A method for increasing the stability of an active pharmaceutical ingredient.

Title: NOVEL FORMULATIONS FOR DERMAL, TRANSDERMAL AND MUCOSAL USE

Abstract: A dermal, transdermal and/or mucosal formulation comprising an active pharmaceutical ingredient, a pharmaceutically acceptable solvent, and an anti-solvent, wherein the active pharmaceutical ingredient is soluble in the solvent in the absence of the anti-solvent, and wherein the active pharmaceutical ingredient is in the solid state in the solvent in the presence of the anti-solvent. A method for increasing the stability of an active pharmaceutical ingredient.
Technical field

[0001] This description, claims and examples generally relate to novel formulations for dermal, transdermal and/or mucosal application, offering improved stability during storage with maintained, good penetration after application.

Background

[0002] There are several different routes for delivering an active pharmaceutical ingredient (API) to a patient in need thereof. These can be divided into oral (including gastric, enteric, and colonic), mucosal (buccal, sublingual, nasal, ophthalmic, vaginal, urethral and anal), pulmonary, transdermal, and injectable (including intravenous, subcutaneous, intramuscular, intraepidural, intracranial, also including implants, inserts, ports and pumps for delivery of an API).

[0003] When choosing between different routes of administration, one needs to consider inter alia the properties of the API, its metabolism, intended dosage and dose frequency, and if the drug is to be taken by the patient themselves or administered by a nurse or physician. The present description, claims and examples relates mainly to dermal, transdermal and/or mucosal formulations, which in turn can be subdivided into topical and systemic, depending on whether the API exerts its effect locally, at the site of application, or systemically.

[0004] Notably, this description, claims and examples also relate to dermal, transdermal and/or mucosal formulations which may have either a local, i.e. topical effect, or a systemic effect. Dermal, transdermal and/or mucosal formulations in general offer many advantages, such as the possibility of easy and safe self-administration, the avoidance or delay of first-pass metabolism, and the possibility of local, targeted administration, in particular in dermatological indications.
Dermal, as well as transdermal formulations include dermatological formulations, i.e. formulations intended for the alleviation, treatment or prevention of diseases of the skin. For the purpose of this description, also cosmetic formulations are included herein, and defined as formulations intended to alleviate, treat or prevent conditions of the skin, which conditions may, or may not, be considered diseases depending on their severity.

Most dermatological formulations are designed to deliver as much as possible of the API to, into and through the skin. There are mainly two routes for a drug to penetrate the skin, either via the intercellular route, i.e. between the cells, or via the transcellular route, i.e. through the cells. It is generally held that the transcellular route is the main pathway for polar substances. The skin is however an effective barrier, developed during evolution to regulate the inward and outward passage of water and electrolytes, and to protect the body from toxic substances. Most of the barrier function is provided by the stratum corneum, the top layer of the epidermis which mainly consists of flat, dead skin cells.

Achieving good penetration is a challenging task, considering that the stratum corneum effectively limits the rate of penetration. Dermatological formulations must therefore be designed in such a way that maximum penetration is achieved. It is generally understood that a drug needs to be presented in the dissolved state, chemically active, in order to maximize penetration.

For mucosal formulations, achieving good penetration is easier, but the mechanisms of intercellular and transcellular transport apply also here.

In addition to penetration, also stability needs to be considered. The stability of a drug, either of the API itself, or the entire formulation, is influenced by many factors. Notably, many APIs are not chemically stable in solution, which makes formulations where the drug is in solution unsuitable. Non-limiting examples of reactions that will compromise the function of the drug include hydrolysis, esterification, dimerization, conjugation, reduction and oxidation. These stability problems explain, at least in part, the popularity of dry, oral formations, such as compressed tablets, capsules and the like.
[0010] The stability of the API in a dermal, dermatological and/or mucosal formulation is of great importance. Stability problems involve the loss of efficacy, the accumulation of potentially toxic degradation products, unacceptable changes of the product appearance, such as color changes, stratification, turbidity etc. Almost regardless of the nature of the stability problem, two main approaches remain. The first, restricting the shelf life of the product, has economical and practical consequences, influencing the price and popularity of the product. In cases where the shelf-life is very short, products need to be discarded, either by the distributor, retailer, or the end-user. The second approach, to tailor the formulation e.g. by adding stabilizers and other excipients, requires considerable skill in order not to compromise other properties of the API.

[0011] Ultimately, if the API is not stable, an otherwise efficient and clinically relevant API can perhaps not be used at all. Thus, there is a need for formulations where the API has an improved stability without compromising other properties, such as the penetration.

[0012] US 5,145,685 (Dow Corning; Walter J. Carmody) describes a method of treating skin disorders, such as acne, by topically applying to the infected area a mixture of an antimicrobial agent and a volatile low viscosity organosilicon compound. The mixture is entrapped within and dispersed uniformly throughout discrete particles of a hydrophobic macroporous highly cross linked polymer. This patent does not describe dissolution of the active pharmaceutical ingredient upon evaporation of a solvent.

[0013] US 5,958,379 (Mika Pharma; Juergen Regenold, Carl Artmann) discloses a dermal, transdermal and/or mucosal formulation containing an easily vaporizable organic solvent, which formulation can be sprayed on the body and which comprises an active substance. The concentration of the active substance increases upon application on the body when the organic solvent vaporizes.

[0014] Several patent applications teach the possibility of increasing penetration of an active pharmaceutical ingredient through skin by evaporation of solvents. For example WO 2007070695 (Zars Inc, Zhang Jie et al.) concerns adhesive
solidifying formulations, methods of drug delivery, and solidified layers for dermal delivery of a drug. The formulation can include a drug, a solvent vehicle, and a solidifying agent. The solvent vehicle can include a volatile solvent system comprising at least one volatile solvent, and a non-volatile solvent system comprising at least one non-volatile solvent, wherein at least one non-volatile solvent is a flux-enabling non-volatile solvent(s) capable of facilitating the delivery of the drug at therapeutically effective rates over a sustained period of time. The formulation can have a viscosity suitable for application to a skin surface prior to evaporation of the volatile solvents system. When applied to the skin, the formulation can form a solidified layer after at least a portion of the volatile solvent system is evaporated.

[0015] WO 2009017767 (Zars Pharma, Sanjay Sharma et al.) discloses adhesive solidifying formulations containing a drug, e.g. minoxidil, a solvent vehicle, and a solidifying agent as disclosed in the above WO 2007070695.

[0016] WO2007070679 (Zars Inc., Zhang Jie et al.) concerns solidifying formulations for dermal delivery of a drug for treating pain, such as musculoskeletal pain, inflammation, joint pain, or neuropathic pain. The formulation can include a drug selected from certain drug classes, a solvent vehicle, and a solidifying agent. The solvent vehicle can include a volatile solvent system comprising at least one volatile solvent, and a non-volatile solvent system comprising at least one non-volatile solvent, wherein the evaporation of at least some of the volatile solvent converts the formulation on the skin into a solidified layer and the non-volatile solvent system is capable of facilitating the topical delivery of the drug(s) at therapeutically effective rates over a sustained period of time.

Definitions

[0018] Before the present invention is described, it is to be understood that the terminology employed herein is used for the purpose of describing particular embodiments only and is not intended to be limiting, since the scope of the present invention will be limited only by the appended claims and equivalents thereof.

[0019] It must be noted that, as used in this specification and the appended claims, the singular forms "a," "an," and "the" include plural referents unless the context clearly dictates otherwise. Also, the term "about" is used to indicate a deviation of at least +/- 2% of the given value, preferably +/- 5%, and most preferably +/- 10% of the numeric values, where applicable. Percentages are given as weight/weight, unless otherwise indicated.

[0020] In addition to the above, the following terms will be used:

[0021] The term "soluble" refers the ability of the solvent to dissolve an amount of the active pharmaceutical ingredient that is relevant for its pharmacological effect. To illustrate this definition, which is clear to a person skilled in the art, one can look at acetylsalicylic acid (ASA), where frequently a dose of 500 mg is accommodated into one tablet or capsule. In order to replace a solid formulation with a liquid or semi-liquid formulation of about 5 to 10 ml, the solubility of ASA in the solvent used needs to be at least in the range of about 50 to 100 mg/ml. Similarly, a steroid drug such as fludrocortisone is supplied in tablets containing 0.1 mg of the active ingredient. Here, in order to replace a solid formulation of fludrocortisone with a liquid or semi-liquid formulation of about 5 to 10 ml, it will be sufficient if a solubility of fludrocortisone in the range of about 0.01 to about to 0.02 mg/ml is achieved in the solvent.

[0022] The terms "stable" and "stability" are used here in relation to the shelf-life of a pharmaceutical product, and are related to the physical change, degradation or chemical decomposition of active pharmaceutical ingredients, which limits the shelf-life of a product. Each active pharmaceutical ingredient has its intrinsic stability, its degradation pathways and degradation products, in part depending on
the formulation of which it is part, and the storage conditions. The major mechanisms of chemical degradation include oxidation, hydrolysis / dehydration, isomerization / epimerization, decarboxylation, dimerization / polymerization, photolysis and rearrangements. If a product is termed to be "stable" it means in this context that it can be stored for a prescribed time without any of these mechanisms advancing to the extent that compromises product efficacy and safety.

[0023] The skilled person is well familiar with the problems of stability, and recognizes the relative nature of this term, as well as the significant advantages of increasing the stability of a product.

[0024] The expression "substantially in solid state in the formulation" defines that the active pharmaceutical ingredient is present in solid state to a major part, or to an extent which significantly increases its stability during storage. Preferably at least 50% of the API in the formulation is in the solid state during storage at the prescribed storage temperature of the particular formulation in question. In practice, storage temperatures in the interval of 2 - 25°C are used for pharmaceutical preparations, wherein the lower part of the interval is prescribed for sensitive APIs and/or formulations with stability problems.

[0025] In the present formulations, the API is preferably in the solid state at a temperature in the above interval, depending on the type of product and API in question, to an extent of at least 50%, preferably at least 60%, more preferably at least 70%, more preferably at least 80%, more preferably at least 90%.

[0026] The terms "solvent" and "solvent system" define one component of the formulation, the liquid or semi-solid phase that contains the API. It is included in this definition, that the solvent and/or solvent system needs to be compatible with the API as well as with the anti-solvent.

[0027] The term "anti-solvent" is used to define a substance, which when present in the formulation, forces the API into the solid state.
Similarly, it is included in this definition that the "anti-solvent" needs to be compatible with the API and with the solvent and/or solvent system in that sense that no unwanted interactions, degradation or chemical reactions occur between the components.

The term "skin" is used in its common, physiological meaning to denote the largest organ of the mammal body, and it is here intended to include the skin of a human or mammal body, including the lips, palms, soles, and lips; whereas the hair and nails are excluded. In veterinary applications, the skin includes both furry and non-furry parts of the animal body, whereas hoofs, cloves and claws are excluded.

The term "mucous membrane" refers to the lining of cavities inside the body, and includes the oral cavity, nasal cavity, larynx, eyelids, vagina, urethra, anus and rectum. While the mucous membranes are continuous with the skin, there are defined borders, such as the vermilion line of the lips. However, for the purpose of this description, only a rough distinction is made between mucous membranes and the skin.

Further, the permeability of the API has been tested in order to investigate the availability of the drug, using standardized laboratory methods described in closer detail in the experimental section.

Finally, by "dermal, dermatological and/or mucosal formulations", it is intended to include common formulations such as a cream, ointment, paste, lotion, gel, foam and spray.

As used herein, unless stated otherwise, the amounts of components in percent refer to percent by weight and are based on the total weight of the formulation.

Summary

The problems outlined above, and other problems evident to a skilled person upon study of the present description, claims and examples, are solved by
formulations described herein, where the API has an increased stability and which, upon application to the skin or a mucous membrane, provide sufficient penetration of the API.

[0035] A general embodiment of the invention is thus a dermal, transdermal, and/or mucosal formulation comprising at least one active pharmaceutical ingredient; a pharmaceutically acceptable solvent and/or solvent system; and a pharmaceutically acceptable anti-solvent, wherein the active pharmaceutical ingredient is substantially in the solid state in said formulation in the presence of said anti-solvent; the active pharmaceutical ingredient is soluble in the solvent and/or solvent system in the absence of said anti-solvent, and the solvent and/or solvent system includes a polar ester.

[0036] In the above, the pharmaceutically acceptable solvent and/or solvent system preferably includes a polar ester miscible with water or ethanol or mixtures thereof.

[0037] According to an embodiment, the pharmaceutically acceptable solvent and/or solvent system includes a polar ester chosen from alkyl or hydroxyalkyl esters of carboxylic acids or hydroxy acids, exemplified but not limited to methyl, ethyl and butyl esters of mono-, di- or tricarboxylic acids, polyol esters of carboxylic acids and mono-, oligo- or poly(alkyl methacrylates).

[0038] Preferably, the pharmaceutically acceptable solvent and/or solvent system includes a polar ester chosen from butyl lactate, triethyl citrate, and mono-, oligo- or polymethacrylates.

[0039] Further, the pharmaceutically acceptable solvent and/or solvent system is preferably liquid or semi-solid at 25°C. Preferably the pharmaceutically acceptable solvent and/or solvent system has a vapor pressure of less than 1 kPa at 25°C. More preferably the pharmaceutically acceptable solvent and/or solvent system has a vapor pressure of less than 0.8 kPa at 25°C, and most preferably the pharmaceutically acceptable solvent and/or solvent system has a vapor pressure of less than 0.5 kPa at 25°C.
According to an embodiment, the anti-solvent is chosen from pharmaceutically acceptable compounds having vapor pressure of more than 1 kPa at 25°C.

Preferably the anti-solvent comprises at least one compound selected from the group consisting of acetone, ethanol, ethyl acetate, heptane, pentane, methyl ethyl ketone, methyl isobutyl ketone, pentane, 1-methoxy-2-propanol, 1-propanol, water, and combinations thereof.

More preferably the anti-solvent comprises at least one compound selected from the group consisting of ethyl acetate, ethanol, heptane, butyl acetate, water and combinations thereof.

According to another embodiment, freely combinable with any one of the above embodiments, the formulation is in the form of a cream, ointment, paste, lotion, gel, foam or spray.

Another embodiment is a method for increasing the stability of an active pharmaceutical ingredient in a dermal and/or mucosal formulation, wherein the active pharmaceutical ingredient is dissolved in a solvent and/or solvent system, whereupon an anti-solvent is added, said anti-solvent being effective to substantially precipitate said active pharmaceutical ingredient, and wherein said solvent and/or solvent system comprises a polar ester.

In the method, the pharmaceutically acceptable solvent and/or solvent system includes a polar ester miscible with water or ethanol or mixtures thereof. Preferably said polar ester is chosen from alkyl or hydroxyalkyl esters of carboxylic acids or hydroxy acids, exemplified but not limited to methyl, ethyl and butyl esters of mono-, di- or tricarboxylic acids, polyl esters of carboxylic acids and mono-, oligo- or poly(alkyl methacrylates). Most preferably said polar ester is chosen from butyl lactate, triethyl citrate, and mono-, oligo- or polymethacrylates.

Further, in the method, the pharmaceutically acceptable solvent and/or solvent system is liquid or semi-solid at 25°C. Preferably the pharmaceutically acceptable solvent and/or solvent system has a vapor pressure of less than 1 kPa.
at 25°C. More preferably the pharmaceutically acceptable solvent and/or solvent
system has a vapor pressure of less than 0.8 kPa at 25°C, and most preferably the
pharmaceutically acceptable solvent and/or solvent system has a vapor pressure
of less than 0.5 kPa at 25°C.

[0047] Further, according to an embodiment of the method, the anti-solvent is
chosen from pharmaceutically acceptable compounds having vapor pressure of
more than 1 kPa at 25°C.

[0048] Preferably said anti-solvent comprises at least one compound selected
from the group consisting of acetone, ethanol, ethyl acetate, heptane, pentane,
methyl ethyl ketone, methyl isobutyl ketone, pentane, 1-methoxy-2-propanol, 1-
propanol, water, and combinations thereof.

[0049] Preferably said anti-solvent comprises at least one compound
selected from the group consisting of ethyl acetate, ethanol, heptane, butyl
acetate, water and combinations thereof.

[0050] According to another embodiment, freely combinable with any one of the
above embodiments of the method, the formulation is prepared in the form of a
cream, ointment, paste, lotion, gel, foam or spray.

[0051] One important advantage of the present invention is that the dermal,
transdermal and/or mucosal formulation will have an increased stability and
therefore a longer shelf-life compared to conventional formulations.

[0052] Another advantage is that, because the active pharmaceutical ingredient
is more stable, the pharmaceutical formulation will contain no or significantly less
degradation products and impurities when it is used by the consumer. Such
degradation products can be harmful to the user, elicit side-effects or irritation, or
interact and negatively influence other components of the formulation.

[0053] Yet another advantage is that a dermal, transdermal and/or mucosal
formulation according to the invention will be cost-efficient. Because the active
pharmaceutical ingredient remains active to a greater extent, a lower
concentration of the active pharmaceutical ingredient can be used in the dermal, transdermal and/or mucosal formulation. Also the longer shelf-life adds to cost-efficiency, as larger batches can be produced, distributed and stored.

Short description of the figures

[0054] Different embodiments of the invention will be described in the description, examples, and claims, and supported by the attached drawings, in which:

[0055] Fig. 1 shows the doxepin penetration as percentage of dose for a formulation according to an embodiment of the invention, compared to that of a commercially available dermatological doxepin formulation (Xepin™), investigated in Example 1; and

[0056] Fig. 2 shows the penetration of dapsone for two formulations according to embodiments of the invention.

Description

[0057] In the following, a detailed description of different embodiments of the invention will be provided.

[0058] The dermal, transdermal and/or mucosal formulation comprises a suspension of the drug consisting of at least three functional parts: an active pharmaceutical ingredient, a solvent and/or solvent system and a anti-solvent that precipitates the active pharmaceutical ingredient. The solvent and/or solvent system has a lower vapor pressure than the anti-solvent such that the formulation is a suspension when the evaporating component, i.e. the anti-solvent, is present while the formulation turns into a solution when the anti-solvent has evaporated.

[0059] The formulations according to different embodiments are intended for local use, in particular for application on skin and mucous membranes or in wounds or in open body cavities for the purpose to treat the skin, mucous membrane, underlying tissue, or for providing a systemic effect. Preferably, the
formulation is a dermal, transdermal and/or mucosal formulation for application on
the skin, specifically excluding nail tissue.

**The solvent system**

[0060] The dermal, transdermal and/or mucosal formulation comprises a solvent
and/or solvent system for the active pharmaceutical ingredient. The solvent, and/or
solvents in the case of a solvent system, is/are chosen from pharmaceutically
acceptable solvents. The solvent preferably has a low evaporation at ambient
temperatures as well as normal skin temperatures. This corresponds to a
temperature range of about 15 to about 40°C.

[0061] Preferably the solvent and/or solvent system has a vapor pressure of
less than 1kPa at 25°C. More preferably the solvent has a vapor pressure of less
than 0.8kPa at 25°C, even more preferably less than 0.5kPa at 25°C.

[0062] Suitable polar ester vehicles comprise polar esters miscible with water or
ethanol or mixtures thereof. Preferably said polar ester is chosen from alkyl or
hydroxyalkyl esters of carboxylic acids or hydroxy acids, exemplified but not
limited to methyl, ethyl and butyl esters of mono-, di- or tricarboxylic acids, polyol
esters of carboxylic acids and mono-, oligo- or poly(alkyl methacrylates). Most
preferably said polar ester is chosen from butyl lactate, triethyl citrate, and mono-,
oligo- or polymethacrylates.

[0063] Further, a compound as defined above, or mixture thereof, may have a
dual function, and may thus also be included in the formulation as part of the
solvent system or as an excipient.

**The active pharmaceutical ingredient**

[0064] The active pharmaceutical ingredient and/or ingredients are selected
from a wide range of different compounds, which are soluble in the solvent
system, compatible with the solvent and/or solvent system defined above, and
suitable for delivery to the skin or a mucosal membrane. This may vary between
APIs depending on the physical as well as pharmacological properties of the API,
such as the particle size, chemical derivatization (e.g. salt or ester form), but is well understood and predictable by a person skilled in the art.

[0065] The amount of active pharmaceutical ingredient present in the invented formulation is determined based on its therapeutic activity and required dose, and is normally in the range of from 0.001% to 10%.

[0066] The amount of active pharmaceutical ingredient included in the formulation is chosen depending on the amount of compound needed to achieve its pharmacological activity and the penetrative properties of the drug.

[0067] Thus, an active pharmaceutical ingredient which is soluble in the solvent system, compatible with said solvent system, and suitable for delivery to the skin or a mucosal membrane, is chosen from the group consisting of: sympathomimetics, sympatholytics, parasympathomimetics, parasympatholytics, ganglioplegics, myorelaxants, antihypertensives, diuretics, cardiotonics, anti-arythmics, anti-angina drugs, cerebral and peripheral vasodilatators, anti-migraine drugs, anti-histaminic drugs, anti-asthma drugs, thrombolytics, general anaesthetics, anxiolytics, antidepressants, neuroleptics, anti-convulsive drugs, hypothalamo-hypophysis regulators, hypo and hyperthyroidics, corticosteroids, glycemia regulators, hypolipidemia drugs, phosphocalcic metabolism regulators, antipyretics, anti-inflammatory drugs, laxatives, anti-anemia drugs, cutaneous disease drugs, antiparasitic drugs, antibiotics, penicillins, cephalosporins, aminosids, sulfamides, diaminopyrimidines, tetracyclins, macrolides, vancomycin, teicoplanin, rifampicin, fusidic acid, lincosamides, quinolones, anticancer drugs, antiviral drugs, and antifungal drugs.

[0068] Similarly, an active pharmaceutical ingredient which is soluble in the solvent system, compatible with said solvent system, and suitable for delivery to the skin or a mucosal membrane, is chosen from the group consisting of: anti-acne agents, anti-gout drugs, local anesthetics, general anesthetics, muscle relaxant drugs, hydrochlorothiazides, angiotensin converting enzyme inhibitors, calcium-channel blockers, anti-angina drugs, anti-migraine drugs, antiemetic drugs, anti-histaminic and anti-asthma drugs, thrombolytics and derivatives thereof,
analgesics, salicylic acid and derivatives thereof, nonsteroidal anti-inflammatory agents, antitussive, tricyclic antidepressants, tetracyclic antidepressants, antidepresants, monoamine oxidase inhibitors, serotonin precursors, lithium salts, and tranquilizers.

[0069] Furthermore, an active pharmaceutical ingredient which is soluble in the solvent system, compatible with said solvent system, and suitable for delivery to the skin or a mucosal membrane, is chosen from the group consisting of: anorectics, nootropics, hypnotics, analeptics, tricyclic neuroleptics, neuroleptics, benzamide neuroleptics, anti-psychotic, anti-convulsive drugs, hypothalamo-hypophysis regulators, anti hypo- and anti hyperthyroidy drugs, glycemia regulators, hypolipidemia drugs, phosphocalcic metabolism regulators, anti-inflammatory drugs, antisecretive gastric drugs, anti-anemia drugs, cutaneous disease drugs; alpha antagonist drugs, antiparasitic drugs, antineoplastic drugs, antiviral drugs, and antifungal drugs.

[0070] Further, an active pharmaceutical ingredient which is soluble in the solvent system, compatible with said solvent system, and suitable for delivery to the skin or a mucosal membrane, is chosen from the group consisting of: alpha-adrenergic agonists, beta-adrenergic agonists, beta-adrenergic blockers, nerve agents for smoking cessation, anticholinergic agents, antiepileptic agents; anti-Parkinson agents, bronchodilators; narcotic antagonists, guanidine derivatives, quinazoline derivatives, reserpine derivatives, and sulfonamide derivatives.

[0071] In particular, an active pharmaceutical ingredient which is soluble in the solvent system, compatible with said solvent system, and suitable for delivery to the skin or a mucosal membrane, is chosen from the group consisting of: anti-inflammatory drugs, antiviral drugs, antibacterial drugs, antiparasitic drugs, antipsoriatic drugs, drugs with effect on pain, drugs with effect on skin microcirculation, drugs with effect on formation on scars, drugs with effect on eczema, drugs with effect on perspiration, drugs with effect on growth of hair, drugs with effect on wound healing, drugs with effect on visible skin properties, drugs with effect on comedone closure, drugs with effect on skin barrier function, and drugs with effect on itching.
It is conceived that APIs can be chosen, which currently are identified for specific indications, but which when administered in a dermal, transdermal and/or mucosal formulation, are effective to alleviate, treat or prevent another indication, currently not associated with that API.

It is further conceived that APIs can be used in combination, and formulated together in the same dermal, transdermal and/or mucosal formulation, under the condition that both, in the case of two APIs, or all, in the case of three or more, are soluble in and compatible with the chosen solvent and/or solvent system.

According to an embodiment, the API is chosen from aciclovir, allopurinol, amitriptyline, amlodipine, azathioprine, baclofen, bambuterol, beclometasone dipropionate, benzoyl peroxide (BPO), betametason dipropionate, bibrocathole, budesonide, calcifediol, calcitriol, captopril, celecoxib, cilazapril (cilazapril), dapsone, dexametasone, doxepine, ergocalciferol, ethambutol, etodolac, felbinac, fenoprofen, flunisolide, fluticasone, ibuprofen, meloxicam, minoxidil, mitoxantrone, mometasone, moxisylyte, nabumetone, piracetam, piroxicam, propylhexedrine, pyritinol, salicylic acid, simvastatin, spironolactone, tenoxicam, terbinafine, terbutaline, tocopherols, urea, as well as compounds exhibiting comparable solubility as these, and combinations thereof.

According to an embodiment, based on available solubility data, the API is preferably chosen from the group consisting of: aciclovir, allopurinol, azathioprine, bambuterol, bibrocathol, budesonide, calcitriol, captopril, celecoxib, ethambutol, flunisolide, fluticasone, meloxicam, minoxidil, mitoxantrone, mometasone, piracetam, piroxicam, tenoxicam, terbinafine, terbutaline, salicylic acid, and spironolactone, including combinations thereof.

Preferably the API is chosen from dapsone, diclofenac, doxepin, mometasone, and piroxicam, as well as compounds with similar solubility properties as these.

The anti-solvent
The third component of the dermal, transdermal and/or mucosal formulation, the anti-solvent, is chosen from pharmaceutically acceptable solvents which are compatible with the API and the solvent and/or solvent system, but which are capable of precipitating the API, or in other word, forcing a significant part of the API into the solid state. Conversely, the API becomes dissolved in the solvent when the anti-solvent evaporates. Preferably the anti-solvent has a vapor pressure of more than 1kPa at 25°C.

Preferably the anti-solvent is chosen from the group consisting of acetone, ethanol, ethyl acetate, heptane, pentane, methyl ethyl ketone, methyl isobutyl ketone, pentane, 1-methoxy-2-propanol, 1-propanol, water, and combinations thereof.

More preferably the anti-solvent comprises at least one compound selected from the group consisting of ethyl acetate, ethanol, heptane, butyl acetate, and water.

The amount of anti-solvent is preferably from about 50% to 99%, more preferably from about 70% to 98% and most preferably from about 80% to 96% of the total composition.

Additional components

In addition, the formulation may include additional components or excipients well known to a person skilled in the art.

For example, so called permeation enhancers may be additionally included in the pharmaceutical formulation. They can be chosen from the group of enhancers suitable for use in a dermal, transdermal and/or mucosal formulation, provided that they are compatible with the API, the solvent and/or solvent system, as well as with the anti-solvent.

The pharmaceutical formulation of the invention may further include a gelling agent or thickener, in order to provide a suitable viscosity of the product during storage and in use. They can be chosen from the group of gelling agents or
thickeners suitable for use in a dermal, transdermal and/or mucosal formulation, provided that they are compatible with the API, the solvent and/or solvent system, as well as with the anti-solvent.

[0084] Where necessary, for example in cases where the dermal, transdermal and/or mucosal formulation comprises water, it may be suitable to include a preservative. The preservative can be chosen from the group of preservatives suitable for use in a dermal, transdermal and/or mucosal formulation, provided that they are compatible with the API, the solvent and/or solvent system, as well as with the anti-solvent.

[0085] The dermal, transdermal and/or mucosal formulation may further comprise an antioxidant to further enhance the stability of the product. The antioxidant can be chosen from the group of antioxidants suitable for use in a dermal, transdermal and/or mucosal formulation, provided that they are compatible with the API, and soluble at least in the solvent and/or solvent system. Examples include, but are not limited to, tocopherol and derivatives thereof, ascorbic acid and derivatives thereof, butylated hydroxyanisole, butylated hydroxytoluene, fumaric acid, malic acid, propyl gallate, metabisulfates and derivatives thereof. The antioxidant is present from about 0.001 % to about 5.0% depending on the type of compound.

[0086] Further, the formulation may comprise buffers such as carbonate buffers, citrate buffers, phosphate buffers, acetate buffers, hydrochloric acid, lactic acid, tartaric acid, diethylamine, triethylamine, diisopropylamine, aminomethylamine. However, other buffers as known in the art may be included, provided that they are compatible with the API, the solvent and/or solvent system, as well as with the anti-solvent.

[0087] A formulation according to this invention can be prepared with chelating agents exemplified by, but not limited to, EDTA or its derivatives and phosphonic acids.
When the dermal, transdermal and/or mucosal formulation is a spray, a propellant such as nitrous oxide, carbon dioxide or hydrofluoralkanes (HFA) (HFA 134a (1,1,1,2-tetrafluoroethane) or HFA 227 (1,1,1,2,3,3-heptafluoropropane)) may be included.

Preferred embodiments

According to a preferred embodiment, the active pharmaceutical ingredient is one which is soluble in a polar ester, and where the dermal, transdermal and/or mucosal formulation comprises a polar ester and where the anti-solvent preferably comprises one of acetone, ethanol, ethyl acetate, heptane, pentane, methyl ethyl ketone, methyl isobutyl ketone, pentane, 1-methoxy-2-propanol, 1-propanol, water, or combinations thereof.

Examples of active pharmaceutical ingredients which are soluble in polar esters include aciclovir, allopurinol, azathioprine, bamberterol, bibrocathol, budesonide, calcitriol, captopril, celecoxib, ethambutol, flunisolide, fluticasone, meloxicam, minoxidil, mitoxantrone, mometasone, piracetam, piroxicam, tenoxicam, terbinafine, terbutaline, salicylic acid, and spironolactone.

Preferably the polar solvent is a pharmaceutically acceptable polar solvent with a vapor pressure of less than 1 kPa at 25°C. More preferably the polar solvent has a vapor pressure of less than 0.8 kPa at 25°C, even more preferably less than 0.5 kPa at 25°C. Such polar ester solvents include but are not limited to hydroxyalkyl esters of carboxylic acids or hydroxy acids, exemplified but not limited to methyl, ethyl and butyl esters of mono-, di- or tricarboxylic acids, polyol esters of carboxylic acids and mono-, oligo- or poly(alkyl methacrylates).

Suitable components for inclusion in the anti-solvent are pharmaceutically acceptable components with a vapor pressure of more than 1 kPa at 25°C. Preferred components for inclusion in the anti-solvent are components selected from the group consisting of ethyl acetate, ethanol, heptane, butyl acetate, water and combinations thereof.
According to one embodiment, dapsone is dissolved in a triethyl citrate based solvent system, and precipitated with a mixture of ethyl acetate and heptane as the anti-solvent. In this composition, dapsone is present at about 0.1 - 2.0%, the solvent system at about 3 - 6%, and the anti-solvent mixture at about 90 - 95% of the total composition.

According to another embodiment, diclofenac is dissolved in a solvent system comprising butyl lactate and isopropyl myristate, and precipitated with a mixture of ethanol and water as the anti-solvent. In this composition, diclofenac is present at about 0.2 - 2.0%, the solvent system at about 8 - 12%, and the anti-solvent at about 80 - 95% of the total composition.

According to yet another embodiment, doxepin is dissolved in a triethyl citrate based solvent system, and precipitated with a mixture of ethyl acetate and heptane as the anti-solvent. In this composition, doxepin is present at about 0.01 - 1.0%, the solvent system at about 4 - 10%, and the anti-solvent at about 80 - 95% of the total composition.

According to yet another embodiment, mometasone is dissolved in a triethyl citrate based solvent system, and precipitated with a mixture of ethanol and water as the anti-solvent. In this composition, mometasone is present at about 0.01 - 1.0%, the solvent system at about 4 - 10%, and the anti-solvent at about 80 - 95% of the total composition.

According to yet another embodiment, piroxicam is dissolved in a solvent system comprising butyl lactate and isopropyl myristate, and precipitated with a mixture of ethanol and water as the anti-solvent. In this composition, piroxicam is present at about 0.05 - 1.0%, the solvent system at about 5 - 14%, and the anti-solvent at about 85 - 95% of the total composition.

EXAMPLES

Example 1. Doxepin

1. 1. Doxepin was dissolved in triethyl citrate and precipitated with ethanol/water
The solubility of doxepin, a known antidepressant and anxiolytic drug, was tested in several pharmaceutically useful solvents. Among these, polar esters exemplified by triethyl citrate were superior in dissolving doxepin and > 3% was dissolved. A formulation containing doxepin according to Table 1 was prepared by dissolution of doxepin in triethyl citrate followed by addition of a mixture of water and ethanol. At this addition doxepin precipitates and the final product is formed.

As a comparison, the commercial product Xepin™ (Bioglan Laboratories) was used.

Table 1. Compositions comprising doxepin

<table>
<thead>
<tr>
<th></th>
<th>A (2.7% doxepin)</th>
<th>B (Xepin™ 5%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doxepin</td>
<td>0.27%</td>
<td>5%</td>
</tr>
<tr>
<td>Triethyl citrate</td>
<td>9.73%</td>
<td>-</td>
</tr>
<tr>
<td>Ethanol/water</td>
<td>90%</td>
<td>-</td>
</tr>
<tr>
<td>Cream base*</td>
<td>-</td>
<td>95%</td>
</tr>
</tbody>
</table>

* The cream base consists of sorbitol, cetyl alcohol, isopropyl myristate, glyceryl stearate, PEG-100 stearate, white soft paraffin, E171 (titanium dioxide), purified water and benzyl alcohol 1% as preservative.

1.2. *In vitro penetration study*

The above doxepin formulation was compared to the commercial product Xepin™ in an *in vitro* penetration study where the penetration through pig ear skin was studied in a Bronaugh diffusion cell.

The following equipment was used for the *in vitro* penetration study: Bronaugh cell equipment, One Retriever IV Fraction Collector (ISCO Inc., USA) with two cell warmers and 14 in-line flow cells (diffusion area of 0.63cm²), a PermeGear ILC14 automated system (PermeGear Inc., USA), Teflon® exit media
tubes D1/16" 1mm 0 (Skandinaviska Genetec AB, Vastra Frolunda, Sweden), a
peristaltic pump (Ismatec® IPC, IDEX Health & Science GmbH, Wertheim-
Mondfeld, Germany), a water bath (Grant GD120), receptor medium flask and a
stainless steel support grid (only for s.c. membranes)

[00102] Degassed (10 min of helium treatment) phosphate buffered saline (PBS)
\( \text{pH} \, 7.14 \), was used as receptor medium. The receptor phase was manufactured on
the day before the \textit{in vitro} penetration experiment was run.

[00103] Full-thickness skin membranes were prepared as follows: The porcine
inner ear skin was dermatomed to a thickness of approximately 600-700 \( \mu \text{m} \).
Membranes (14mm diameter) were punched from the dermatomed skin pieces.
The thickness of the skin membranes was determined using a micrometer.
Membranes thinner than 0.6 mm were discarded. The skin membranes were
prepared the day before the \textit{in vitro} experiment and stored in the refrigerator
covered with aluminum foil until use. The skin membranes were placed in the
Bronaugh cell equipment and allowed to hydrate for one hour at 32°C. (No support
grid is necessary for the dermatomed full thickness skin membranes.)

[00104] Epidermal membranes (previously also referred to as stratum corneum
membranes) were prepared as follows: The inner ear skin was removed using a
scalpel, and divided into smaller pieces. The skin pieces were then immersed in
60°C water for 90 seconds. The epidermal membrane was separated from the
underlying dermis using a scalpel and forceps. Each membrane was checked to
detect possible damages.

[00105] The skin membranes were prepared the day before the \textit{in vitro}
experiment and stored in the refrigerator until they were used. The epidermal
membranes were equilibrated for 30 minutes at 32°C before being mounted in the
Bronaugh cells. (A support grid used was used for the epidermal membranes.)

[00106] The \textit{in vitro} experiments were performed using \( 4 + 4 \) Bronaugh flow
through cells as follows: About 100mg formulation was applied in each cell, which
corresponds to a dose of about 0.15g formulation/cm\(^2\) (cell area 0.63cm\(^2\)).
Fractions were collected after 2, 4, 6 and 24 hours in the experiment with full thickness skin (WS). Fractions were collected after 2, 4, 19.5 and 24 hours in the experiment with epidermal membranes (SC). All fractions were weighed to confirm the flow and the time of sampling. The samples were stored in HPLC vials in the refrigerator until analysis by HPLC. The results are shown in Fig. 1 where filled squares (■) denote the values for the 2.7% doxepin formulation (A), and open rhomboids (0) denote the values for the Xepin™ 5% product (B).

Example 2. Dapsone

2.1. Dapsone was dissolved in triethyl citrate, or in a solution of poly(methyl methacrylate) in triethyl citrate, and precipitated with hexane/ethanol or ethanol/water

Two formulations of dapsone (diamino-diphenyl sulfone) were manufactured according to the compositions in Table 2 below. Dapsone was dissolved in triethyl citrate, or in a solution of poly(methyl methacrylate) in triethyl citrate. When the anti-solvents were added, a suspension was formed.

Table 2. Compositions comprising dapsone

<table>
<thead>
<tr>
<th></th>
<th>C (ISM1 1178N) (mg)</th>
<th>D (ISM1 1179N) (mg)</th>
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</thead>
<tbody>
<tr>
<td>Triethyl citrate</td>
<td>91</td>
<td>66.75</td>
</tr>
<tr>
<td>Poly(methyl methacrylate)</td>
<td>-</td>
<td>23.25</td>
</tr>
<tr>
<td>Dapsone</td>
<td>9</td>
<td>6</td>
</tr>
<tr>
<td>Hexane</td>
<td>450</td>
<td>-</td>
</tr>
<tr>
<td>Ethanol</td>
<td>450</td>
<td>700</td>
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<tr>
<td>Water</td>
<td>-</td>
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<tr>
<td>Total</td>
<td>1000</td>
<td>1000</td>
</tr>
</tbody>
</table>
2.2. *In vitro penetration study*

[001 09] The penetration of dapsone was tested in Franz cell equipment using silicon membranes. In the penetration study formulations without the anti-solvent were used. The compositions are shown in Table 3.

<table>
<thead>
<tr>
<th></th>
<th>C’ (ISM11178N)</th>
<th>D’ (ISM11179N)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>(mg)</td>
<td>(mg)</td>
</tr>
<tr>
<td>Triethyl citrate</td>
<td>91</td>
<td>66.75</td>
</tr>
<tr>
<td>Poly(methyl methacrylate)</td>
<td>-</td>
<td>23.25</td>
</tr>
<tr>
<td>Dapsone</td>
<td>9</td>
<td>6</td>
</tr>
<tr>
<td>Total</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

[001 10] The in vitro penetration study was performed in Franz cell equipment using silicone membranes, silastic sheeting NRV 0.005 matt lot. SM05057619. The integrity of the membrane was done visually and by testing leakage of receptor solution in the Franz cell equipment when mounted in the cells.

[001 11] The experiment was run for 24 hours. The equipment used in the study is defined in Example 1. The temperature of the water bath was set to 34.5°C giving a temperature of 32°C in the cells. A mixture of 50% ethanol and 50% water, adjusted with HCl to pH 2.7 was used as receptor solution. The reason for using a mixture of water and ethanol as receptor solution is the low water solubility of dapsone.

[001 12] Samples were withdrawn at 6 and at 24 hours (termination). The formulations C’ (ISM1 1178) and D’ (ISM1 1179) applied in 3 cells each. Dapsone was analysed on a HPLC-UV with a RP C18 column using 50/50 MeCN/H2O (v/v)
isocratic elution. Dapsone was monitored at 294 nm. The results are shown in Fig.
2, where filled squares (■) denote the values for ISM1 1179 (D’), and open
rhomboids (0) denote the values for ISM1 1178N(C).

[0013] It can be seen that the penetration of dapsone was similar for the two
formulations although the composition exhibiting a higher concentration (C’,
ISM1 1178N) initially exhibited a faster penetration rate.

Example 3. Solubility of dapsone

[0014] The solubility of dapsone was tested in different solvents. The solubility
of dapsone in butylene glycolester of caprylic/capric acid, triethyl citrate and in
poly(methyl methacrylate)/ethanol 20/80 were 2.5%, 9%, and 6.5% respectively.
This means that dapsone has a higher solubility in polar esters than in nonpolar
ones.

Example 4. Solubility of diclofenac

[0015] Diclofenac, a well known non-steroidal anti-inflammatory drug (NSAID),
was dissolved in a mixture of butyl lactate and isopropyl myristate, forming a clear
solution. Upon addition of a mixture of ethanol and water, a precipitate was
formed. When the ethanol/water mixture evaporated, a clear solution was formed.
The composition is shown in Table 4.

Table 4. Composition comprising diclofenac

<table>
<thead>
<tr>
<th></th>
<th>Batch No. ISM12027</th>
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<tbody>
<tr>
<td>Diclofenac</td>
<td>0.40 g</td>
</tr>
<tr>
<td>Butyl lactate</td>
<td>3.29 g</td>
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<tr>
<td>Isopropylmyristate</td>
<td>4.85 g</td>
</tr>
<tr>
<td>Ethanol</td>
<td>72.32 g</td>
</tr>
</tbody>
</table>
Example 5. Solubility of piroxicam

[0016] Piroxicam, another well-known NSAID, was dissolved in a mixture of butyl lactate and isopropylmyristate, forming a clear solution. Upon addition of a mixture of ethanol and water, a precipitate was formed. When the ethanol/water mixture evaporated, a clear solution was formed. The composition is shown in Table 5.

Table 5. Composition comprising piroxicam

<table>
<thead>
<tr>
<th>Component</th>
<th>Batch No. ISM12028</th>
</tr>
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<tbody>
<tr>
<td>Piroxicam</td>
<td>0.12 g</td>
</tr>
<tr>
<td>Butyl lactate</td>
<td>3.97 g</td>
</tr>
<tr>
<td>Isopropyl myristate</td>
<td>4.03 g</td>
</tr>
<tr>
<td>Ethanol</td>
<td>71.17 g</td>
</tr>
<tr>
<td>Water</td>
<td>20.71 g</td>
</tr>
</tbody>
</table>

Example 6. Solubility of doxepin

[0017] Doxepin, a known antidepressant and anxiolytic drug, was dissolved in triethyl citrate, forming a clear solution. Upon addition of a mixture of ethyl acetate and heptane, a precipitate was formed. When the anti-solvent mixture evaporated, a clear solution was formed. The composition is shown in Table 6.
Table 6. Composition comprising doxepin

<table>
<thead>
<tr>
<th></th>
<th>Batch No. ISM12023E</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doxepin</td>
<td>0.14 g</td>
</tr>
<tr>
<td>Triethyl citrate</td>
<td>5.19 g</td>
</tr>
<tr>
<td>Ethyl acetate</td>
<td>46.68 g</td>
</tr>
<tr>
<td>Heptane</td>
<td>48.00 g</td>
</tr>
</tbody>
</table>

Example 7. Solubility of mometasone

[001 18] Mometasone, a glucocorticosteroid for topical use, was dissolved in triethyl citrate, forming a clear solution. Upon addition of a mixture of ethanol and water, a precipitate was formed. When the anti-solvent mixture evaporated, a clear solution was formed. The composition is shown in Table 7.

Table 7. Composition comprising Mometasone

<table>
<thead>
<tr>
<th></th>
<th>Batch No. ISM12022B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mometasone</td>
<td>0.07 g</td>
</tr>
<tr>
<td>Triethyl citrate</td>
<td>6.64 g</td>
</tr>
<tr>
<td>Ethanol</td>
<td>29.94 g</td>
</tr>
<tr>
<td>Water</td>
<td>63.36 g</td>
</tr>
</tbody>
</table>

Example 8. Solubility of dapsone

[001 19] Dapsone, diamino-diphenyl sulfone, was dissolved in triethyl citrate, forming a clear solution. Upon addition of a mixture of ethyl acetate and heptane, a
precipitate was formed. When the anti-solvent mixture evaporated, a clear solution was formed. The composition is shown in Table 8.

Table 8. Composition comprising dapsone

<table>
<thead>
<tr>
<th></th>
<th>Batch No. ISM12021E</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dapsone</td>
<td>0.42 g</td>
</tr>
<tr>
<td>Triethyl citrate</td>
<td>4.74 g</td>
</tr>
<tr>
<td>Ethylacetate</td>
<td>41.90 g</td>
</tr>
<tr>
<td>Heptane</td>
<td>52.96 g</td>
</tr>
</tbody>
</table>

[00120] Although the invention has been described with regard to its preferred embodiments, which constitute the best mode presently known to the inventors, it should be understood that various changes and modifications as would be obvious to one having the ordinary skill in this art may be made without departing from the scope of the invention as set forth in the claims appended hereto.

---
CLAIMS

1. A dermal, transdermal, and/or mucosal formulation comprising at least one active pharmaceutical ingredient; a pharmaceutically acceptable solvent and/or solvent system; and a pharmaceutically acceptable anti-solvent, characterized in that

- the active pharmaceutical ingredient is substantially in the solid state in said formulation in the presence of said anti-solvent;
- the active pharmaceutical ingredient is soluble in the solvent and/or solvent system in the absence of said anti-solvent, and
- the solvent and/or solvent system includes a polar ester.

2. The formulation according to claim 1, wherein the pharmaceutically acceptable solvent and/or solvent system includes a polar ester miscible with water or ethanol or mixtures thereof.

3. The formulation according to claim 1, wherein the pharmaceutically acceptable solvent and/or solvent system includes a polar ester chosen from alkyl or hydroxyalkyl esters of carboxylic acids or hydroxy acids, exemplified but not limited to methyl, ethyl and butyl esters of mono-, di- or tricarboxylic acids, polyol esters of carboxylic acids and mono-, oligo- or poly(alkyl methacrylates).

4. The formulation according to claim 1, wherein the pharmaceutically acceptable solvent and/or solvent system includes a polar ester chosen from butyl lactate, triethyl citrate, and mono-, oligo- or polymethacrylates.

5. The formulation according to claim 1, wherein the pharmaceutically acceptable solvent and/or solvent system is liquid or semi-solid at 25°C.

6. The formulation according to claim 1, wherein the pharmaceutically acceptable solvent and/or solvent system has a vapor pressure of less than 1 kPa at 25°C.
7. The formulation according to claim 6, wherein the pharmaceutically acceptable solvent and/or solvent system has a vapor pressure of less than 0.8 kPa at 25°C.

8. The formulation according to claim 6, wherein the pharmaceutically acceptable solvent and/or solvent system has a vapor pressure of less than 0.5 kPa at 25°C.

9. The formulation according to claim 1, wherein the anti-solvent is chosen from pharmaceutically acceptable compounds having vapor pressure of more than 1 kPa at 25°C.

10. The formulation according to claim 1, wherein the anti-solvent comprises at least one compound selected from the group consisting of acetone, ethanol, ethyl acetate, heptane, pentane, methyl ethyl ketone, methyl isobutyl ketone, pentane, 1-methoxy-2-propanol, 1-propanol, water, and combinations thereof.

11. The formulation according to claim 1, wherein the anti-solvent comprises at least one compound selected from the group consisting of ethyl acetate, ethanol, heptane, butyl acetate, water and combinations thereof.

12. The formulation according to any one of the claims above, wherein the formulation is in the form of a cream, ointment, paste, lotion, gel, foam or spray.

13. A method for increasing the stability of an active pharmaceutical ingredient in a dermal and/or mucosal formulation, characterized in that the active pharmaceutical ingredient is dissolved in a solvent and/or solvent system, whereupon an anti-solvent is added, said anti-solvent being effective to substantially precipitate said active pharmaceutical ingredient, and wherein said solvent and/or solvent system comprises a polar ester.

14. The method according to claim 13, wherein the pharmaceutically acceptable solvent and/or solvent system includes a polar ester miscible with water or ethanol or mixtures thereof.
15. The method according to claim 13, wherein the pharmaceutically acceptable solvent and/or solvent system includes a polar ester chosen from alkyl or hydroxyalkyl esters of carboxylic acids or hydroxy acids, exemplified but not limited to methyl, ethyl and butyl esters of mono-, di- or tricarboxylic acids, polyol esters of carboxylic acids and mono-, oligo- or poly(alkyl methacrylates).

16. The method according to claim 13, wherein the pharmaceutically acceptable solvent and/or solvent system includes a polar ester chosen from butyl lactate, triethyl citrate, and mono-, oligo- or polymethacrylates.

17. The method according to claim 13, wherein the pharmaceutically acceptable solvent and/or solvent system is liquid or semi-solid at 25°C.

18. The method according to claim 13, wherein the pharmaceutically acceptable solvent and/or solvent system has a vapor pressure of less than 1 kPa at 25°C.

19. The method according to claim 18, wherein the pharmaceutically acceptable solvent and/or solvent system has a vapor pressure of less than 0.8 kPa at 25°C.

20. The method according to claim 18, wherein the pharmaceutically acceptable solvent and/or solvent system has a vapor pressure of less than 0.5 kPa at 25°C.

21. The method according to claim 13, wherein the anti-solvent is chosen from pharmaceutically acceptable compounds having vapor pressure of more than 1 kPa at 25°C.

22. The method according to claim 13, wherein the anti-solvent comprises at least one compound selected from the group consisting of acetone, ethanol, ethyl acetate, heptane, pentane, methyl ethyl ketone, methyl isobutyl ketone, pentane, 1-methoxy-2-propanol, 1-propanol, water, and combinations thereof.
23. The method according to claim 13, wherein the anti-solvent comprises at least one compound selected from the group consisting of ethyl acetate, ethanol, heptane, butyl acetate, water and combinations thereof.

24. The method according to any one of the claims above, wherein the formulation is in the form of a cream, ointment, paste, lotion, gel, foam or spray.
Doxepin penetration as % of dose

Fig. 1
Fig. 2
A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/00 A61K47/06 A61K47/10 A61K47/14 A61K9/70
ADD.

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 , BIOSIS, EMBASE, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
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</table>

Further documents are listed in the continuation of Box C.

See patent family annex.

* Special categories of cited documents:
  *A* document defining the general state of the art which is not considered to be of particular relevance
  *E* earlier application or patent but published on or after the international filing date
  *L* document which may throw doubts on priority claim(s) on which the document is cited to establish the publication date of another citation or other special reason (as specified)
  *O* document referring to an oral disclosure, use, exhibition or other means
  *P* document published prior to the international filing date but later than the priority date claimed
  *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
  *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
  *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
  *Z* document member of the same patent family

Date of the actual completion of the international search: 5 June 2012
Date of mailing of the international search report: 13/06/2012

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

Authorized officer: Cattel 1, James
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<td>X</td>
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