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(54) Title: NOVEL RESVERATROL COMPOSITIONS

(57) Abstract: The present invention relates to compositions for topical use comprising solubilized resveratrol in a stable emulsion in a solvent system which does not cause irritation to the skin, wherein the solvent system comprises dimethyl isosorbide. The compositions according to present invention can preferably be used for transdermal applications for the treatment of various skin diseases such as psoriasis, acne and herpes simplex virus. The present invention also relates to the process to make such compositions.



WO 2009/129627 A1

NOVEL RESVERATROL COMPOSITIONS

Field of the Invention

The present invention is directed to novel stable compositions for topical use containing solubilized resveratrol. In particular, the present invention is directed to topical compositions containing solubilized resveratrol in an emulsion with solvents which do not cause skin irritation.

Background of the Invention

Resveratrol (3,5,4'-trihydroxystilbene) is a molecule that was isolated from the roots of white hellebore around 1940. Resveratrol (including trans-resveratrol, cis-resveratrol, cis-resveratrol glucoside and trans-resveratrol glucoside) is present in wine, particularly red wine, and in the early 1990's it was speculated to be the reason for the cardio-protective efficacy of wine.

Resveratrol is a poorly soluble compound and compositions containing it have a tendency to exhibit crystal precipitation when insufficient solvent is used to solubilize it. It is also well known that this molecule is very sensitive to external sources and can undergo degradation upon exposure to heat or light.

Emulsions are understood as being mixtures of two immiscible substances. An emulsion consists of a dispersed phase and a continuous phase. The dispersed phase is generally understood to be the phase which is not the predominant phase in terms of weight (or volume). For example, butter and margarine are known to be water-in-oil emulsions. Milk on the other hand is known to be an oil-in-water emulsion. In general, emulsions are cloudy, in light of the numerous phase interfaces which scatter light passing through the emulsion. Emulsions also tend to be unstable and revert back to their separated states. To create an emulsion there must be stirring or any other type of mixing of the two phases and the emulsifier in order to create a homogenous mixture.

Resveratrol is known to create instability in emulsion systems. It is therefore challenging to incorporate resveratrol in concentration above 0.1% in an emulsion. Incorporation of resveratrol in an emulsion usually causes a phase separation and a colour

change to yellowish-brown. It is not known by which mechanism resveratrol is causing phase separation or colour change in emulsion systems.

International Patent Application WO 2001/30314 (Pillai, *et al.*, published May 3, 2001) relates to cosmetic skin care compositions containing resveratrol in combination with selected retinoids. Also disclosed are methods of conditioning the skin by application of such cosmetic skin care compositions. This application discloses compositions comprising a cosmetically acceptable vehicle which acts as diluant, dispersant or carrier for resveratrol and the retinoid. The composition presented contains between 0.00001 and 10% by weight of resveratrol, and most preferably in the range of from 0.1 to 5% by weight. With the exception of the alcoholic lotion, the compositions do not include a solvent. The resveratrol present in those compositions is understood to be in a solid state and no indication is given as to the stability of the proposed compositions.

United States Patent Application Publication No. 2002/0173472 (Pezzuto, *et al.*, published November 21, 2002) is directed towards the topical administration of resveratrol, noting that it is extremely effective in preventing or treating certain skin conditions, disorders and diseases, for example, skin conditions associated with inflammation, skin damage associated with exposure to the sun, and the effects of natural aging. This application discloses pharmaceutical formulations, in particular, microemulsions, for administering resveratrol.

In the topical formulations disclosed in the application, it is preferable to include solubilizers and/or skin permeation enhancers, along with emulsifiers, emollients and preservatives, though only the microemulsion compositions are composed of solubilized resveratrol. The two compositions contain 10% of resveratrol (trans-resveratrol), diethylene glycol monoethyl ether (available commercially as Transcutol®), PEG-8 Caprylic/Capric triglycerides (Labrasol™), PEG 400, and water. The compositions disclosed in the application can contain up to 90% by weight of solvent. Formulations with high concentration of solvent can be very irritating to the skin if applied on damaged or sensitive skin or if the application area is large. This application does not provide any data as to the stability (physical and chemical) of the resveratrol contained in the disclosed compositions.

In International Patent Application WO 2004/103265 (Kim *et al.*, published December 2, 2004) there are disclosed whitening and antioxidative cosmetic compositions containing resveratrol and methods for preparing such compositions. The application discloses a stabilized cosmetic composition including resveratrol as a main component and either a primary stabilizer selected from cyclodextrin, polyethyleneglycol and a mixture thereof, or a combination of the primary stabilizer and a secondary stabilizer selected from an alpha-lipoic acid, a water-soluble whitening composition, a phellodendron extract, an alteromonas ferment extract, and a mixture thereof, and a method for preparing same. It also states that the solubility of resveratrol in those compositions is enhanced in polyol or ethanol and problems such as crystal precipitation at low temperature, off-flavor and discolouration upon exposure to sun light can be solved. However, the chemical stability of the compositions disclosed in this application is poor. The most stable composition disclosed exhibits an approximately 5% decrease in the assay value after 3 months, regardless of whether the composition is stored at room temperature (approximately 25°C), 4°C or 40°C. Further, the application does not disclose any stability data of more than 3 months of storage. Furthermore, cyclodextrins were used to stabilize resveratrol. The size of cyclodextrins makes it unlikely that the encapsulated resveratrol would be able to cross the skin barrier. Therefore, the resveratrol in those compositions would be unlikely to reach sites of action located in the epidermis or dermis.

In International Patent Application WO 2006/029484 (Declercq, *et al.*, published March 23, 2006) there are disclosed topical compositions containing phosphorylated polyphenols in combination with a topically acceptable carrier. The phosphorylated polyphenols have a higher water solubility in comparison with non-phosphorylated polyphenols. The composition presented contained propylene glycol which could act as a solvent. However, the low concentration of phosphorylated resveratrol (0.2 %) present in this composition is easily solubilized in the water phase. It is stated that these compositions provide a greater stability of biological activity as well as compositional integrity than is possible with unmodified polyphenol. This application also provides a method for rendering water-soluble an insoluble polyphenol, however, no long term stability data is provided.

In Canadian Patent No. 2,266,763 (Breton *et al.*, published October 10, 1999) there are disclosed compositions containing at least one hydroxystilbene designed to encourage exfoliation of the skin. However, there are no indications as to whether the resveratrol present in those compositions is solubilized. The compositions disclosed contain between 0.1% and 5 % of resveratrol and butylene glycol is the only excipient which can help in the solubilization of resveratrol. This document does not provide any data regarding the stability of the compositions.

In French Patent No. 2,862, 533 (Rubinstein, published April 28, 2006) there are disclosed compositions containing at least one hydroxystilbene which is to be used to promote a slimming effect. Some of the compositions presented contained an encapsulated active in its solid form. The emulsifier used is either a polymer or non-ionic.

In European Patent Application No. 0 953 346 and United States Patent Application Publication No. 2003/0031693 there are disclosed compositions comprising at least one hydroxystilbene (for EP 0 953 346) as well as at least one ascorbic acid compound (for US 2003/0031693) to promote a slimming effect or for treating skin afflictions. The compositions disclosed contain between 0.1 and 1 % of resveratrol and no solvent is used. They present classic water-in-oil emulsions made with non-ionic surfactants and oily solutions. Both applications present the same compositions but give no indication as to their stability.

In light of the prior art, there remains the need to have compositions containing solubilized resveratrol and having acceptable stability to optimize the delivery of resveratrol in the skin more effectively than those provided to date.

Summary of Invention

The inventors have surprisingly and unexpectedly discovered that they could prepare compositions for topical use containing solubilized resveratrol in a stable emulsion in a solvent system which does not cause irritation to the skin. Furthermore, it was also unexpected that resveratrol could be used in the compositions at such high concentrations, up to 15% (more preferably up to 8 %) by weight of the formulation products.

In one aspect of the present invention, there is provided a stable composition which contains solubilized resveratrol for topical use in a mammal. Preferably, the mammal is a human.

In an embodiment of the present invention, the compositions for topical use comprise solubilized resveratrol in an emulsion, one or more solvent, and an emulsifier.

In a preferred embodiment, the solvent present in the composition is dimethyl isosorbide. Another solvent that can be used in the compositions according to the present invention is diethylene glycol monoethyl ether. In a further embodiment, a mixture containing both dimethyl isosorbide and diethylene glycol monoethyl ether can be used. The use of dimethyl isosorbide increases the tolerability of the formulation in comparison with classic solvents.

The emulsifier used to stabilize the compositions can be a non-ionic emulsifier, a cationic emulsifier or a polymer. Preferably, the emulsifier is a cationic emulsifier.

Oil-in-water and water-in-oil emulsions, as well as gels, ointments and solutions, can be formulated as stable compositions according to the present invention where the amount of trans-resveratrol present can range up to about 15% by weight of the composition. A person skilled in the art will know that the desired range of resveratrol contained within the compositions of the present invention depends on the indication for the use thereof.

According to a preferred embodiment of the present invention, the compositions for topical use comprise:

- (i) from about 0.01 to about 15% by weight of trans-resveratrol;
- (ii) from about 1.0 to about 90% by weight of dimethyl isosorbide alone or in a mixture with another solvent; and
- (iii) from about 0.01 to about 10% by weight of an emulsifier selected from the group consisting of cationic and non-ionic emulsifiers.

Preferably, the compositions for topical use according to the present invention comprise:

- (i) from about 1 to about 10% by weight of trans-resveratrol;

- (ii) from about 2 to about 60% by weight of dimethyl isosorbide alone or in a mixture with another solvent; and
- (iii) from about 0.01 to about 10% by weight of an emulsifier selected from the group consisting of cationic and non-ionic emulsifiers.

Also preferably, the compositions for topical use according to the present invention comprise:

- (i) from about 2 to about 8% by weight of trans-resveratrol;
- (ii) from about 4 to about 60% by weight of dimethyl isosorbide alone or in a mixture with another solvent; and
- (iii) from about 0.01 to about 10% by weight of an emulsifier selected from the group consisting of cationic and non-ionic emulsifiers.

Preferably, the weight to weight of resveratrol to the solvent system, ranges as follows:

- a) for a composition comprising 1% resveratrol, there should be from 1 to 10% of solvent, more preferably from 3 to 7% and most preferably approximately 5%;
- b) for a composition comprising 5% resveratrol, there should be from 10 to 40% of solvent, more preferably from 20 to 30% and most preferably approximately 25%;
- c) for a composition comprising 10% resveratrol, there should be from 40 to 60% of solvent, more preferably from 45 to 55% and most preferably approximately 50%; and
- d) for a composition comprising 15% resveratrol, there should be from 60 to 90% of solvent, more preferably from 70 to 80% and most preferably approximately 75%.

It is known in the field that the amount of emulsifier required to form an emulsion depends on a number of factors including: emulsifier type, % dispersed phase, the nature of

phase to be emulsified, the desired droplet size and the nature and concentration of active ingredient.

These several factors render it difficult to give precise concentration ranges of emulsifier which are expected to form a stable emulsion. It is also known that a mixture of 2 or more emulsifiers of different type can optimize the stability of the emulsion. However, given the above and the experiments conducted, the inventors have determined that cationic and polymeric emulsifiers can form stable emulsions of resveratrol when used in a range from 0.1 to 10%, more preferably ranging from 0.2 to 5% by weight of the composition. Non-ionic emulsifiers can form stable emulsions of resveratrol when used in a range ranging from 1 to 15%, more preferably ranging from 2 to 10% by weight of the composition.

In one aspect of the present invention, there is provided the use of compositions for the treatment of psoriasis, acne and herpes simplex virus are presented as well as cosmetic compositions for wrinkle reduction.

In another aspect of the present invention, there is provided a process to make a composition according to present invention, comprises the following steps:

- (1) preparing a first mixture by solubilizing the resveratrol in a solvent system comprising dimethyl isosorbide;
- (2) preparing a second mixture made up of an aqueous phase by incorporating hydrophilic excipients together;
- (3) preparing a third mixture comprising an oil phase by incorporating hydrophobic excipients together with an emulsifier;
- (4) mixing the second and third mixtures together; and
- (5) adding the first mixture to the mixture obtained in step (4).

Preferably, the second mixture and the third mixture are each heated to approximately the same temperature to ensure that all hydrophobic and hydrophilic elements are well dissolved. Preferably, the temperature is selected from 70 to 80°C. Also preferably, once the second mixture and the third mixture are combined the resulting mixture is cooled down prior to the addition of the resveratrol containing mixture (the first

mixture). In addition, in a preferred embodiment, one or more steps of pH adjustments are also included to ensure that the resulting mixture is stable.

Detailed Description

Formulations containing resveratrol can either be water-in-oil or oil-in-water emulsions. They can also be solutions or gels. Resveratrol formulations can be used in transdermal systems or in other systems for topical delivery like ophthalmic, otic or nail delivery.

The compositions of the present invention are topical compositions containing a solubilized active ingredient in a stable emulsion. The active ingredient present in the topical compositions of the present invention is resveratrol (including trans-resveratrol, cis-resveratrol, cis-resveratrol glucoside and trans-resveratrol glucoside). In the preferred embodiments of the present invention, the active ingredient is trans-resveratrol. Trans-resveratrol, derived from synthetic and natural origin, is commercially available from several sources including Sochinaz SA and Orchid Pharmaceuticals. It is understood that other forms of resveratrol, including cis-resveratrol, cis-resveratrol glucoside and trans-resveratrol glucoside, can also be used in the compositions of the present invention. The amount of resveratrol present in the compositions of the present invention range from 0.01 to 15% by weight, and is preferably in an amount ranging from about 2 to about 8% by weight.

In one embodiment of the present invention, the compositions for topical use contain solubilized resveratrol in an emulsion, with one or more solvents, preferably dimethyl isosorbide and an emulsifier, preferably a cationic emulsifier.

Solvents which may be included in the topical compositions of the present invention include one or more of pharmaceutically acceptable solvents, such as, for example dimethyl isosorbide, polyethylene glycol 200 to 600, diethylene glycol monoethyl ether, ethanol, hexylene glycol and PEG-8 caprylic/capric glycerides. The total amount of solvent present in the compositions of the invention may be from 0.1% to about 90% weight percent.

Dimethyl isosorbide (known chemically as 1,4:3,6 dianhydro-2,5-di-o-methyl-D-glucitol), is available commercially from Croda under the trademark Arlasolve DMI. A

purified version commercialized under the trademark Super Refined Arlasolve DMI is also available. Dimethyl isosorbide is a unique solubilizer, emulsifier and emollient with unusual properties. It is practically non-toxic, water soluble, oil soluble, has a high boiling point and low freezing point. Dimethyl isosorbide is miscible with many organic solvents, pH stable, non-greasy, non-drying, non-irritating, colourless, practically odourless, inert and non-volatile. The amount of dimethyl isosorbide present in the compositions of the present invention range from about 1 to about 90% by weight of the composition, and is preferably present in the composition in the range from about 3 to about 50% by weight of the composition.

The use of dimethyl isosorbide increases the tolerability of the formulation in comparison with classic solvents.

In another embodiment, the solvent used is diethylene glycol monoethyl ether, and in yet another embodiment, the solvent used may be a mixture containing both dimethyl isosorbide and diethylene glycol monoethyl ether.

Emulsifiers which may be included in the topical compositions include any pharmaceutically or cosmetically acceptable emulsifier. Such emulsifiers include but are not limited to: fatty acid esters of polyethylene glycol, such as PEG-100 stearate; fatty acid esters of polyols, such as glyceryl stearate; polymeric emulsifiers, such as poloxamers; and cationic emulsifiers such as polyquaternium-37 and behentrimonium methosulfate. Preferably, the emulsifier is a cationic emulsifier, such as polyquaternium-37. Most preferably, the emulsifier is a polyquaternium-37.

The emulsions also contain two other types of compounds (in addition to the emulsifiers): hydrophilic excipients and hydrophobic excipients. Whether an excipient is hydrophobic or hydrophilic would be clear to a person skilled in the art.

The excipients (also referred to as ingredients) present in the compositions of the present invention include excipients commonly used in compositions directed at topical use such as dermatological compositions. Such ingredients include but are not limited to: antioxidants, moisturizers, thickeners, emollient, wetting agents, bases, preservatives and protective agents. These excipients are present in amounts which are used in conventional

topical compositions and, for example, preferably constitute from 0.01% to 20% relative to the total weight of the composition.

Emollients which may be included in the topical compositions of the present invention include any pharmaceutically acceptable emollient which include but are not limited to: mineral oils, oils of plant origins, oils of animal origins, synthetic oils, silicone oils and fluoro oils. Fatty alcohols, fatty acids and waxes can also be used as fatty substances. The amount of emollient present in the compositions of the invention may be from about 1.0% to about 90% by weight of the composition, and preferably up to 20%, and most preferably up to 10% by weight of the composition.

Moisturizers which may be included in the compositions according to the present invention include any pharmaceutically acceptable moisturizer, such as, for example, glycerin, sodium hyaluronate, or propylene glycol. Preferably, the moisturizer is glycerin. The amount of moisturizer present in the compositions of the invention may range from 0.1 to about 10% by weight of the total composition.

Thickeners which may be included in the topical compositions of the present invention include any pharmaceutically acceptable hydrophilic or lipophilic thickener. Such thickeners include but are not limited to: cetyl alcohol, stearyl alcohol, carbomers, natural gums and clays, poloxamers, and bentones. The thickeners may be present in the compositions of the invention in an amount ranging from about 0.1 to about 20% by weight of the total composition. A person skilled in the art will understand that, for example, a carbomer is generally present in amounts ranging from about 0.1 to about 0.5% by weight of the composition, while a cetyl alcohol is generally present in amounts ranging from about 3 to about 5% by weight of the composition and a poloxamer can be present in amounts ranging up to about 20% by weight of the composition.

Preservatives which may be included in the topical compositions of the present invention include any pharmaceutically or cosmetically acceptable preservatives. Such preservatives include but are not limited to, for example, methylparaben, propylparaben, caprylyl glycol, ethylhexylglycerin, imidurea. Preferably, the preservative is a combination of methylparaben and propylparaben. The preservatives present in the compositions of the

invention may be present in amounts ranging from about 0.05 to about 1% by weight of the composition.

Bases which may be included in the topical compositions of the present invention include any pharmaceutically acceptable base. Such bases include but are not limited to, for example, sodium hydroxide, triethanolamine and sodium lactate. Preferably, the base is triethanolamine. The amount of base present in the composition of the invention may range from about 0.1 to about 5 %, depending upon the strength of the base.

Other active agents which may be included in the topical compositions of the present invention include any pharmaceutically or cosmetically acceptable actives. Such active agents include, but are not limited to, for example, proteins or protein hydrolysates, amino acids, polyols, urea, allantoin, sugars and sugar derivatives, vitamins, plant extracts and hydroxyl acids. These other active agents may be present in amounts ranging from 0.01 to 20%.

The compositions according to the present invention were formulated according to conventional pharmaceutical techniques.

The compositions of the present invention presented excellent stability after 3 days when stored at 50°C. A person skilled in the art will understand that the stability is determined by the lack of phase separation and lack in change of texture and/or colour, two very critical parameters in assessing stability of topical products. The use of the word stable in the present description is meant to illustrate that the emulsion containing the active ingredient does not have major physical modifications (phase separation, change in viscosity, colour or odour) over time.

Process for Preparing Compositions

The process for preparing a composition according to the present invention comprises the following steps:

- 1) preparing a first mixture by solubilizing the resveratrol in a solvent system comprising dimethyl isosorbide;
- 2) preparing a second mixture made up of an aqueous phase by incorporating hydrophilic excipients together;

- 3) preparing a third mixture comprising an oil phase by incorporating hydrophobic excipients together with an emulsifier;
- 4) mixing the second and third mixtures together;
- 5) adding the first mixture to the mixture obtained in step (4).

Preferably, the second mixture and the third mixture are each heated to approximately the same temperature to ensure that all hydrophobic and hydrophilic elements are well dissolved. Preferably, the temperature is selected from 70 to 80°C. Also preferably, once the second mixture and the third mixture are combined the resulting mixture is allowed to cool prior to the addition of the emulsifier and consequently prior to the addition of the resveratrol containing mixture (the first mixture). Preferably, additional steps for adjusting the pH are included to ensure that the resulting mixture is stable. The inventors have noticed that the speed of the addition of the mixture containing resveratrol to the mixture of step (4) (above) has an effect on the quality of the stability that is desired and the quality of the emulsion. Consequently, the inventors have determined that it was preferable to add the first mixture at a rate which allows proper and thorough mixing within the mixture of step (4).

It is to be understood that while the invention has been described in conjunction with the preferred specific embodiments thereof, that the description above as well as the examples which follow are intended to illustrate and not limit the scope of the invention. Other aspects, advantages and modifications within the scope of the invention will be apparent to persons skilled in the art.

Examples

The following examples are illustrative of the applicability of the present invention and are not intended to limit its scope. Modifications and variations can be made therein without departing from the spirit and scope of the invention. Although any method and material whether similar or equivalent to those described herein can be used in the practice for testing the present invention, the preferred methods and materials as described.

All of the percentages given hereinabove and below are percentages by weight (i.e. w/w).

Example 1

The solubility (in % (g/100g)) of resveratrol in a number of solvents was studied. The solubility was assessed by visual inspection of the solutions prepared.

TABLE I - Solubility (in % (g/100g)) of resveratrol in a number of solvents

Solvent chemical name	Commercial name (supplier)	Solubility (mg/ml) by HPLC	Solubility % (g/100g) by visual determination
Diethylene glycol monoethyl ether*	Transcutol P	237.0 mg/ml	Between 15-20%
Dimethyl isosorbide**	Arlasolve DMI	196.5 mg/ml	~ 20%
PEG 8***	Carbowax 400	183.2 mg/ml	~ 20%

*Transcutol P density (25°C) = 0.988 g/ml

** Arlasolve DMI density (25°C) = 1.1635 g/ml

*** Carbowax 400 density (25°C) = 1.128 g/ml

Example 2*Stability in solution*

Several solutions of resveratrol in different solvents were stored at 40°C for 1 month and the visual appearance was evaluated. This accelerates the interaction, if any, between the solvent and the resveratrol.

No changes in visual appearance were observed for the three compositions listed above in Table I.

Example 3

The chemical stability of resveratrol was studied on a 10% w/v resveratrol solution in Arlasolve DMI after 1 month at 40°C.

TABLE II - Chemical stability of resveratrol on a 10% w/v resveratrol solution in Arlasolve DMI after 1 month at 40°C

TEST	Initial	1M 40°C/75%RH
Assay of resveratrol - HPLC	89.5 mg/ml	89.0 mg/ml
Cis-resveratrol and unknown - HPLC	Cis-resveratrol: not detected Unknowns: Not detected	Cis-resveratrol: 0.91% Unknowns: Not detected

Example 4

A composition according to the present invention containing 2.50% by weight resveratrol is disclosed in Table III.

TABLE III - Composition according to the present invention containing 2.50% resveratrol for use in the treatment of psoriasis

Ingredient	% wt
Trans-resveratrol	2.50
Dimethyl isosorbide	5.00
Diethylene glycol monoethyl ether, USP-NF/EP	7.50
Purified water, USP	63.75
Carbomer, NF	0.35
Glycerin 99%, USP	3.00
Methylparaben, NF	0.20
Glyceryl stearate, PEG-100 stearate	6.00
Cetyl esters, NF	3.00
Beeswax white, NF	1.00
Cetyl alcohol, NF	0.90
Stearyl alcohol, NF	0.90
Medium chain triglycerides, EP	3.00
Propylparaben, NF	0.05
Dimethicone, NF	2.50
Triethanolamine, NF	0.35
	100

The composition disclosed in Table III is an oil-in-water beige emulsion with 2.5% of solubilized resveratrol. The pH of this composition is around 7. This emulsion was stable after 3 days at 50°C. No phase separation was observed.

Example 5

The long term stability of the composition obtained in Example 4 was studied. The cream obtained from Example 4 was packaged in aluminum tubes and placed in a stability chamber at 40°C/75% relative humidity. The results for stability study are set out in Table IV below. The results indicate that the resveratrol in the composition of Example 4 was stable for 6 months at 40°C/75% relative humidity.

TABLE IV – Stability at 40°C/75% RH

TEST	Initial	1 month	3 months	6 months
Resveratrol assay	2.46% (w/v)	2.42%	2.32%	2.40%
Cis-resveratrol	Not detected	Not detected	0.29%	Not detected

Example 6

A GMP batch (of 50 kg) of the identical formulation as set out in Example 4 (above) was manufactured and placed in a complete International Conference on Harmonisation ("ICH") stability program. The results in Tables V and VI were obtained using with a validated HPLC method.

The process for the manufacture of this batch is set out below. The entire manufacturing process is done under sodium lamps to prevent the isomerization of the trans-resveratrol.

Step 1: The dimethyl isosorbide and the diethylene glycol monoethyl ether are added in a stainless steel container and mixed at a speed of 40 +/- 10 rpm for a minimum of 5 minutes.

Step 2: The resveratrol is sprinkled over the solvent solution of **Step 1** under constant mixing until a clear solution is obtained. The stainless steel container is covered after the resveratrol addition.

Step 3: Purified water is poured in a Coulter tank and heated at 73-75°C.

Step 4: Carbomer 940 is added to the water of **Step 3** under medium speed agitation with a Leeson mixer. The suspension is mixed until the Carbomer is hydrated.

Step 5: Glycerin and Methylparaben are added to the mix of **Step 4** and the solution is stirred until complete dissolution.

Step 6: The following excipients are added in a stainless steel container and heated at 73-75°C under mixing: Glyceryl stearate & PEG-100 stearate, Cetyl ester wax, White wax, Cetyl alcohol, Stearyl alcohol, Medium chain triglycerides, Propylparaben, and Dimethicone. Mixing is done at moderate speed until everything is melted and mixed uniformly.

Step 7: The phase of Step 6 is slowly added to the phase of Step 5 under homogenization with a homogenizer.

Step 8: The homogenization is continued for 20 minutes after the incorporation of the oil phase.

Step 9: The mix of Step 8 is cooled down to 40 +/- 2°C with mixing at a reduced speed.

Step 10: The phase of Step 2 is slowly added to the emulsion of Step 9 under agitation. The pH is measured and noted in the batch record.

Step 11: Triethanolamine and Purified water are mixed in a small container and added in aliquot to the emulsion of Step 10 until a pH of 7.0 +/- 0.1 is obtained.

Step 12: The emulsion of Step 11 is cooled down to 25 +/- 2°C. The pH is measured at the top and bottom of the tank and the viscosity is taken on a sample.

The bulk cream was subsequently packaged in aluminium tubes.

TABLE V - Stability at 40°C/75% RH

TEST	Initial	1 month	3 months
Resveratrol assay	2.58%	2.59%	2.54%
Cis-resveratrol	0.04%	0.02%	0.03%
Total Unknowns	0.22%	0.35%	0.37%

TABLE VI - Stability at 25°C/60% RH

TEST	Initial	3 months
Resveratrol assay	2.58%	2.56%
Cis-resveratrol	0.04%	0.02%
Total Unknowns	0.22%	0.07%

Example 7 - Composition for the treatment of acne

This is a silky off-white oil in water emulsion-gel containing 2.0% of solubilized resveratrol. The pH is slightly acidic due to the presence of a cationic emulsifier. This composition was found to be stable after 3 days stored at 50°C. No phase separation was observed.

TABLE VII - Composition according to the present invention containing 2% resveratrol

Oil in water emulsion-gel		
Commercial Name	INCI Name	% wt
Water	Aqua	80.58
Ultrageel 300	Polyquaternium-37	2.00
Methylparaben	Methylparaben	0.32
Polypore E200	Allyl Methacrylates Crosspolymer	1.00
Propylparaben	Propylparaben	0.08
Resveratrol	Resveratrol	2.00
Arlasolve DMI	Dimethyl Isosorbide	10.00

Myritol 318	Caprylic Capric Triglycerides	4.00
Triethanolamine	Triethanolamine	0.02
		100.00

TABLE VIII - Stability results for the composition of Example 7 at 25°C in glass bottle

Stability results @ 25°C in glass bottle					
	Texture	Color	Odor	pH	Viscosity
Initial	Silky gel	Shiny off white	Specific	5.05	> 50000 cps
After 72 hrs	Silky gel	Shiny off white	Specific	5.05	> 50000 cps

TABLE IX - Stability results for the composition of Example 7 @ 50°C in glass bottle

Stability results @ 50°C in glass bottle					
	Texture	Color	Odor	pH	Viscosity
Initial	Silky gel	Shiny off white	Specific	5.05	> 50000 cps
After 72 hrs	Silky gel	Shiny off white	Specific	4.37	> 50000 cps

Example 8 - Composition for the treatment of Herpes simplex virus (HSV)

The composition according to Example 8 is set out in Table X below. The composition is a shiny-yellowish oil in water emulsion-gel containing 8% of solubilized resveratrol. This emulsion-gel has a very low viscosity. This composition is stable after 3 days at room temperature (25°C) and at 50°C. No phase separation was observed.

TABLE X - Composition according to the present invention for use in the treatment of HSV

Oil in water emulsion-gel		
Commercial Name	INCI Name	% wt
Surfhose SE Cosme C-1803	Sucrose Tristearate	3.50
Arlasolve DMI	Dimethyl Isosorbide	40.00
Resveratrol	Resveratrol	8.00
Beeswax White NF	Cera Alba	3.00
Propylparaben	Propylparaben	0.05
Water	Aqua	38.95
Glycerin	Glycerin	4.00
Xanthan Gum	Xanthan Gum	0.40

Natrosol 250HHR	Hydroxyethylcellulose	0.90
Magnesium Sulfate	Magnesium Sulfate	1.00
Methylparaben	Methylparaben	0.20
		100.00

TABLE XI - Stability results for the composition of Example 8 @ 25°C in glass bottle

Stability results @ 25°C in glass bottle					
	Texture	Color	Odor	pH	Viscosity
Initial	Silky cream	Shiny off white	Specific	NA	> 50000 cps
After 72 hrs	Silky cream	Shiny off white	Specific	NA	> 50000 cps

TABLE XII - Stability results for the composition of Example 8 @ 50°C in glass bottle

Stability results @ 50°C in glass bottle					
	Texture	Color	Odor	pH	Viscosity
Initial	Silky cream	Shiny off white	Specific	NA	> 50000 cps
After 72 hrs	Silky cream	Shiny off white	Specific	NA	> 50000 cps

Example 9 - Composition containing a cationic emulsifier (oil-in-water emulsion)

TABLE XIII - Composition according to the present invention containing 2% resveratrol and a cationic emulsifier

Ingredient	% wt
Trans-resveratrol	2.00
Dimethyl isosorbide	6.00
Polyethylene glycol 400, NF	6.00
Isopropyl palmitate	3.25
Dimethicone, NF	3.75
Medium chain triglycerides, EP	3.00
Cetyl alcohol, NF	3.75
Behenyl TMS (Behentrimonium methosulfate and cetearyl alcohol)	4.00
Vivapur MCG (microcrystalline cellulose & CMC sodium), NF	1.0
Glycerin, USP	3.0
Methylparaben, NF	0.20
Propylparaben, NF	0.05
Purified water, USP	64.00
	100

Example 10 - Composition for use as an anti-wrinkle cream**TABLE XIV - Composition according to the present invention for use as an anti-wrinkle cream containing 2.50% resveratrol**

Ingredient	% wt
Trans-resveratrol	2.50
Purified water, USP	70.48
Polyquaternium-37 (Synthalen CR)	2.00
Caprylic/Capric Triglyceride (and) Spilanthes Acmella Flower Extract (Gatuline intense)	3.00
Caprylyl glycol (Lexguard O)	0.90
Ethylhexylglycerin (Sensiva SC-50)	0.50
Dimethyl isosorbide	5.00
Diethylene glycol monoethyl ether, USP-NF/EP	7.50
Sodium hyaluronate (HyaCare)	0.10
Purified water, USP	8.00
Triethanolamine	0.02
	100

Example 11

Table XV discloses the components, and quantity of components, of a composition according to the present invention containing 2.50% by weight of resveratrol. This composition is a silky shiny off-white cream. This composition was found to be stable after 3 days at room temperature (25°C) and 50°C. No phase separation was observed (see Tables XVI and XVII).

TABLE XV - Composition according to the present invention containing 2.50% resveratrol

Oil in Water Emulsion		
Commercial Name	INCI Name	% wt
Arlacel 165	Glyceryl Stearate, PEG-100 Stearate	6.00
Crodamol SS	Cetyl Esters	3.00
Beeswax White NF	Cera Alba	1.00
Crodacol C-95	Cetyl Alcohol	0.90
Crodacol S-95	Stearyl Alcohol	0.90
Myritol 318	Caprylic Capric Triglycerides	3.00
Dow corning Q7-9120 100 cst	Dimethicone	2.50
Propylparaben	Propylparaben	0.05

Water	Aqua	63.75
Glycerine	Glycerin	3.00
Carbopol 940	Carbomer	0.35
Methylparaben	Methylparaben	0.20
Triethanolamine 99%	Triethanolamine	0.35
Arlasolve DMI	Dimethyl Isosorbide	12.50
Resveratrol	Resveratrol	2.50
		100.00

TABLE XVI - Stability results for the composition of Example 11 @ 25°C in glass bottle

Stability results @ 25°C in glass bottle					
	Texture	Color	Odor	pH	Viscosity
Initial	Silky cream	Shiny off white	Specific	6.56	> 50000 cps
After 72 hrs	Silky cream	Shiny off white	Specific	6.50	> 50000 cps

TABLE XVII - Stability results for the composition of Example 11 @ 50°C in glass bottle

Stability results @ 50°C in glass bottle					
	Texture	Color	Odor	pH	Viscosity
Initial	Silky cream	Shiny off white	Specific	6.56	> 50000 cps
After 72 hrs	Silky cream	Shiny off white	Specific	6.45	> 50000 cps

Example 12

Table XVIII discloses the components, and quantity of components, of a composition according to the present invention containing 2.50% by weight of resveratrol. This composition is a silky shiny off-white cream. This composition was found to be stable after 3 days at room temperature (25°C) and 50°C. No phase separation was observed (see Tables XIX and XX).

TABLE XVIII - Composition according to the present invention containing 2.50% resveratrol

Oil in water emulsion with a cationic emulsifier		
Commercial Name	INCI	% wt
Water	Aqua	77.22
Methylparaben	Methylparaben	0.20
Butylene glycol	Butylene glycol	3.00
Incroquat Behenyl TMS	Behentrimonium Methosulfate, Cetearyl alcohol	2.50
Propylparaben	Propylparaben	0.08
Dow corning Q7-9120 100CST	Dimethicone	2.00
Arlasolve DMI	Dimethyl Isosorbide	12.50
Resveratrol	Resveratrol	2.50
		100.00

TABLE XIX - Stability results for the composition of Example 12 @ 25°C in glass bottle

Stability results @ 25°C in glass bottle					
	Texture	Color	Odor	pH	Viscosity
Initial	Silky cream	Shiny off white	Specific	3.96	> 50000 cps
After 72 hrs	Silky cream	Shiny off white	Specific	3.96	> 50000 cps

TABLE XX - Stability results for the composition of Example 12 @ 50°C in glass bottle

Stability results @ 50°C in glass bottle					
	Texture	Color	Odor	pH	Viscosity
Initial	Silky cream	Shiny off white	Specific	3.96	> 50000 cps
After 72 hrs	Silky cream	Shiny off white	Specific	3.96	> 50000 cps

Example 13

Table XXI discloses the components, and quantity of components, of a composition according to the present invention containing 8% by weight of resveratrol. This composition is a silky shiny off-white cream. This composition was found to be stable after 3 days at room temperature (25°C). No phase separation was observed (see Table XXII).

TABLE XXI - Composition according to the present invention containing 8 % resveratrol

PEG ointment		
Commercial Name	INCI	% wt
Resveratrol	Resveratrol	8.00
Arlasolve DMI	Dimethyl Isosorbide	40.00
Dow corning Q7-9120 100CST	Dimethicone	16.00
Carbowax PEG 3350	PEG-75	35.95
Propylparaben	Propylparaben	0.05
		100.00

TABLE XXII - Stability results for the composition of Example 12 @ 25° in glass bottle

Stability results @ 25°C in glass bottle					
	Texture	Color	Odor	pH	Viscosity
<i>Initial</i>	Silky cream	Shiny off white	Specific	NA	> 50000 cps
<i>After 72 hrs</i>	Silky cream	Shiny off white	Specific	NA	> 50000 cps

What is claimed:

1. A composition for topical use comprising solubilized resveratrol in a stable emulsion in a solvent system, the solvent system comprising dimethyl isosorbide, and wherein the composition does not cause irritation to the skin.
2. The composition according to claim 1, wherein the resveratrol is present in concentrations ranging up to 15% by weight of the composition.
3. The composition according to claim 2, wherein the resveratrol is present in concentrations ranging up to 8% by weight of the composition.
4. The composition according to any one of claims 1 to 3, wherein the solvent system further comprises a second solvent.
5. The composition according to claim 4, wherein the second solvent is diethylene glycol monoethyl ether.
6. The composition according to any one of claims 1 to 5, further comprising an emulsifier.
7. The composition according to claim 6, wherein the emulsifier is selected from the group consisting of: non-ionic emulsifier, a cationic emulsifier and polymer.
8. The composition according to claim 6, wherein the emulsifier is selected from the group consisting of: fatty acid esters of polyethylene glycol, such as PEG-100 stearate; fatty acid esters of polyols, such as glyceryl stearate; polymeric emulsifiers, such as poloxamers; cationic emulsifiers, such as polyquaternium-37 and behentrimonium methosulfate; and combinations thereof.
9. The composition according to any one of claims 1 to 8, wherein the composition is in the form of an oil-in-water emulsion, water-in-oil emulsion, gel, ointments or solution.
10. A composition for topical use comprising solubilized resveratrol in a stable emulsion comprising an emulsifier in the presence of a solvent system, the solvent system consisting of dimethyl isosorbide.

11. A composition for topical use comprising solubilized resveratrol in a stable emulsion comprising an emulsifier in the presence of a solvent system, the solvent system consisting of diethylene glycol monoethyl ether.
12. A composition for topical use comprising solubilized resveratrol in a stable emulsion comprising an emulsifier in the presence of a solvent system, the solvent system consisting of dimethyl isosorbide and diethylene glycol monoethyl ether.
13. The composition according to any one of claims 10 to 12, wherein the emulsifier is selected from the group consisting of: fatty acid esters of polyethylene glycol, such as PEG-100 stearate; fatty acid esters of polyols, such as glyceryl stearate; polymeric emulsifiers, such as poloxamers; cationic emulsifiers, such as polyquaternium-37 and behentrimonium methosulfate; and combinations thereof.
14. The composition according to any one of claims 1 to 13, wherein the composition further comprises one or more of the following excipients: antioxidants, moisturizers, thickeners, emollients, wetting agents, bases, preservatives and protective agents.
15. The composition according to any one of claims 1 to 14, wherein the composition further comprises emollients selected from the group consisting of: mineral oils, oils of plant origins, oils of animal origins, synthetic oils, silicone oils, fluoro oils, fatty alcohols, fatty acids and waxes.
16. The composition according to any one of claims 1 to 15, wherein the composition further comprises moisturizers selected from the group consisting of: glycerin, sodium hyaluronate, and propylene glycol.
17. The composition according to any one of claims 1 to 16, wherein the composition further comprises thickeners selected from the group consisting of: pharmaceutically acceptable hydrophilic or lipophilic thickener, such as cetyl alcohol, stearyl alcohol, carbomers, natural gums and clays, poloxamers, and bentones.

18. The composition according to any one of claims 1 to 17, wherein the composition further comprises preservatives selected from the group consisting of: methylparaben, propylparaben, caprylyl glycol, ethylhexylglycerin, and imidurea.

19. The composition according to any one of claims 1 to 18, wherein the composition further comprises bases selected from the group consisting of: pharmaceutically acceptable base, such as sodium hydroxide, triethanolamine and sodium lactate.

20. The composition according to any one of claims 1 to 19, wherein the composition comprises an additional active agent, in addition to resveratrol, wherein the additional active agent selected from the group consisting of: proteins or protein hydrolysates, amino acids, polyols, urea, allantoin, sugars and sugar derivatives, vitamins, plant extracts and hydroxyl acids.

21. The composition according to claim 20, wherein the other active agents are present in amounts ranging from 0.01 to 20%.

22. A composition for topical administration comprising:

from about 0.01 to about 15% by weight of solubilized trans-resveratrol;

from about 1.0 to about 90% by weight of dimethyl isosorbide, alone or in a mixture with another solvent; and

from about 0.01 to about 10% by weight of an emulsifier selected from the group consisting of cationic and non-ionic emulsifiers.

23. A composition for topical administration comprising:

from about 1 to about 10 % by weight of solubilized trans-resveratrol;

from about 2 to about 60% by weight of dimethyl isosorbide alone or in a mixture with another solvent; and

from about 0.01 to about 10% by weight of an emulsifier selected from the group consisting of cationic and non-ionic emulsifiers.

24. A composition for topical administration comprising:

from about 2 to about 8 % by weight of solubilized trans-resveratrol;

from about 4 to about 60 % by weight of dimethyl isosorbide alone or in a mixture with another solvent; and

from about 0.01 to about 10% by weight of an emulsifier selected from the group consisting of cationic and non-ionic emulsifiers.

25. The composition according to any one of claims 1 to 24, for use in the treatment of psoriasis.

26. The composition according to any one of claims 1 to 24, for use in the treatment of acne.

27. The composition according to any one of claims 1 to 24, for use in the treatment of herpes simplex virus.

28. The composition according to any one of claims 1 to 24, for use in wrinkle reduction.

29. A process to prepare a composition according to any one of claims 1 to 28, comprising the following steps:

- (1) preparing a first mixture by solubilizing the resveratrol in a solvent system comprising dimethyl isosorbide;
- (2) preparing a second mixture made up of an aqueous phase by incorporating hydrophilic excipients together;
- (3) preparing a third mixture comprising an oil phase by incorporating hydrophobic excipients together with an emulsifier;
- (4) mixing the second and third mixtures together; and
- (5) adding the first mixture to the mixture obtained in step (4).

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA2009/000546

A. CLASSIFICATION OF SUBJECT MATTER

IPC: **A61K 31/05** (2006.01) , **A61K 47/22** (2006.01) , **A61K 8/34** (2006.01) , **A61K 8/49** (2006.01) ,
A61K 9/06 (2006.01) , **A61K 9/08** (2006.01) (more IPCs on the last page)
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 31/05 (2006.01) , **A61K 47/22** (2006.01) , **A61K 8/34** (2006.01) , **A61K 8/49** (2006.01) , **A61K 9/06** (2006.01) ,
A61K 9/08 (2006.01) , **A61K 9/10** (2006.01) , **A61K 9/107** (2006.01) , **A61P 17/06** (2006.01) , **A61P 17/10** (2006.01) ,
A61P 31/12 (2006.01) , **A61Q 19/08** (2006.01)

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

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

EPOQUE, Canadian Patent Database, Delphion, PubMed, Espacenet (search terms: resveratrol, dimethyl isosorbide, ethyl carbitol, dioxitol, carbitol, diethylene glycol monoethyl ether, Arlasolve)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 1,726,292 A1 (de la Torre, F., et al.) 29 November 2006 (29-11-2006) para [0010]- [0013], [0017], [0022]	1-4, 6 -10, 14, 15, 16, 18
X	US 2002/0173472 A1(Pezzuto, J. M., et al.) 21 November 2002 (21-11-2002) Abstract, claims 1, 11, 19, 28, 29, 67	11, 25, 28
Y	para [0046]-[0048], [0050]-[0057], Example 1, claims 64-67	4-9, 12-18, 20-24
Y	EP 1,138,323 A2 (Pelliccia, M. T., et al.) 04 October 2001 (04-10-2001) Abstract, claims 2- 8	26
Y	WO 00/12534 A2(Dochierty, J.) 09 March 2000 (09-03-2000) Abstract, p. 5, line 33 - p. 7, line 30	27
A	CA 2,298,464 (Burghart, W, et al.) 28 January 1999 (28-01-1999) Abstract, claim 1	1-29
A	CA 2,425,218 (Jacobs, M., et al.) 18 April 2002 (18-04-2002) claim 8	1-29

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

☒ See patent family annex.

* Special categories of cited documents :	"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
"A" document defining the general state of the art which is not considered to be of particular relevance	"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
"E" earlier application or patent but published on or after the international filing date	"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
"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)	"&" document member of the same patent family
"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	

Date of the actual completion of the international search

2 July 2009 (02-07-2009)

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Gatineau, Quebec K1A 0C9
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Authorized officer

Cristina Belyea 819- 934-6739

INTERNATIONAL SEARCH REPORTInternational application No.
PCT/CA2009/000546**Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of the first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons :

1. ☐ Claim Nos. :
because they relate to subject matter not required to be searched by this Authority, namely :
2. ☐ Claim Nos. :
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically :
3. ☐ Claim Nos. :
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows :

Group A: Claims 1-10, 12-21 (in part), 22-24, 25-29 (in part) - are directed to a composition comprising resveratrol in a stable emulsion in a solvent system, wherein the solvent system comprises dimethyl isosorbide, the use of this composition in the treatment of psoriasis, acne, herpes simplex virus and to reduce wrinkles; and

Group B: Claims 11, 12-21 (in part), 25-29 (in part) - are directed to a composition comprising resveratrol in a stable emulsion in a solvent system, wherein the solvent system comprises diethylene glycol monoethyl ether, the use of this composition in the treatment of psoriasis, acne, herpes simplex virus and to reduce wrinkles .

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☒ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claim Nos. :
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim Nos. :

Remark on Protest ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/CA2009/000546

Patent Document Cited in Search Report	Publication Date	Patent Family Member(s)	Publication Date
EP 1726292A1	29-11-2006	AU 2006250994A1	30-11-2006
		CA 2608031A1	30-11-2006
		CN 101170989A	30-04-2008
		JP 2008542251T	27-11-2008
		MX 2007014754A	12-02-2008
		US 2009082473A1	26-03-2009
		WO 2006125981A1	30-11-2006
US 2002173472A1	21-11-2002	AT 323473T	15-05-2006
		AU 8842098A	29-07-1999
		CA 2389167A1	03-05-2001
		CA 2389167C	18-03-2008
		DE 60027463D1	24-05-2006
		DE 60027463T2	30-11-2006
		DK 1239849T3	21-08-2006
		EP 1239849A2	18-09-2002
		EP 1239849B1	19-04-2006
		ES 2261274T3	16-11-2006
		PT 1239849E	31-07-2006
		US 6008260A	28-12-1999
		US 6414037B1	02-07-2002
		WO 0130336A2	03-05-2001
		WO 0130336A3	27-12-2001
		WO 0130336A9	27-12-2002
		WO 0130336B1	24-01-2002
EP 1138323A2	04-10-2001	EP 1138323A3	24-10-2001
		IT 1318425B1	25-08-2003
		IT MI20000630A1	24-09-2001
		IT MI20000630D0	24-03-2000
		US 2001056071A1	27-12-2001
WO 0012534A2	09-03-2000	AU 746756B2	02-05-2002
		AU 5576099A	21-03-2000
		CA 2342582A1	09-03-2000
		US 6197834B1	06-03-2001
		US 6355692B2	12-03-2002
		US 7037945B2	02-05-2006
		US 2001020043A1	06-09-2001
		US 2006035984A1	16-02-2006
		WO 0012534A3	08-06-2000
CA 2298464A1	28-01-1999	AT 234101T	15-03-2003
		AU 736539B2	02-08-2001
		AU 8198598A	10-02-1999
		DE 59807484D1	17-04-2003
		EP 1009410A1	21-06-2000
		EP 1009410B1	12-03-2003
		ES 2196574T3	16-12-2003
		US 6306843B1	23-10-2001
		WO 9903474A1	28-01-1999
CA 2425218A1	18-04-2002	AT 401875T	15-08-2008
		AU 9678501A	22-04-2002
		AU 2001296785B2	16-03-2006
		AU 2003301817A1	07-06-2004
		AU 2003301817B2	20-11-2008
		BG 107720A	30-01-2004
		BR 0114813A	25-01-2005
		CA 2503719A1	21-05-2004
		CN 1468096A	14-01-2004

INTERNATIONAL SEARCH REPORTInternational application No.
PCT/CA2009/000546

BR	0114813A	25-01-2005
CA	2503719A1	21-05-2004
CN	1468096A	14-01-2004
CN	1708295A	14-12-2005
CN	100423717C	08-10-2008
CZ	20030966A3	17-09-2003
DE	60322412D1	04-09-2008
EA	005572B1	28-04-2005
EP	1324755A1	09-07-2003
EP	1562572A2	17-08-2005
EP	1562572B1	23-07-2008
ES	2310687T3	16-01-2009
HK	1079446A1	06-02-2009
HU	0302478A2	28-11-2003
HU	0302478A3	30-05-2005
IL	155263D0	23-11-2003
JP	2004510816T	08-04-2004
JP	2006507300T	02-03-2006
MX	PA03003150A	14-07-2003
MX	PA05004697A	18-10-2005
NO	20031648A	04-06-2003
NO	20031648D0	10-04-2003
NZ	525166A	27-10-2006
NZ	539778A	30-11-2007
PL	361134A1	20-09-2004
SK	4402003A3	11-09-2003
UA	75094C2	15-08-2003
US	6489363B2	03-12-2002
US	6919378B2	19-07-2005
US	2002099097A1	25-07-2002
US	2003125391A1	03-07-2003
WO	0230413A1	18-04-2002
WO	2004041245A2	21-05-2004
WO	2004041245A3	15-07-2004
WO	2004041245B1	14-10-2004
ZA	200302665A	05-07-2004

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A61P 31/12 (2006.01) , *A61Q 19/08* (2006.01)