylnaringenine, isoxanthohumole, naringenine, eriodictyol, hesperetine, silybine, taxifoline, etc.), isoflavones (genisteine, daidzeine, daidzine, formonetine, genisteine, neobavaisoflavone, pueranine, etc.),
30 antocyanidines (cyanidine, pelargonidine, delphinidine, petunidine, malvidine, etc.) and flavanols (catechines, gallocatechine, epigallocatechinegallate, etc.).

Preferably, the composition according to the invention also contains at least a second additional active triterpene-type substance, e.g. a limonoid.

According to the invention, said at least one first additional
5 active polyphenol-type substance and said at least a second additional active triterpene-type substance constitute inhibitors/modulators of efflux pump activity, including that of P-gp.

Preferably, the composition according to the invention also contains at least one inhibitor and/or one modulator of P-gp activity. For
10 example, said at least one inhibitor and/or one modulator of P-gp activity could be piperine (an alkaloid).

Preferably, the composition according to the invention is presented in the form of pellets, granules, a powder, effervescent or non-effervescent tablets, a solution (for injection or not), a suspension, a gel, a
15 pomade or any other suitable form compatible with administration to an animal or a human being.

Other embodiments of a composition according to the invention are described in appended Claims.

The invention also concerns a production process for a
20 composition according to the invention, characterised in that it includes the following steps:

- a) a step to bring together at least one protoberberine alkaloid and at least one polymer—at the same time or deferred in time—to feed into an extruder,
- 25 b) a mixing step in said extruder of said at least one protoberberine alkaloid and said at least one polymer to form a mixture, and
- c) a Hot Melt Extrusion (HME) step on said mixture obtained in Step b), carried out in said extruder to generate an extrudate in which said protoberberine alkaloid consists of at least one first amorphous phase
30 and possibly a second crystalline phase.

Such a process according to the invention yields a composition in the form of an extrudate in which said protoberberine alkaloid as active substance consists of at least one first amorphous phase and possibly a second crystalline phase dispersed through said at least one polymer. In this composition according to the invention, the protoberberine alkaloid is markedly more soluble (especially in the gut environment) and at the same time its bioavailability is significantly greater than the same alkaloid's solubility and bioavailability in current compositions. It has been shown that the composition according to the invention presents in the form of an extrudate in which a protoberberine alkaloid (the active substance) consisting of at least a first amorphous phase and possibly a second crystalline phase is dispersed through at least one polymer.

Unexpectedly, it has also been shown in the framework of this invention that, even if the protoberberine alkaloid is heat-sensitive, it is not broken down even if the process used to make the composition in extrudate form involves subjecting the alkaloid to high temperature (HME). Also unexpectedly, it has also been shown that the protoberberine alkaloid in a composition in the form of an extrudate according to the invention is dispersed (distributed) uniformly.

More particularly, Hot Melt Extrusion (HME) carried out by means of the process according to the invention induces melting of the active substance (the protoberberine alkaloid) and the polymer at a temperature equal to or above their melting points. However, in certain embodiments of a composition according to the invention, active substance and polymer may melt at a temperature below their melting points. This will happen for example if the composition according to the invention includes a plasticising agent or if the active substance itself has plasticising activity. Such melting of active substance and polymer will yield a solid dispersion in which the active substance (the protoberberine alkaloid) consisting of at least a first amorphous phase and possibly a second crystalline phase is dispersed through at least one polymer.

Advantageously, the process according to the invention includes a preliminary pre-blending step of said at least one protoberberine alkaloid and said at least one polymer in such a way as to generate a pre-blend for feeding into the extruder.

5 In a preferred fashion, according to the process according to the invention, said hot melt extrusion step is carried out at a temperature of between 20 and 180°C, preferably at a temperature of between 40 and 115°C, preferentially at a temperature of between 80 and 90°C, preferably at a temperature of 110°C, more preferably at a temperature of 100°C.

10 Advantageously, in the process according to the invention, said hot melt extrusion step is carried out with the extrusion screw rotating at a speed of between 20 and 300 revolutions per minute, preferably between 100 and 250 rpm, preferentially at 200 rpm.

Preferentially, the process according to the invention includes
15 an additional cooling step when the material comes out of the extruder.

Advantageously, the process according to the invention includes an additional processing step when the material comes out of the extruder, e.g. cutting up of the extrudate in a pelletiser or pulverisation of said extrudate.

20 Other embodiments of the process according to the invention are described in appended Claims.

This invention also bears on use of a composition according to the invention as a dietary supplement and/or a cosmetic product and/or a medicinal product for human or veterinary use.

25 In particular, this invention concerns a composition for use in preventive and/or curative treatment in human beings and/or animals, for diseases related to the cardiovascular system (hypotension, vasoconstriction, ventricular hypertrophy, arrhythmia, etc.), diseases related to the blood (hypercholesterolaemia, platelet aggregation, etc.), diseases
30 related to the gastrointestinal system (diarrhoea, digestive inflammation, modulation of the intestinal microbiota, etc.), diseases related to the

endocrine system (hyperglycaemia, etc.), diseases related to the immune system, diseases related to the central nervous system, skin diseases, diseases due to the presence of micro-organisms and cancer (anti-tumour, etc.) and in the preventive/curative treatment of diabetes.

5 More particularly, this invention concerns a composition for use in the treatment of human beings and/or animals to prevent or cure obesity, diabetes, hypercholesterolaemia, metabolic syndrome and irritable bowel syndrome (IBS).

10 Other embodiments of a composition according to the invention are described in appended Claims.

Other characteristics, details and advantages of the invention will emerge from the examples given hereafter which are non-limiting and make reference to the appended Figures.

15 Figure 1 is a graph showing the degree of dissolution of a protoberberine alkaloid, in this case that of berberine (dissolved BBR [%]), over time with two compositions according to the invention containing berberine (BBR), a polymer (PVP) and a plasticising agent (PEG or glycerol).

20 Figure 2 is a graph showing the degree of dissolution of a protoberberine alkaloid, in this case that of berberine (dissolved BBR [%]), over time with two compositions according to the invention containing berberine (BBR), a polymer (HPC or PVP) and a plasticising agent (glycerol).

25 Figure 3 is a graph showing the degree of dissolution of a protoberberine alkaloid, in this case that of berberine (dissolved BBR [%]), over time with three compositions according to the invention containing berberine (BBR), a polymer (HPC) and different proportions of a plasticising agent (glycerol: 0%, 5% and 10%).

30 Figure 4 is a graph showing the degree of dissolution of a protoberberine alkaloid, in this case that of berberine (dissolved BBR [%]), over time with two compositions according to the invention containing different proportions of berberine (BBR, 40% and 50%), a polymer (HPC) and a plasticising agent (glycerol).

Figure 5 is a graph showing the degree of dissolution of a protoberberine alkaloid, in this case that of berberine (dissolved BBR [%]), over time with two compositions according to the invention containing berberine (BBR), a polymer (HPC) and a plasticising agent (glycerol), the "age" of the two compositions being 0 days and 3 months.

Figure 6 is a graph showing the the concentration of a protoberberine alkaloid, in this case berberine, in a composition according to the invention, depending on whether the composition was freshly made or made 3 months before (T3M), 5 months before (T5M) or 8 months before (T8M).

Figure 7 is a graph showing the the degree of dissolution of a protoberberine alkaloid, in this case that of berberine, in a composition according to the invention, depending on whether the composition was freshly made or made 3 months before (T3M), 5 months before (T5M) or 8 months before (T8M).

Figure 8 is a thermogram generated by DSC analysis of compositions according to the invention containing berberine as the protoberberine alkaloid and by analysis of crystalline berberine in powder form.

Figure 9 is a graph showing the degree of dissolution of a protoberberine alkaloid, in this case that of tetrahydropalmatine (dissolved THP [%]), over time with two compositions according to the invention containing tetrahydropalmatine (THP).

Figure 10 is a graph showing the degree of dissolution of a protoberberine alkaloid, in this case that of tetrahydropalmatine (dissolved THP [%]), over time with compositions according to the invention containing tetrahydropalmatine (THP), the polymer hydroxypropylcellulose (HPC) and different types of plasticising agent.

Figure 11 is a graph showing the degree of dissolution of a protoberberine alkaloid, in this case that of tetrahydropalmatine (dissolved THP [%]), over time with compositions according to the invention containing

tetrahydropalmatine (THP), the polymer polyvinylpyrrolidone (PVP) and different types of plasticising agent.

Figure 12 is a graph showing the degree of dissolution of a protoberberine alkaloid, in this case that of tetrahydropalmatine (dissolved THP [%]), over time with two compositions according to the invention containing tetrahydropalmatine (THP), a polymer and a plasticising agent.

Examples

10 Example 1: production process for a composition according to the invention in the form of an extrudate containing berberine as the protoberberine alkaloid

Compositions according to the invention containing berberine as the protoberberine alkaloid (the active substance) as presented in Example 2 below were produced according to the following process which this invention also provides:

- a) a preliminary pre-blending step in which powdered, crystalline berberine is blended with at least one polymer;
- b) a step to bring together said pre-blend produced in Step a) to feed into a Thermo-Fischer® Pharma 11 extruder;
- c) a mixing step on said pre-blend in said extruder to produce a mixture;
- d) a hot melt extrusion step on said mixture obtained in Step c) in said extruder to generate an extrudate, the hot melt extrusion step being carried out with the extrusion screw rotating at a speed of 200 revolutions per minute at a temperature of between 40°C and 110°C; and
- e) a step to cut up the extrudate obtained in Step d) in a pelletiser in such a way as to obtain pellets of the order of 2-3 millimetres in size.

The temperature at which the hot melt extrusion step is carried out will depend on the constituents of the mixture, in particular the natures of the protoberberine alkaloid, the polymer and/or the plasticising agent. Those skilled in the art will be able to determine this.

5

Example 2: testing of dissolution of compositions according to the invention containing berberine as the protoberberine alkaloid

For various compositions obtained according to the production process described in Example 1, dissolution over time of the protoberberine alkaloid in the resultant extrudates was tested. Berberine was selected as the protoberberine alkaloid for dissolution testing. As indicated above, the extrudates present in the form of pellets of the order of 2-3 millimetres in size.

All dissolution tests were carried out using paddle dissolution apparatus at a temperature of 37°C with mixing at 50 rpm in 900 ml of a dissolution solution containing 0.1N HCl. Dissolution tests were carried out in line with Pharmacopoeia guidelines 07/2010:51701 (Recommendations on Dissolution Testing).

20 a) Dissolution Test 1: effect of adding a plasticising agent in a composition according to the invention containing berberine, a polymer and a plasticising agent

Two different plasticising agents were used to formulate the following two compositions for extrusion according to the invention, both containing berberine, a polymer and a plasticising agent:

Composition 1: 40% (m/m) powdered, crystalline berberine (BBR) + 50% (m/m) polyvinylpyrrolidone (PVP - Kollidon 12 PF, BASF) as the polymer + 10% (m/m) glycerol (Roth) as plasticising agent;

30 Composition 2: 40% (m/m) powdered, crystalline berberine (BBR) + 50% (m/m) polyvinylpyrrolidone (PVP - Kollidon 12 PF, BASF) as the

polymer + 10% (m/m) polyethylene glycol (PEG - Kollisolv PEG 400, BASF) as plasticising agent;

These two compositions were compared vis-a-vis dissolution of the berberine over time in a dissolution test as detailed above; berberine alone in a powdered, crystalline state was tested in parallel (control).

Results are presented in Figure 1. As can be seen, the percentage of berberine in solution over time is significantly higher with compositions according to the invention (BBR + PVP + glycerol and BBR + PVP + PEG) than with crystalline berberine on its own. The amount of crystalline BBR on its own that dissolved is of the order of 35% whereas it is of the order of 40% from Composition 2 above (BBR + PVP + PEG) and 60-70% from Composition 1 above (BBR + PVP + glycerol).

This demonstrates the advantages of a composition according to the invention when it comes to optimising the solubility of berberine to enhance its bioavailability, the berberine being at least in part in an amorphous state.

b) Dissolution Test 2: effect of the polymer used in a composition according to the invention containing berberine, a polymer and a plasticising agent

Two different polymers were used to formulate the following two compositions for extrusion according to the invention, both containing berberine, a polymer and a plasticising agent:

Composition 1: 40% (m/m) powdered, crystalline berberine (BBR) + 50% (m/m) polyvinylpyrrolidone (PVP - Kollidon K30, BASF) as the polymer + 10% (m/m) glycerol (Roth) as plasticising agent;

Composition 2: 40% (m/m) powdered, crystalline berberine (BBR) + 50% (m/m) hydroxypropylcellulose (HPC - HPC SSL, Nisso) as the polymer + 10% (m/m) glycerol (Roth) as plasticising agent;

These two compositions were compared vis-a-vis dissolution of the berberine over time in a dissolution test as detailed above; berberine alone in a powdered, crystalline state was tested in parallel (control).

Results are presented in Figure 2. As can be seen, the percentage of berberine in solution over time is very significantly higher with compositions according to the invention (BBR + PVP + glycerol and BBR + HPC + glycerol) than with crystalline berberine on its own.

This demonstrates that different polymers can be added to a composition according to the invention that also contains a plasticising agent to optimise the solubility of the berberine that is at least in part in an amorphous state and thereby enhance its bioavailability. It also demonstrates the advantages of combining berberine with a polymer and a plasticising agent since doing so can increase berberine solubility to up to 100%.

c) Dissolution Test 3: effect of the proportion of plasticising agent in a composition according to the invention containing berberine, a polymer and a plasticising agent

Three different proportions of glycerol were included as plasticising agent to formulate the following three compositions for extrusion according to the invention, both containing berberine, a polymer and a plasticising agent:

Composition 1: 50% (m/m) powdered, crystalline berberine (BBR) + 50% (m/m) hydroxypropylcellulose (HPC - HPC SSL, Nisso) as the polymer + 0% (m/m) glycerol (Roth) as plasticising agent;

Composition 2: 50% (m/m) powdered, crystalline berberine (BBR) + 45% (m/m) hydroxypropylcellulose (HPC - HPC SSL, Nisso) as the polymer + 5% (m/m) glycerol (Roth) as plasticising agent;

Composition 3: 50% (m/m) powdered, crystalline berberine (BBR) + 40% (m/m) hydroxypropylcellulose (HPC - HPC SSL, Nisso) as the polymer + 10% (m/m) glycerol (Roth) as plasticising agent;

5 These three compositions were compared vis-a-vis dissolution of the berberine over time in a dissolution test as detailed above; berberine alone in a powdered, crystalline state was tested in parallel (control).

Results are presented in Figure 3. As can be seen, the percentage of berberine in solution over time is significantly higher with compositions cording to the invention (BBR + HPC + 0% glycerol, BBR +
10 HPC + 5% glycerol and BBR + HPC + 10% glycerol) than with crystalline berberine on its own.

It should be noted that the results for the BBR + HPC + 0% glycerol composition show that simply adding a polymer (in this case HPC) already improves the solubility of berberine over time. The addition of a
15 plasticising agent (in this case, glycerol) further enhances the solubility of the berberine over time since doing so can increase berberine solubility to up to 100%.

Comparison of different proportions of glycerol shows that, compared with 5% glycerol, 10% glycerol speeds up the dissolution of
20 berberine over time in the first 30 minutes.

This demonstrates the advantages of adding a plasticising agent to a composition according to the invention in order to further improve solubility of the berberine and thereby enhance its bioavailability, the berberine being at least in part in an amorphous state. It also demonstrates
25 that a higher proportion of plasticising agent in a composition according to the invention results in faster dissolution of the berberine, at least at first, i.e. in the first 30 minutes of the dissolution test.

d) Dissolution Test 4: effect of the proportion of alkaloid (berberine) in a composition according to the invention containing berberine, a polymer and a plasticising agent

5 Two different proportions of berberine were used to formulate the following two compositions for extrusion according to the invention, both containing berberine, a polymer and a plasticising agent:

Composition 1: 40% (m/m) powdered, crystalline berberine (BBR) +
10 50% (m/m) hydroxypropylcellulose (HPC - HPC SSL, Nisso) as the polymer + 10% (m/m) glycerol (Roth) as plasticising agent;

Composition 2: 50% (m/m) powdered, crystalline berberine (BBR) +
40% (m/m) hydroxypropylcellulose (HPC - HPC SSL, Nisso) as the polymer + 10% (m/m) glycerol (Roth) as plasticising agent;

15 These two compositions were compared vis-a-vis dissolution of the berberine over time in a dissolution test as detailed above; berberine alone in a powdered, crystalline state was tested in parallel (control).

Results are presented in Figure 4. As can be seen again, the percentage of berberine (including at least an amorphous phase) in solution
20 over time is very significantly higher with compositions according to the invention (BBR + HPC + glycerol) than with crystalline berberine on its own. With respect to the proportion of berberine (40 or 50%), it can be seen that the berberine is completely dissolved (100%) at either proportion.

25 e) Dissolution Test 5: stability over time of compositions according to the invention containing berberine, a polymer and a plasticising agent

Two compositions for extrusion containing berberine, a polymer and a plasticising agent of different "ages" (T_0 and $T_{3\text{months}}$) were
30 tested.

These compositions contain 40% (m/m) powdered, crystalline berberine (BBR) + 50% (m/m) hydroxypropylcellulose (HPC - HPC SSL, Nisso) as the polymer + 10% (m/m) glycerol (Roth) as plasticising agent.

These two compositions were compared vis-a-vis dissolution
5 of the berberine over time in a dissolution test as detailed above; berberine alone in a powdered, crystalline state was tested in parallel (control).

Results are presented in Figure 5. As can be seen, the percentage of berberine (including at least an amorphous phase) dissolved over time is identical whether the composition according to the invention is
10 fresh (T_0) or has been "aged" for three months ($T_{3\text{months}}$).

Example 3: Consistency Test - consistency of the concentration of berberine in pellets produced by extrusion

15 In order to determine the consistency of the actual berberine concentration in extrudates obtained using the process according to the invention compared with the amount of berberine input into the hot melt extrusion step, pellets of a size of the order of 2 mm ($n = 3-5$ per batch tested) of different compositions according to the invention were dissolved in order
20 to determine how much berberine is actually in solution.

To do this, 1-3 mg of the extrudate were weighed out and then dissolved in 1-2 ml DMSO. The resultant solution was analysed by HPLC after dilution in the mobile phase (20- or 50-fold dilution). More specifically, materials were analysed on a Shimadzu HPLC machine in the conditions
25 presented in Table 2 below to determine the experimental berberine concentration (per cent by weight) in the pellets tested.

Table 2

Column	Nucleodur EC (100 x 4.6 mm; 5 µm) (C18) Macherey-Nagel
Mobile phase	A: Water-0.1% TFA ; B: Acetonitrile-0.1% TFA* Isocratic: 70:30 *TFA: trifluoroacetic acid
Flow rate	0.8 ml/min
Volume injected	20 µl
Wavelength	346 nm

Results are presented in Figure 3 below.

5 Table 3

Formulation (% by weight)	Glycerol concentration (% by weight)	Theoretical BBR concentration (% by weight)	Experimental BBR concentration (% by weight)
50% HPC + 40% BBR	10	40	35.9±1.8
40% HPC + 50% BBR	10	50	45.8±0.1
45% HPC + 50% BBR	5	50	40.3±1.6
50% HPC + 50% BBR	0	50	50.1±3.6
50% PVP + 40% BBR	10	40	34.6±4.4

As can be seen, standard deviation values calculated for the experimental concentrations are low which shows that, within the various test batches of a given composition according to the invention, berberine is evenly dispersed through the different pellets, i.e. through the resultant extrudate.

Example 4: testing of stability of a composition according to the invention over time in terms of the concentration of the protoberberine alkaloid and its degree of dissolution

A test was carried out to determine the stability over time of a composition according to the invention containing 50% (m/m) berberine (BBR), 40% (m/m) hydroxypropylcellulose (HPC - HPC SSL, Nisso) as

polymer and 10% (m/m) glycerol (Roth) as plasticising agent, the composition having been obtained using the production process described in Example 1. Compositions (samples) were kept at room temperature in closed containers in the dark.

5 At each time-point (T0, T+3months, T+5months and T+8months), the amount of berberine released and the concentration of berberine were assayed. Each assay was carried out as follows:

-Concentration: 1-3 mg of extrudate were dissolved in 1 mL of DMSO. The resultant solution was analysed by HPLC after dilution in the mobile phase
10 (20- or 50-fold dilution) (see example 3 for HPLC run details);

-Dissolution test (release): 500 mg of pellets of a composition according to the invention (500 mg pellets containing 250 mg berberine) et 250 mg of powdered, crystalline berberine were tested for solubility. These tests were carried out in paddle dissolution apparatus (see Example 2) with the
15 conditions presented in Table 4.

Table 4

Weight	500 mg extrudate or 250 mg berberine
Temperature	37°C
Speed	50 rpm
Dissolution medium	900 ml of 0.1N HCl

Results are presented in Figures 6 and 7. Figure 6 shows
20 berberine concentration in the composition, depending on whether it had been freshly produced (T0) or produced 3 months before (T3M), 5 months before (T5M) or 8 months before (T8M). It can be seen that berberine concentration is practically constant over time.

Figure 7 shows the amount of berberine released from the
25 composition, depending on whether it had been freshly produced (T0) or produced 3 months before (T3M), 5 months before (T5M) or 8 months before

(T8M). It can be seen that the amount released is practically constant from all the differentially aged compositions.

Moreover, this figure, advantageously, shows again that a composition according to the invention in the form of an extrudate in which the alkaloid (berberine) includes at least an amorphous phase is significantly more soluble than powdered, crystalline berberine.

Example 5: Thermal testing by differential scanning calorimetry (DSC)

Differential scanning calorimetry—a technique familiar to those skilled in the art—measures the differential in heat exchange between a reference and a test product. This technique can be used to determine melting point, crystallisation temperature, phase transition temperatures and the latent heat of transitions.

In particular, this method yields curves in which the presence of an endothermal peak (due to the absorption of heat) signals the melting point of the test sample. A melting point indicates the presence of a crystalline form in the sample. In contrast, if no melting point is seen, the material is in an amorphous state.

Such thermal analysis was carried out on the following compositions:

- 10 mg of pure powdered, crystalline berberine;
- 10 mg of a composition according to the invention containing 50% (m/m) berberine (BBR) and 50% (m/m) hydroxypropylcellulose (HPC - HPC SSL, Nisso) as polymer, the composition having been obtained using the production process described in Example 1;
- 10 mg of a composition according to the invention containing 50% (m/m) berberine (BBR), 40% (m/m) hydroxypropylcellulose (HPC - HPC SSL, Nisso) as polymer and 10% (m/m) glycerol (Roth) as plasticising agent, the composition having been obtained using the production process described in Example 1.

DSC analysis was carried out according to the protocol presented in Table 5 below according to several segments. Several segments were undertaken to evaporate any residual moisture present in the powdered, crystalline berberine or the compositions according to the invention.

Table 5

Segment	Starting T° (°C)	Final T° (°C)	Heating (°C/min)	Heating time (min)
1	30	30	0	1
2	30	90	10	6
3	90	90	0	15
4	90	30	-10	6
5	30	30	0	1
6	30	165	10	13.5
7	165	165	0	1

Results are presented in Figure 8 that shows Segment #6 from 30 to 165°C at a heating rate of 10°C/min. This thermogram shows that compositions according to the invention including a plasticising agent and a polymer (solid line) or including a polymer but no plasticising agent (dotted line) are compositions in which berberine (the protoberberine alkaloid) consists at least in part of an amorphous phase. In practice, in contrast to pure, powdered, crystalline berberine (broken line), the curves for compositions according to the invention show no peak indicating passage from a crystalline phase to an amorphous state.

Example 6: Bioavailability of a composition according to the invention in rats, in particular that of a composition according to the invention containing berberine as the protoberberine alkaloid

5 In vivo experiments were carried out on rats weighing 250 g (female Sprague Dawley rats). Three groups of 6 rats each were composed as follows:

1. control: hydroxypropylcellulose (n=6);
2. pure powdered, crystalline berberine (n=6);
- 10 3. composition extruded according to the invention: 50% berberine + 40% HPC + 10% glycerol (pellets) (n=6).

 To groups 2 and 3, the berberine was administered orally to the rats at doses of between 50 and 500 mg/kg. Subsequently, 200-300 µL blood samples were drawn from the caudal vein. Hydroxypropylcellulose was
15 administered orally to the control animals at doses of between 60 and 750 mg/kg.

 Blood samples were drawn at the following time points: 0, 30, 60 and 90 min then 2, 4, 6, 8, 12 and 24 hours. Samples were collected into heparinised tubes. After mixing, the heparinised tubes were centrifuged
20 (3000g) for 15 minutes at 4°C. Then the plasma supernatant was harvested and stored at -80°C until it could be analysed by LC-MS.

 HPLC analysis carried out to determine the amount of berberine present in the plasma showed significantly higher quantities of berberine and its metabolites in blood samples taken from Group 3 rats than
25 the quantities found in blood samples taken from Group 2 rats. This suggests that a composition according to the invention including a polymer and in which said protoberberine alkaloid comprises at least a first amorphous phase as well as possibly a second crystalline phase, is characterised by enhanced bioavailability compared with a composition of the background art
30 exclusively composed of pure, powdered, crystalline berberine.

Example 7: Production process for a composition according to the invention in the form of an extrudate containing tetrahydropalmatine as the protoberberine alkaloid

5 Compositions according to the invention containing tetrahydropalmatine as the protoberberine alkaloid (the active substance) as presented in Example 8 below were produced according to the following process which this invention also provides:

- 10 a) a preliminary pre-blending step in which powdered, crystalline tetrahydropalmatine is blended with at least one polymer;
- b) a step to bring together said pre-blend produced in Step a) to feed into a Thermo-Fischer® Pharma 11 extruder;
- c) a mixing step on said pre-blend in said extruder to produce a mixture;
- 15 d) a hot melt extrusion step on said mixture obtained in Step c) in said extruder to generate an extrudate, the hot melt extrusion step being carried out with the extrusion screw rotating at a speed of 200 revolutions per minute at a temperature of between 40°C and 110°C; and
- 20 e) a step to cut up the extrudate obtained in Step d) in a pelletiser in such a way as to obtain pellets of the order of 2-3 millimetres in size.

 The temperature at which the hot melt extrusion step is carried out will depend on the constituents of the mixture, in particular the natures of the protoberberine alkaloid, the polymer and/or the plasticising agent. Those
25 skilled in the art will be able to determine this.

Example 8: Testing of dissolution of compositions according to the invention containing tetrahydropalmatine as the protoberberine alkaloid

5 For various compositions obtained according to the production process described in Example 7, dissolution over time of the protoberberine alkaloid in the resultant extrudates was tested. Tetrahydropalmatine was selected as the protoberberine alkaloid for dissolution testing. As indicated above, the extrudates present in the form of pellets of the order of 2-3
10 millimetres in size.

All dissolution tests were carried out using paddle dissolution apparatus at a temperature of 37°C with mixing at 50 rpm in 900 ml of a dissolution solution of H₂O. Dissolution tests were carried out in line with Pharmacopoeia guidelines 07/2010:51701 (Recommendations on
15 Dissolution Testing).

a) Dissolution test 1: effect of the presence of a polymer or a plasticising agent on the solubility of tetrahydropalmatine in compositions according to the invention

20

Hydroxypropylcellulose was included as the polymer and glycerol as the plasticising agent to formulate and compare two compositions for extrusion according to the invention. The two following compositions for extrusion were made up:

25

Composition 1: 50% (m/m) powdered, crystalline tetrahydropalmatine (THP) + 50% (m/m) hydroxypropylcellulose (HPC – HP SSL, Nisso) as the polymer;

Composition 2: 50% (m/m) powdered, crystalline
30 tetrahydropalmatine (THP) + 40% (m/m) hydroxypropylcellulose (HPC –

HPC SSL, Nisso) as the polymer + 10% (m/m) glycerol (Roth) as the plasticising agent.

These two compositions were compared vis-a-vis dissolution of the berberine over time in a dissolution test as detailed above; berberine alone in a powdered, crystalline state was tested in parallel (control).

Results are presented in Figure 9. As can be seen, the percentage of tetrahydropalmatine in solution over time is significantly higher with compositions according to the invention (THP + HPC and THP + HPC + glycerol) than with crystalline tetrahydropalmatine on its own.

This demonstrates the advantages of a composition according to the invention when it comes to optimising the solubility of tetrahydropalmatine to enhance its bioavailability. In practice, these results show that:

- a composition according to the invention in the form of an extrudate including a polymer and a protoberberine alkaloid with at least a first amorphous phase and possibly a second crystalline phase, significantly increases the solubility of tetrahydropalmatine and therefore enhances its bioavailability;
- addition of a plasticising agent (in this case glycerol) further increases the solubility of tetrahydropalmatine and therefore further enhances its bioavailability.

b) Dissolution test 2: effect of the nature of the plasticising agent on the solubility of tetrahydropalmatine from compositions according to the invention containing tetrahydropalmatine, a polymer and a plasticising agent

A series of plasticising agents were tested in compositions according to the invention, namely glycerol, polyethylene glycol (PEG) and triethyl citrate (TEC), depending on whether the composition according to the

invention contains hydroxypropylcellulose (HPC) or polyvinylpyrrolidone (PVP) as the polymer.

The following compositions for extrusion were made up:

5 Composition 1: 50% (m/m) tetrahydropalmitine (THP) + 40% (m/m) hydroxypropylcellulose (HPC - HPC SSL, Nisso) as the polymer + 10% (m/m) glycerol (Roth) as the plasticising agent;

 Composition 2: 50% (m/m) tetrahydropalmitine (THP) + 40% (m/m) hydroxypropylcellulose (HPC - HPC SSL, Nisso) as the polymer +
10 10% (m/m) polyethylene glycol (PEG - PEG 6000, VWR) as the plasticising agent;

 Composition 3: 50% (m/m) tetrahydropalmitine (THP) + 40% (m/m) hydroxypropylcellulose (HPC - HPC SSL, Nisso) as the polymer + 10% (m/m) triethyl citrate (TEC- Sigma) as the plasticising agent;

15 Composition 4: 50% (m/m) tetrahydropalmitine (THP) + 40% (m/m) polyvinylpyrrolidone (PVP - Kollidon 30, BASF) as the polymer + 10% (m/m) glycerol (Roth) as the plasticising agent;

 Composition 5: 50% (m/m) tetrahydropalmitine (THP) + 40% (m/m) polyvinylpyrrolidone (PVP - Kollidon 30, BASF) as the polymer + 10%
20 (m/m) polyethylene glycol (PEG - 6000, VWR) as the plasticising agent;

 Composition 6: 50% (m/m) tetrahydropalmitine (THP) + 40% (m/m) polyvinylpyrrolidone (PVP - Kollidon 30, BASF) as the polymer + 10% (m/m) triethyl citrate (TEC- Sigma) as the plasticising agent;

 After extrusion, these compositions were compared vis-a-vis
25 dissolution of the tetrahydropalmitine over time in a dissolution test as detailed above; tetrahydropalmitine alone in a powdered, crystalline state was tested in parallel (control).

 Results are presented in Figures 10 and 11 for the polymers hydroxypropylcellulose (HPC) and polyvinylpyrrolidone (PVP) respectively.
30 As can be seen, whichever polymer is used (HPC or PVP) and whatever the plasticising agent (glycerol, PEG or TEC), tetrahydropalmitine was

significantly more soluble from compositions according to the invention in which the tetrahydropalmatine comprises at least in part an amorphous phase compared with pure crystalline tetrahydropalmatine.

5 c) Dissolution test 3: effect of the nature of the polymer on the solubility of tetrahydropalmatine from compositions according to the invention containing tetrahydropalmatine, a polymer and a plasticising agent

Two different polymers were tested in compositions according
10 to the invention, namely hydroxypropylcellulose (HPC) and polyvinylpyrrolidone (PVP).

The following compositions for extrusion were made up:

Composition 1: 50% (m/m) tetrahydropalmatine (THP) + 40%
15 (m/m) hydroxypropylcellulose (HPC - HPC SSL, Nisso) as the polymer + 10% (m/m) glycerol (Roth) as the plasticising agent;

Composition 2: 50% (m/m) tetrahydropalmatine (THP) + 40%
(m/m) polyvinylpyrrolidone (PVP 30, BASF) as the polymer + 10% (m/m) glycerol (Roth) as the plasticising agent;

20 After extrusion, these compositions were compared vis-a-vis dissolution of the tetrahydropalmatine over time in a dissolution test as detailed above; tetrahydropalmatine alone in a powdered, crystalline state was tested in parallel (control).

Results are presented in Figure 12. As can be seen, whichever
25 polymer is used (HPC or PVP), tetrahydropalmatine was significantly more soluble from compositions according to the invention in which the tetrahydropalmatine comprises at least in part an amorphous phase compared with pure crystalline tetrahydropalmatine.

It is fully understood that this invention is in no way limited to
30 the embodiments described above and that modifications could be made without going beyond the scope of the Claims.

CLAIMS

1. Composition in the form of an extrudate containing at least one protoberberine alkaloid as active substance and at least one polymer,
5 said composition being characterised in that said protoberberine alkaloid consists at least in part of a first amorphous phase and possibly a second crystalline phase.

2. Composition according to Claim 1, characterised in that said protoberberine alkaloid is selected from the group consisting of alborine,
10 anibacanine, anisocycline, artavenustine, berberastine, berberine, berberubine, berlambine, canadine, capaurimine, capaurine, caseadine, caseamine, cavidine, cerasodine, cerasonine, cheilanthifoline, clarkeanidine, columbamine, constrictosine, coptisine, coreximine, corybulbine, corycavamine, corycavine, corydalidzine, corydalmine,
15 corymotine, corynoxidine, corypalmine, corysamine, corytenchine, coulteropine, cryptopine, cyclanoline, dauricoside, discretamine, fississaine, govanine, groenlancidine, gusanlung-A, gusanlung-B, gusanlung-D, hunnemanine, jatrorrhizine, lambertine, lienkonine, malacitanine, manibacanine, mecambidine, muramine, orientalidine,
20 pallimamine, palmatine, pessoine, phellodendrine, prechilenine, protopine, schefferine, scoulerine, sinactine, spiduxine, spinosine, stephabinamine, stephabine, stepharanine, stepholidine, stylopine, tetrahydropalmatine, thaicanine, thaipetaline, thalictricavine, thalidastine, thalifendine, xilopinine, yuanamide, dihydroberberine,
25 dehydrocorydalmine, palmatrubine, dehydrodiscretamine, dehydrocheilanthifoline, demethylenberberine, epiberberine, pseudocoptisine, pseudopalmatine, pseudojatrorrhizine, pseudoepiberberine, pseudocolumbamine, dehydrodiscretine, dehydrocoreximine, thalifaurine, corysamine, dehydrothalictrifoline,
30 dehydrothalictricavine, dehydrocorydaline, dehydroapocavidine,

lincagenine, dehydrocapaurimine, 13-methyl-pseudoepiberberine, mequinine, as well as derivatives, salts and mixtures thereof.

3. Composition according to either of Claims 1 or 2, characterised in that said polymer in a composition according to the invention is selected from the group consisting of copolymers of ammonium methacrylate, hydroxypropylcellulose (HPC), polyvinyl acetate, ethylcellulose, hydroxypropylmethylcellulose phthalate, polyvinylpyrrolidone (PVP), hydroxypropymethylcellulose (HPMC), hydroxypropymethylcellulose acetosuccinate, cellulose acetobutyrate, cellulose acetophthalate, polyvinylpyrrolidone-co-vinyl acetate, polyethylene-co-vinyl acetate, co-methacrylic acid polyvinyl acetate, polyethylene oxide, polylactide-co-glycolide, polyvinyl alcohol, pectin, polycarbophile, polycaprolactone, carnauba wax, ethylene-vinyl acetate copolymer, lecithin, castor and hydrogenated soy oil, waxes (microcrystalline waxes, etc.), natural or synthetic starch (cornstarch, pregelatinised starch, potato starch, etc.), maltodextrin, isomalt, chitosan, gums (xanthan gum, etc.), agar, lactose, soluble or insoluble natural or synthetic fibers such as inulin, β -glucan and Konjac fibers, as well as derivatives and mixtures thereof.

4. Composition according to any of the preceding Claims, characterised in that it also includes at least one plasticising agent.

5. Composition according to Claim 4, characterised in that said at least one plasticising agent is selected from the group consisting of polyols, lipids, lecithins, sucrose esters, triethyl citrate, polyethylene glycol, glycerol, dibutyl sebate, butyl stearate, glycerol monostearate, diethyl phthalate, and mixtures thereof.

6. Composition according to any of the preceding Claims, characterised in that it also contains at least one additive selected from the group consisting of lubricants, surfactants, antioxidants, chelating agents and mixtures thereof.

7. Composition according to any of the preceding Claims, characterised in that it also contains at least one first additional active polyphenol-type substance selected from the group consisting of phenolic acids, stilbenes, phenolic alcohols, lignanes, flavonoids and mixtures thereof.

8. Composition according to any of the preceding Claims, characterised in that it also contains an additional active triterpine-type substance, e.g. a limonoid.

9. Composition according to any of the preceding Claims, characterised in that it also contains at least one inhibitor and/or modulator of P-gp activity.

10. Composition according to any of the preceding Claims, characterised in that it is presented in the form of pellets, granules, a powder, effervescent or non-effervescent tablets, a solution (for injection or not), a suspension, a gel, a pomade or any other suitable form compatible with administration to an animal or a human being.

11. Production process for a composition according to any of Claims 1 through 10, characterised in that it includes the following steps:

- a) a step to bring together at least one protoberberine alkaloid and at least one polymer—at the same time or deferred in time—to feed into an extruder,
- b) a mixing step in said extruder of said at least one protoberberine alkaloid and said at least one polymer to form a mixture, and
- c) a Hot Melt Extrusion (HME) step on said mixture obtained in Step b), carried out in said extruder to generate an extrudate in which said protoberberine alkaloid consists of at least a first amorphous phase and possibly a second crystalline phase.

12. Process according to Claim 11, characterised in that it includes a preliminary pre-blending step of said at least one protoberberine alkaloid and said at least one polymer in such a way as to generate a pre-blend for feeding into the extruder.

13. Process according to either of Claims 11 or 12, characterised in that said Hot Melt Extrusion step is carried out at a temperature of between 20 and 180°C, preferably at a temperature of between 40 and 115°C, preferentially at a temperature of between 80 and 90°C, preferably at a temperature of 110°C, more preferably still at a temperature of 100°C.

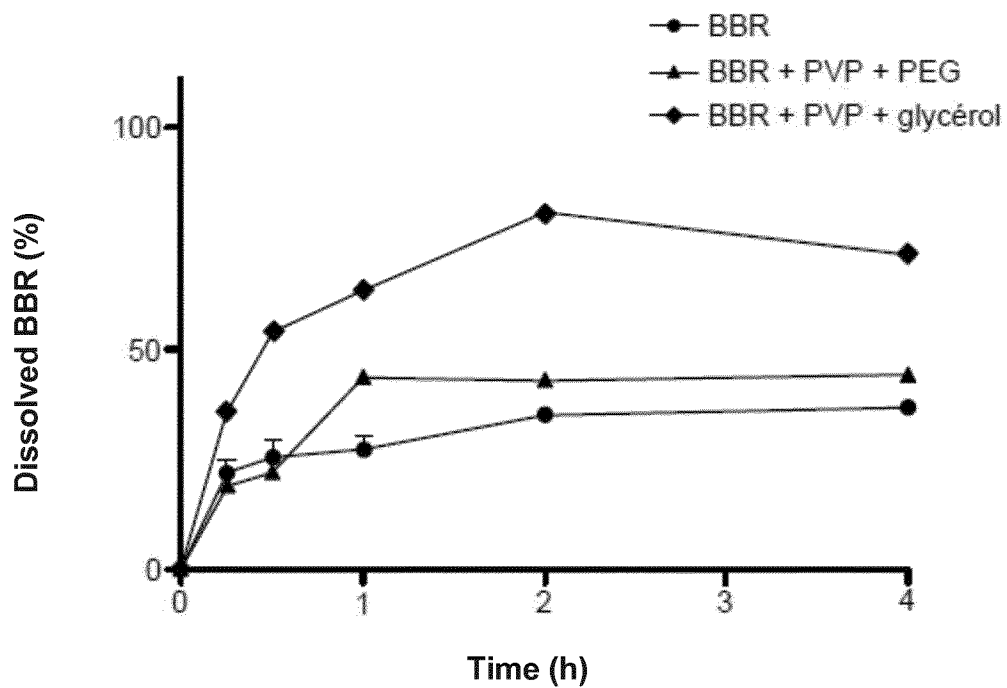
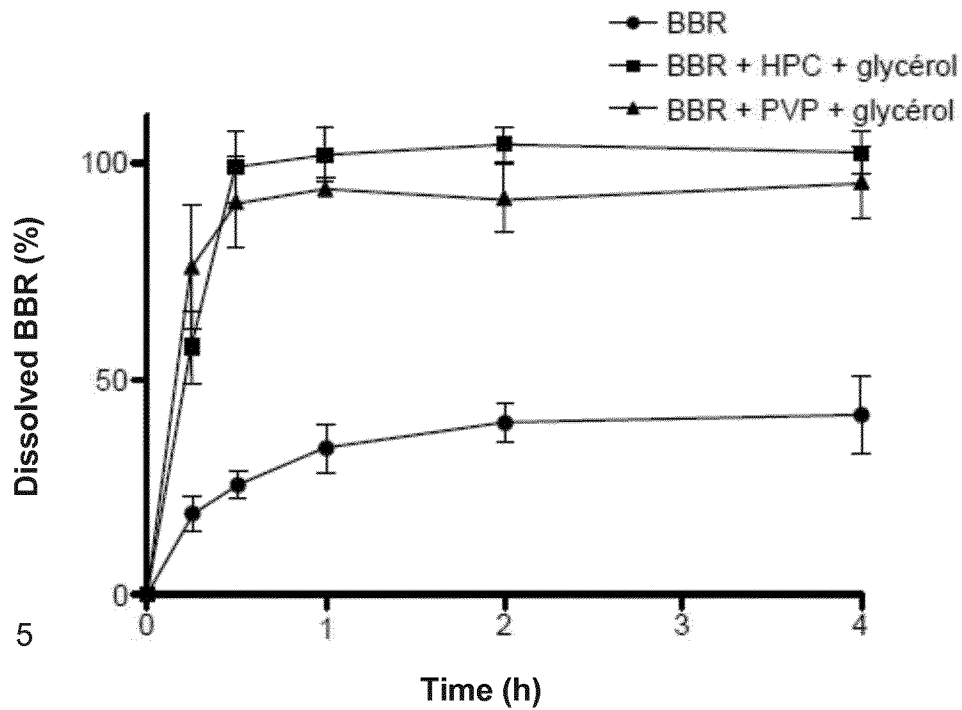
14. Process according to any of Claims 11 through 13, characterised in that said Hot Melt Extrusion step is carried out with the extrusion screw rotating at a speed of between 20 and 300 revolutions per minute, preferably between 100 and 250 rpm, preferentially at 200 rpm.

15. Process according to any of Claims 11 through 14, characterised in that it includes an additional cooling step when the material comes out of the extruder.

16. Process according to any of Claims 11 through 15, characterised in that it includes an additional processing step when the material comes out of the extruder, e.g. cutting up of the extrudate in a pelletiser and/or pulverisation of said extrudate.

17. Composition according to any of Claims 1 through 10, for use in preventive and/or curative treatment in human beings and/or animals, for diseases related to the cardiovascular system, diseases related to the blood, diseases related to the gastrointestinal system, diseases related to the endocrine system, diseases related to the immune system, diseases related to the central nervous system, skin diseases, diseases due to the presence of micro-organisms and cancer and in the preventive/curative treatment of diabetes.

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**FIG. 1****FIG. 2**

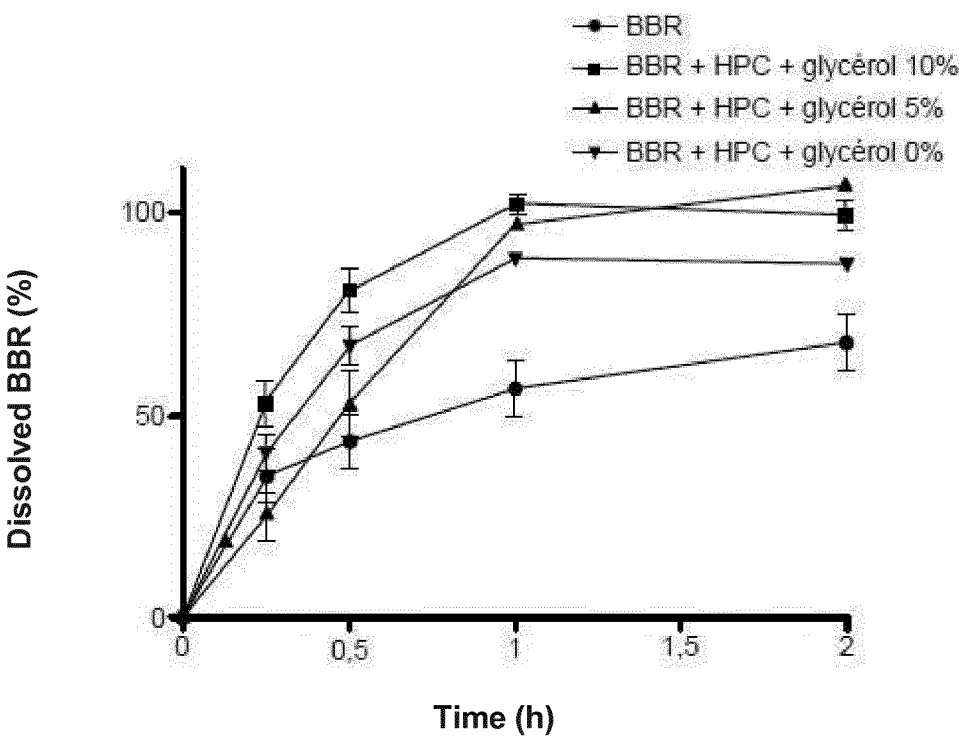


FIG. 3

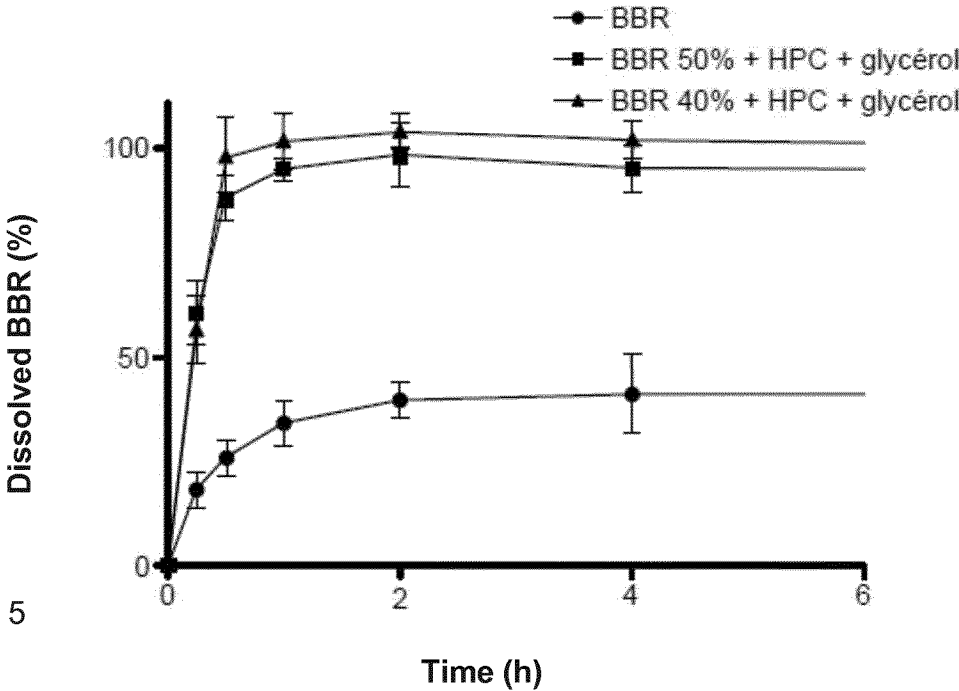


FIG. 4

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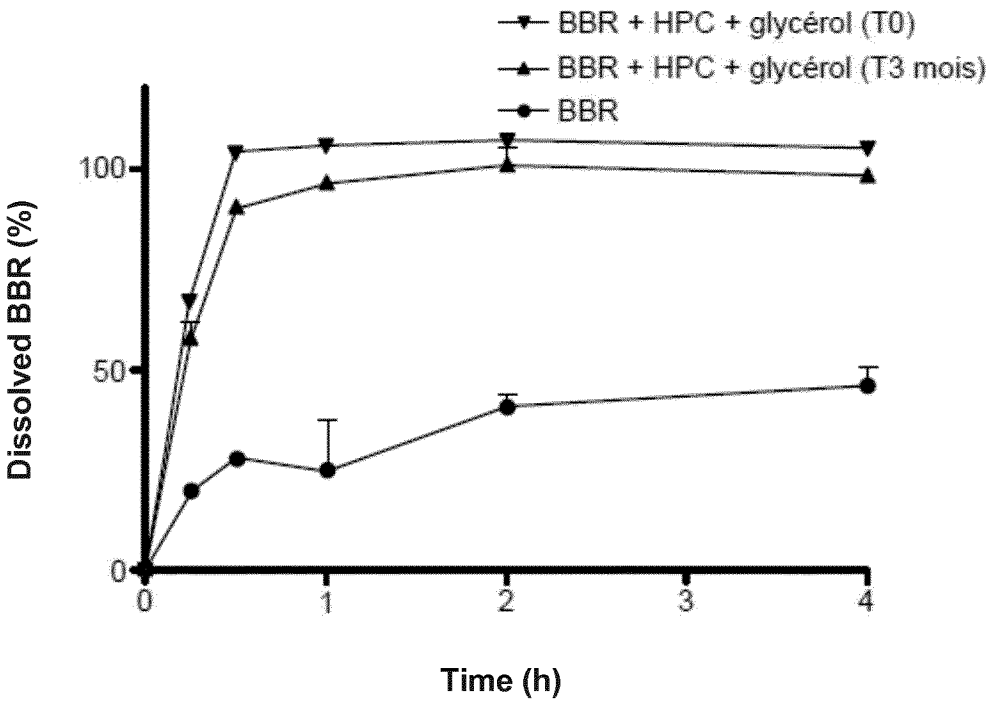
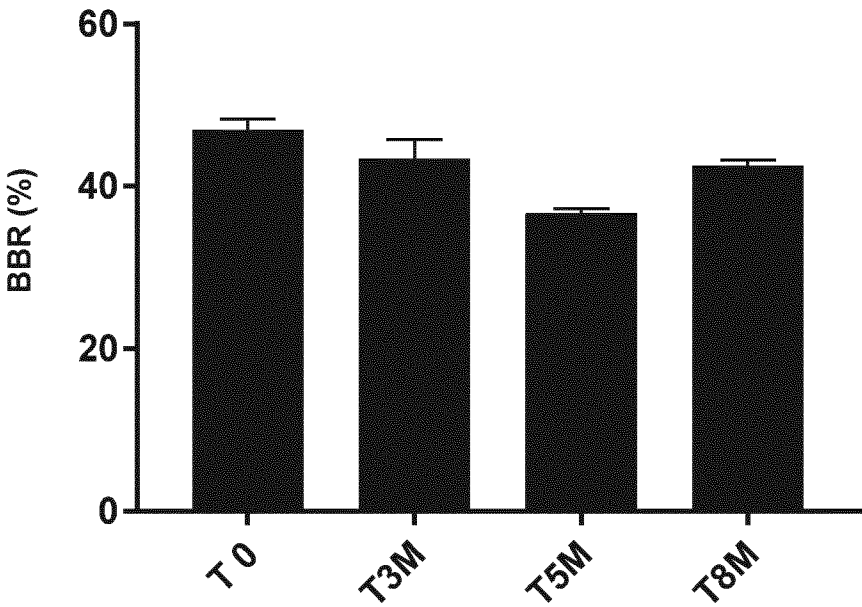


FIG. 5



⁵
FIG. 6

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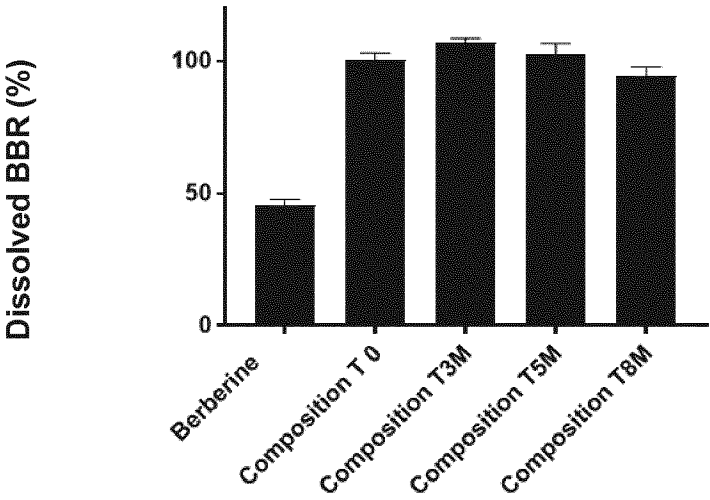
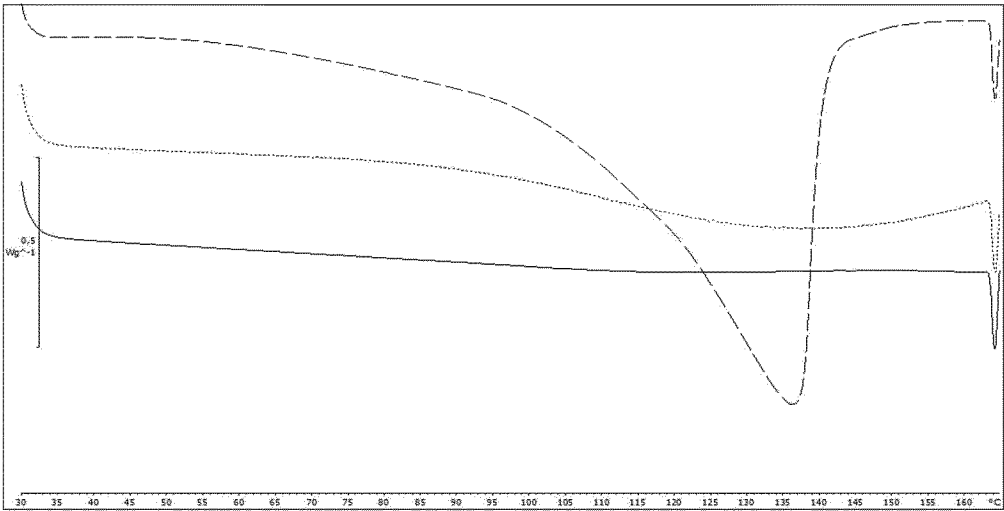


FIG. 7



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FIG. 8

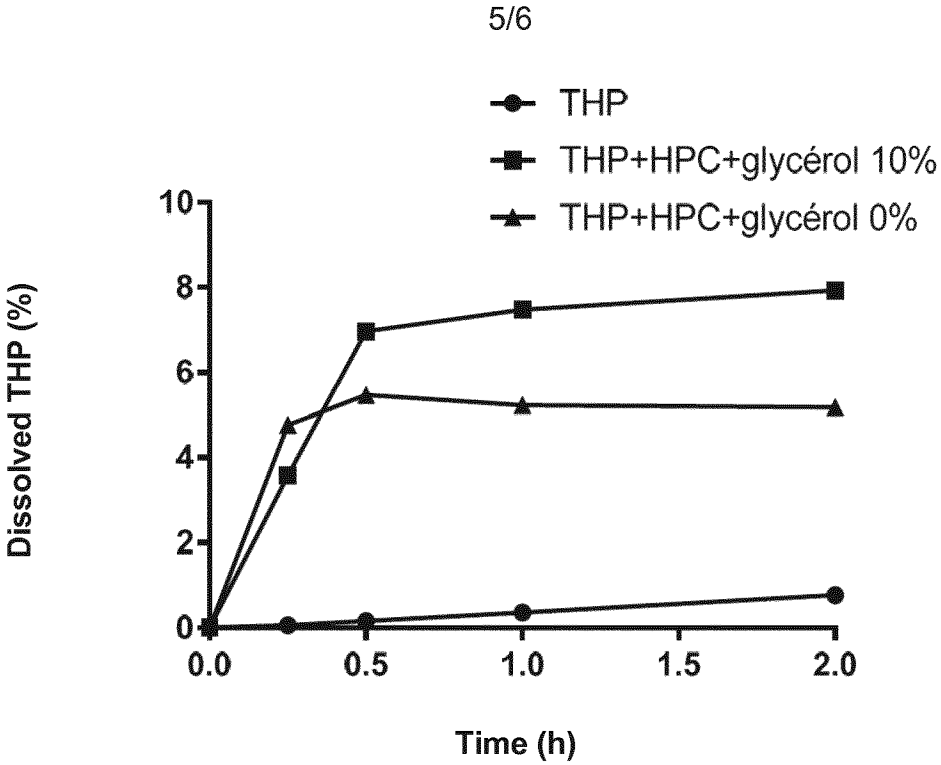


FIG. 9

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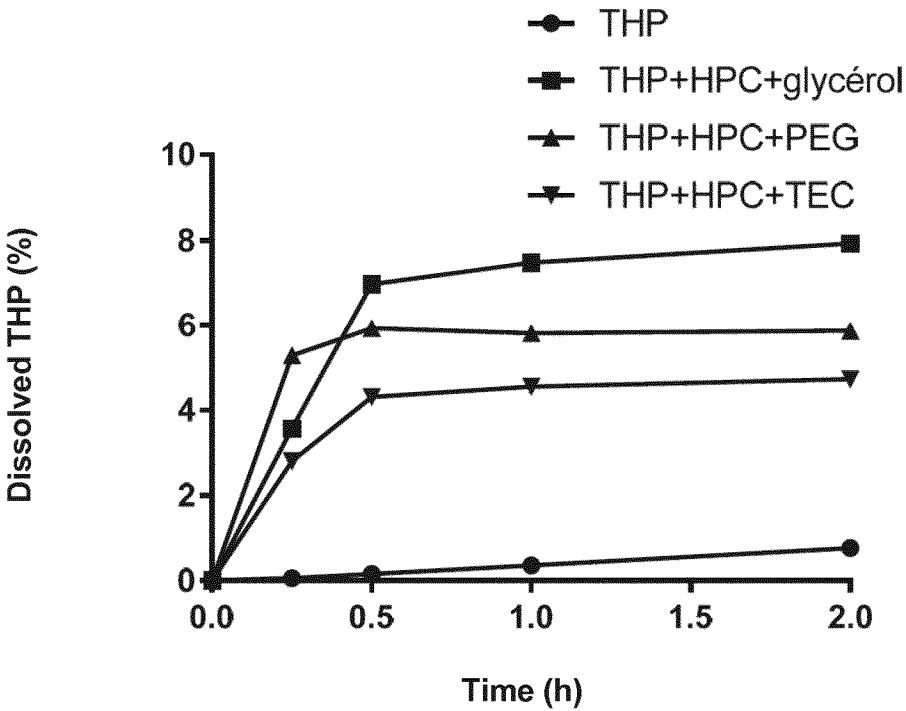
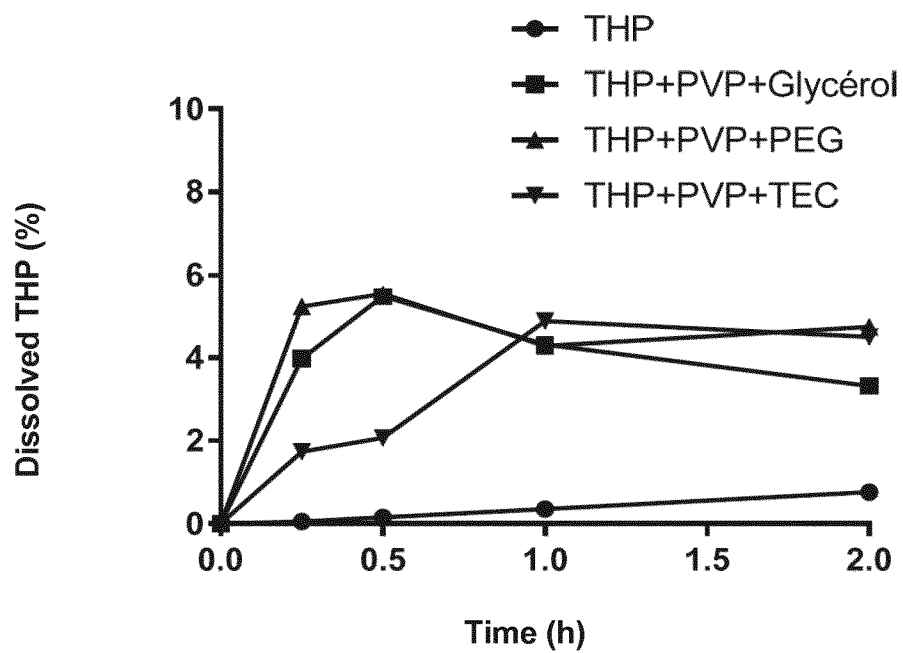
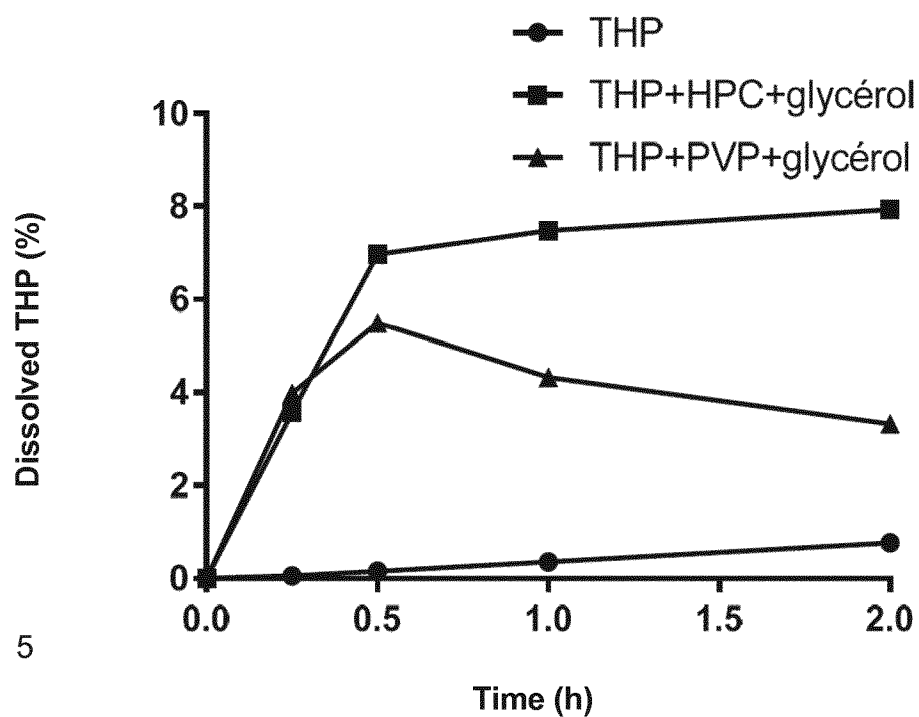


FIG. 10

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**FIG. 11****FIG. 12**

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2018/072900

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/16 A61K31/4375
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, WPI Data, BIOSIS, CHEM ABS Data, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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Further documents are listed in the continuation of Box C.



See patent family annex.

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Date of the actual completion of the international search

7 November 2018

Date of mailing of the international search report

21/11/2018

Name and mailing address of the ISA/

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Authorized officer

Lemarchand, Aude

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2018/072900

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
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Information on patent family members

International application No

PCT/EP2018/072900

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