



AU9225615

(12) PATENT ABRIDGMENT **(11) Document No. AU-B-25615/92**
(19) AUSTRALIAN PATENT OFFICE **(10) Acceptance No. 672177**

(54) Title
MEDICATION VEHICLES MADE OF SOLID LIPID PARTICLES (SOLID LIPID NANOSPHERES - SLN)

International Patent Classification(s)
(51)⁵ **A61K 009/16** **A61K 009/51**

(21) Application No. : **25615/92**

(22) Application Date : **16.09.92**

(87) PCT Publication Number : **WO93/05768**

(30) Priority Data

(31) Number	(32) Date	(33) Country
4131562	18.09.91	DE GERMANY

(43) Publication Date : **27.04.93**

(44) Publication Date of Accepted Application : **26.09.96**

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(56) Prior Art Documents
EP 418153
AU 47099/89
AU 44437/89

(57) Claim

1. A process for the manufacture of a drug carrier which comprises tenside-containing or tenside-free particles of lipid or lipid-like (lipoid) material or mixtures thereof and having a diameter range of 10nm to 10µm, whereby the particles have an average diameter of between 40 and 1000 nm and are solid at room temperature characterised in that the particles when in a melted or softened state are homogenised under high pressure in a dispersion medium being water, aqueous solution or a liquid miscible with water, or the particles when in a solid state are dispersed under high pressure in the dispersion medium, whereby the particles are finely dispersed.

29. A drug carrier consisting of tenside-free particles of lipid or lipid-like (lipoid) material or mixtures thereof and having a diameter of 10nm to 10µm, manufactured by means of a high-pressure homogenisation process in accordance with one of the claims 1 to 28, whereby the majority of the particles have an average diameter of between 40 and 1000nm and are solid at room temperature.



(51) Internationale Patentklassifikation ⁵ : A61K 9/16, 9/51	A1	(11) Internationale Veröffentlichungsnummer: WO 93/05768 (43) Internationales Veröffentlichungsdatum: 1. April 1993 (01.04.93)
(21) Internationales Aktenzeichen: PCT/EP92/02132 (22) Internationales Anmeldedatum: 16. September 1992 (16.09.92) (30) Prioritätsdaten: P 41 31 562.6 18. September 1991 (18.09.91) DE (71) Anmelder (für alle Bestimmungsstaaten ausser US): MEDAC GESELLSCHAFT FÜR KLINISCHE SPEZIALPRÄPARATE GMBH [DE/DE]; Fehlandtstrasse 3, D-2000 Hamburg 36 (DE). (72) Erfinder; und (75) Erfinder/Anmelder (nur für US): LUCKS, Stefan [DE/DE]; Deliusstrasse 23A, D-2300 Kiel 1 (DE). MÜLLER, Rainer [DE/DE]; Samwerstrasse 8, D-2300 Kiel 1 (DE).		(74) Anwalt: GRAF ZU STOLBERG, Ulrich; Uexküll & Stolberg, Beselerstr. 4, D-2000 Hamburg 52 (DE). (81) Bestimmungsstaaten: AU, CA, CS, HU, JP, KR, PL, RU, US, europäisches Patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, SE). Veröffentlicht <i>Mit internationalem Recherchenbericht.</i>  672 77
(54) Title: MEDICATION VEHICLES MADE OF SOLID LIPID PARTICLES (SOLID LIPID NANOSPHERES - SLN) (54) Bezeichnung: ARZNEISTOFFTRÄGER AUS FESTEN LIPIDTEILCHEN (FESTE LIPIDNANOSPHEREN (SLN)) (57) Abstract Medication vehicles have particles made of lipids, lipid-like (lipoid) materials or mixtures thereof, with a diameter from 10 nm to 10 µm, that are solid at the ambient temperature. Because of their solid core, these medication vehicles allow active substances to be controllably released over a longer period, allow hydrophilic medicaments to be incorporated into the solid core and are relatively quickly decomposable, producing no toxic by-products. (57) Zusammenfassung Arzneistoffträger, der Teilchen aus Lipid, lipidähnlichem (lipoidem) Material oder Mischungen davon umfaßt, die einen Durchmesser von 10 nm bis 10 µm aufweisen und bei Raumtemperatur fest sind. Dieser Arzneistoffträger ermöglicht aufgrund seines festen Kerns eine kontrollierbare Freisetzung von Wirkstoffen über einen längeren Zeitraum, die Einarbeitung von hydrophilen Arzneistoffen in den festen Kern und eine relativ schnell Abbaubarkeit, wobei keine toxischen Nebenprodukte entstehen.		

Drug carrier consisting of solid lipid particles

- Solid lipid nanospheres -

The invention relates to a drug carrier, its dispersion in ^{an aqueous} ~~a watery~~ medium, a method to produce it, as well as its use. It concerns in particular a drug carrier consisting of lipid or lipoid particles.

In the field of medicinal agents there is a continuous search for carriers which allow drug application in various ways, i.e. carriers which are available in a form that permits the respective drug to be administered as deemed most suitable, e.g. in an intravenous, intra-articular, intramuscular or subcutaneous manner.

Carriers are known which consist, e.g. of solid microparticles, microspheres and microcapsules (mean diameter in the micrometer range), as well as nanoparticles and nanocapsules (mean diameter in the nanometer range). Microparticles and nanoparticles consist of a solid polymer matrix. With respect to microcapsules and nanocapsules, liquid or solid phases are enclosed by film-forming polymers. Such particles consist of or have coatings of polymers, such as



polylactides (PLA), polylactide-glycolides (PLA/GA) or polyalkyl
 cyanoacrylates. Polylactide and polylactide-glycolide as particle matrix and
 as coatings have, however, the disadvantage of degrading only very slowly,
 i.e. the degradation takes weeks up to months. Multiple applications of a
 5 drug with such a carrier lead to an accumulation of polymer in the
 organism and possibly cause toxic effects. Although particles based on
 polymers, such as polyalkyl cyanoacrylates, metabolize up to 80% in the
 organism within a period of 24 hours, toxic formaldehyde is set free during
 the decomposition. To produce the polymeric particles, carbon hydrogen
 10 chlorides, such as dichloromethane, have to be used as solvents for the
 polymer, and these solvents in turn are toxic on their part (T.R. Tice and
 D.H. Lewis, Microencapsulation Process, US-PS 4,389,330). Furthermore, on
 account of their size, microparticles may cause embolisms when injected
 intravenously, and therefore one usually refrains from this procedure.
 15 Another disadvantage of polymeric particles is the fact that when sterilising
 in an autoclave, the glass temperature is exceeded, thus resulting in an
 aggregation of particles. Such drug carriers or drugs can therefore not be
 sterilised in this manner and have to be subjected to the disadvantageous
 procedure of gamma irradiation.

20 Also known to serve as drug carriers are fat emulsions. Fat
 emulsions are oil-in-water emulsions in which the dispersed (inner) phase is
 liquid. In the trade literature such fatty emulsions are also referred to as
 "lipid microspheres", and highly disperse fat emulsions with a mean particle
 size in the nanometer range are also called "nano-emulsions" (H.G. Weder
 25 and M. Muetsch, Eur. Pat. EP 90-810436, June 1990). These fat emulsions
 comprise two liquid phases. After diluting with body fluids, fat emulsions
 set incorporated medicinal agents free



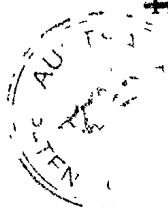
within a relatively fast time (e. g. after injection into the blood). The t (50%) is in the 30 to 60-second range, which is correlated to the rate of diffusion of the medicinal agents in the oil that is of relatively low viscosity. Furthermore, the liquid, dispersed phase of the fat emulsions (= oil) will be completely metabolized in the body within a few hours, which liberates from the oil also extremely lipophile substances. Such quick liberations may also lead to the so-called peaks of the medicinal agents in the plasma so that toxic side effects are possible due to this brief overdosing. In addition, the loss of active substance before it reaches the target organ is relatively large when passively aiming at macrophages of the liver and spleen.

Through P. Eldem, P. Speiser and A. Hincal, Pharmaceutical Research 8, 47-54 (1991) micropellets on a lipid basis have become known, the mean diameter of which again is in the micrometer range.

Known are also drug carriers in which liposomes or substances which resemble or are analogous to liposomes, such as niosomes, having an aqueous liquid core, are enclosed by one or several phospholipid double membranes.

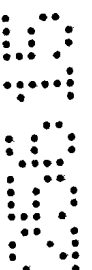
Furthermore, subparticulate or semiparticulate systems are known in which substances are dissolved with the help of solving agents, such as tensides, to an extent that micells or mixed micells will form. What they are here are no longer dispersions but already solutions.

~~Therefore, the object of the invention is to make available a drug carrier which can form a~~



The present invention consists in a process for the manufacture of a drug carrier which comprises tenside-containing or tenside-free particles of lipid or lipid-like (lipoid) material or mixtures thereof and having a diameter range of 10nm to 10µm, whereby the particles have an average diameter of
5 between 40 and 1000 nm and are solid at room temperature characterised in that the particles when in a melted or softened state are homogenised under high pressure in a dispersion medium, being water, aqueous solution or a liquid miscible with water or the particles when in a solid state are dispersed under high pressure in the dispersion medium, whereby the particles are
10 finely dispersed.

With respect to the drug carrier it concerns particles that are solid at room temperature (i.e. about 20°C) and the size of which is in the nanometer range. Such particles can be defined as "solid lipid nanosphered" (SLN). These particles can be dispersed in an aqueous medium, thus resulting in a
15 solid/liquid dispersion. The particle size of the dispersed phase is in the range of >10nm up to a few micrometers (about 10µm). The average particle size (diameter determined by photon correlation spectroscopy) is predominantly in the 100 to 1000nm range and especially in the 100 to 800nm range. By selecting suitable processing parameters and by choosing appropriate excipients (e.g. a higher tenside concentration), it is possible to
20 make the SLN smaller than 100nm, especially in the 40 to 80nm range.



The SLN consists of lipid or lipid-like substances which can be degraded by the organism like fat from foodstuffs. The degradation of lipids occurs at a faster rate than the decomposition of synthetic polymers such as PLA.

5 PLA/GA. Another advantage is that in the degradation or in the metabolisation of lipids, no toxic metabolites are produced, as is the case in particles of a polyalkyl cyanacrylate base. Reference is made in this connection to the toxicity of fatty emulsions used in parenteral nutrition since the 1950's.

10 Since in SLN it concerns solid, lipid particles with a relevantly high viscosity, the rate of diffusion and liberation of an active substance embedded therein is reduced. Thus, contrary to the fat emulsions, consisting of a liquid-dispersed phase it is possible to achieve a controlled liberation over a longer period. On account of the longer liberation period, the formation of plasma peaks of the respective active substance is
15 prevented and side effects, which occur as a result of such peak values, are eliminated. Due to the delayed liberation, the loss of active substance after application and before reaching the respective target organ is smaller than in fat emulsions in which the active substances are liberated comparatively fast.

20 The active substance or substances are dissolved or dispersed in the lipid or lipid particles. Furthermore, the active substances can be adsorbed at the surface of the particles. On account of the solid matter character it is also possible to incorporate in the lipid or lipid phase hydrophilic substances in the form of an aqueous solution of the active substance. After incorporating
25 and subsequently dispersing the obtained SLN in the aqueous dispersion medium, a W/F/W system (i.e. water-in-fat water) is produced. On account of its solid aggregate state,



the lipid core incorporates the ~~water~~^{aqueous} drug solution better than it is possible in comparable, multiple emulsions of water-in-oil-in water (W/O/W).

Another advantage of the solid, lipid nanospheres is the fact that, in contrast to the polymeric particles, they can be sterilized in an autoclave without causing an aggregation of the particles. In this way the disadvantages connected to ~~radiosterilization~~^{gamma irradiation} can be avoided.

Contrary to microparticles of the micrometer range, the SLN can be injected intravenously without difficulty and without the risk of embolism due to their small particle size in the nanometer range. When producing the SLN, no toxic adjuvants have to be used such as e.g. slightly volatile solvents of chlorohydrocarbons.

The drug carrier according to the invention can be produced in the following manner:

1. by dispersing the inner phase (of the lipid or lipid) in a melted or softened state. The dispersing is carried out above room temperature and can be achieved by various procedures such as, for example, the methods described below;
2. by dispersing the solid inner phase in a solid state. For this purpose, the solid phase is finely broken down and dispersed in water or in a ~~water~~^{aqueous} medium.

Prior to this, the dispersed lipid or lipid core, which is solid at room temperature, was loaded with one or more medicinal agents. This can be achieved by dissolving or dispersing the active substance in the lipid/lipoid, by adsorbing the active substance at the surface of the lipid/lipoid,



or by dispersing it in the lipid/lipoid in the form of a watery solution.

As dispersed phase, lipids and lipoids can be used in the widest sense as individual compounds or as mixtures. Examples of these include the following: natural or synthetic triglycerides or mixtures thereof, mono and diglycerides alone or in mixtures thereof or with e.g. triglycerides, natural and synthetic waxes, fatty alcohols, including their esters and ethers, as well as lipid peptides. Especially suitable are synthetic monoglycerides, diglycerides and triglycerides as individual substances or as mixtures (e.g. hard fat), glycerin trifatty acid ester (e.g. glycerin trilaurate, glycerin myristate, glycerin palmitate, glycerin stearate and glycerin behenate) and waxes such as, for example, ceryl palmitate and cera alba (bleached wax, DAB 9).

^{content}
The ~~ratio~~ of the inner or lipid phase, related to the basic preparation, is 0.1 to 30% by weight and preferably 1 to 10% by weight.

Should it be necessary to use dispersion-stabilizing additives to produce stable dispersions, these can be incorporated to stabilize the particles in the form of pure substances or in the form of mixtures. The quantity to be used in relation to the total weight of the watery dispersion ranges in per cent by weight from 0.01 to 20 and preferably from 0.5 to 5. The following substances come into consideration as stabilizing agents:

- a) tensides, particularly ethoxylated sorbitan fatty acid ester, blockpolymers and blockcopolymers (such as e.g. poloxamers and poloxamines), polyglycerin ethers and polyglycerin esters, lecithins of various origin (e. g. egg-lecithin or soya-lecithin),



chemically modified lecithins (e.g. hydrated lecithin), as well as phospholipids and sphingolipids, mixtures of lecithins with phospholipids, sterols (e.g. cholesterol and cholesterol derivatives, as well as stigmasterin), esters and ethers of sugars or sugar alcohols with fatty acids or fatty alcohols (e.g. saccharosemonostearate):

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- b) sterically stabilising substances, such as poloxamers and polyoxyethylene-polyoxypropylene-blockpolymers), ethoxylated sorbitan fatty acid ester, ethoxylated mono- and diglycerides, ethoxylated lipids and lipoids, ethoxylated fatty alcohols or fatty acids, and
- c) charge enhancing or charged compounds such as dicetylphosphate, phosphatidylglycerin, as well as saturated and unsaturated fatty acids, sodium cholate, sodium glycolcholate, sodium taurocholate or mixtures thereof, amino acids or anti-flocculants such as sodium citrate (see J.S. Lucks, W. Müller, R.H. Müller, Int. J. Pharmaceutics 63, 183-188 (1990));
- d) viscosity increasing substances such as cellulose ethers and cellulose esters (e.g. methyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, sodium carboxymethyl cellulose), polyvinyl derivatives, such as polyvinyl alcohol, polyvinyl pyrrolidon, polyvinyl acetate, alginates, polyacrylates (e.g. carbopol), xanthenes and pectins.

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The charge enhancing stabilisers are incorporated, if necessary, in relation to the basic preparation, preferably in a quantity of 0.01 to 10% and most preferably in a quantity of 0.05 to 2%. The viscosity increasing substances are likewise incorporated, if necessary, in relation to the basic preparation, preferably in a quantity of 0.01 to 10%, and even more preferably in a quantity of 0.1 to 10% and most preferable at 0.5 to 5%.



As outer phase (continuous phase, dispersion medium) water, aqueous solutions or liquids miscible with water, such as glycerin or polyethylene glycol, are used. The aqueous solutions can be non-isotonic or isotonic for this purpose. To be taken into consideration as aqueous solutions are mixtures of water with one or several other components such as the following: glycerin, mannose, glucose, fructose, xylose, trehalose, mannitol, sorbitol, xylitol or other polyols such as polyethylene glycol, as well as electrolytes such as sodium chloride. These components are then put proportionately into the basic preparation in a quantity of 0.1 to 50% and preferably 1 to 30%.

The SLN are produced generally by dispersing the inner phase (of the lipid or lipid) into the outer phase (water, aqueous solution or a liquid that is miscible with water) at above room temperature ($>20^{\circ}\text{C}$). When dispersing it is preferable to avoid using ultrasonic probes in order to prevent contamination by metal particles (e.g. Ti). The temperature shall be selected so that the substance to be dispersed is in a liquid state or at least in a softened state. Thus, many lipids are dispersed at 70°C to 80°C . The production is usually accomplished in two stages:

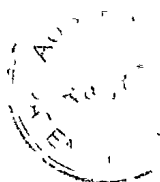
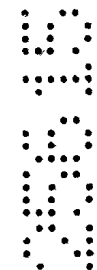
1. by making a pre-dispersion, e.g. with a stirrer or with a rotor-stator-disperser (e.g. Ultra Turrax). If necessary, one or several dispersion-stabilising substances are added;
2. by subsequently dispersing in a high-pressure homogeniser at an increased pressure (e.g. a gap homogeniser, such as APV Gaulin or French Press, a jet stream homogeniser such as the microfluidizer). In systems with good dispersible capacity, step 1 can be eliminated.



Tenside-free SLN is produced by dispersing the lipid or lipoid phase in an aqueous solution which contains one or several viscosity increasing substances either alone or in combination with other substances, such as sugars, sugar alcohols, especially glucose, mannose, trehalose, mannitol, sorbitol, as well as others. Furthermore, it is possible to use a combination of the viscosity increasing substance(s) or the combination thereof with sugars or sugar alcohols, or in a further combination with charged compounds. Suitable charged compounds, for example, are the following: sodium citrate, sodium pyrophosphate, sodium sorbate.

The active substance(s) can be incorporated by various methods, as for example:

1. by dissolving the active substance in the inner phase;
2. by dissolving the active substance in a solvent that is mixable with the inner phase and by adding this solution to the inner phase. The solvent will subsequently be partially or completely removed, if required;
3. by dissolving the active substance in the inner phase (e.g. by dispersing a solid matter or by controlled precipitation of the active substance in the inner phase);
4. by dissolving the active substance in the outer, water phase (e.g. amphiphilous substances) and enclosing the active agent during the production process in a particle-stabilising tenside film;
5. by adsorption of the active substance on the surface of the particles;



6. by dissolving the active substance in the lipid/lipoid phase by means of a ^{solubilising} ~~solving~~ agent (e.g. a blockcopolymer or a sorbitan fatty acid ester), and subsequently dispersing the lipid/lipoid phase in order to produce the preliminary dispersion. The active substance is then present in the SLN as a solid solution;
7. by incorporating ^{aqueous} ~~watery~~ solutions of the active substance into the lipid/lipoid phase and subsequently dispersing the lipid/lipoid phase in order to make the preliminary dispersion, thus producing a W/F/W system which is analogous to the multiple emulsions.

The sterilization can be accomplished according to the procedures outlined in the pharmacopeia, as for example by means of autoclaves (121°C, 2 bar, DAB 9) or according to other recognized procedures.

The realms of use of the drug carrier according to the invention with the solid liquid nanospheres are manifold. For example, it can be used for the following drug applications: parenteral, enteral, pulmonary, topical (nasal, dermal, intra-ocular) and in body cavities.

With respect to the parenteral application, it concerns in particular the following:

1. Intravenous ^{administration} ~~dose~~ (targeting the liver, spleen and bone marrow, particles circulating in the blood and the controlled liberation of active substances, such as peptide drugs, cytostatics, immunostimulants, growth factors, such as the colony stimulating factor (regulation of leucocytes) and the growth factor.

2. Intramuscular administration (depot dosage forms for extended or prolonged release of the active substances, e.g. peptide drugs or hormones).
- 5 3. Intra-articular administration (e.g. for antirheumatics and immunosuppressives for arthritis).
4. Intracavitary administration (e.g. for cytostatics and peptide drugs for forms of cancer in the peritoneum and in the pleura cavity).
5. Subcutaneous administration (e.g. slow release of the drug for cytostatics in skin cancer).
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The enteral forms of application are suited especially to the following:

1. incorporation of lipid-soluble vitamins;
2. lymphatic adsorption (e.g. drug-targeting of cytostatics to the lymph nodes);
- 15 3. presentation of antigens (e.g. oral immunisation with the help of Peyer's plaques), and
4. uptake of peptide medicinal agents with the help of M-cells.

20 As pulmonary forms of application, especially the following come into consideration:

1. aerosols, dosing aerosols (spraying of the aqueous SLN-dispersion).
2. installation of the dispersion.



Examples of topical applications:

1. dermatological drugs for application of e.g., corticoids and antimycotics;
2. Eye drops or eye gels, e.g. for β -blocker, but also for
3. cosmetics analogous to the liposomal preparations.

Examples of drugs to be incorporated into the SLN (as salt, ester, ether or in a ^{Free}liberated form)

Analgetics/Antirheumatics

Morphine, codeine, piritamide, fentanyl and fentanyl derivatives, levomethadon, tramadol, diclofenac, ibuprofen, indometacin, naproxen, piroxicam, penicillamine

Anti-allergics

Pheniramine, dimetinden, terfenadine, astemizol, loratidine, doxylamine, meclozine, bamipin, clemastin

Antibiotics/Chemotherapeutics

from these: polypeptide antibiotics such as colistin, polymyxin B, teicoplanin, vancomycin; antimalarial such as quinine, halofantrin, mefloquine, chloroquine; virustatics such as ganciclovir, foscarnet, zidovudin, aciclovir and others such as dapson,



fosfomycin, fusafungin, trimetoprim

Anti-epileptics

Phenytoin, mesuximide, ethosuximide, primidon, phenobarbital, valproic acid, carbamazepin, clonazepam

Antimycotics

a) internal:

Nystatin, natamycin, amphotericin B, flucytosine, miconazole, fluconazole, itraconazole

b) external, in addition:

Clotrimazole, econazole, tioconazole, fenticonazole, bifonazole, oxiconazole, ketoconazole, isoconazole, tolnaftate

Corticoid (internal)

Aldosterone, fludrocortisone, betametasone, dexametasone, triamcinolone, fluocortolone, hydroxycortisone, prednisolone, prednylidene, cloprednole, methylprednisolone

Dermatics

a) Antibiotics:

Tetracycline, erythromycin, neomycin, gentamycin, clindamycin, framycetin, tyrothricin, chlortetracycline, mupirocin, fusidic acid



- b) Virustatics as above, but in addition:
Podophyllotoxin, vidarabine, tromantadine
- c) Corticoids as above, but in addition:
Amezinonide, flupredniden, alclometason, clobetasol, diflorason, halcinonide, fluocinolone, clqocortolone, flumetason, difluocortolone, flurandrenolide, halometason, desoximetason, fluocinolide, fluocortinbutyl, flupreniden, prednicarbate, desonide

Diagnostics

- a) radioactive isotopes such as Te99m, In111 or I131, covalently bound to lipids or lipoids or other molecules or in complexes
- b) highly substituted iodine-containing compounds such as, e.g., lipids

Haemostyptics/Antihaemorrhagics

Blood clotting factors VIII, IX

Hypnotics, Sedatives

Cyclobarbitol, pentobarbitol, phenobarbitol, methaqualone, benzodiazepines (flurazepam, midazolam, nitrazepam, lormetazepam, flunitrazepam, triazolam, brotizolam, temazepam, loprazolam)

Pituitary hormones, hypothalamic hormones, regulatory peptides and their inhibiting agents

Corticotrophin, tetracosactide, choriogonadotropin, urofolitropin, urogonadotropin, somatropin, metergoline, bromocriptin, terlipressin, desmopressin, oxytocin, argipressin,



ornipressin, leuprorelin, triptorelin, gonadorelin, buserelin, nafarelin, goselerin, somatostatin

Immunotherapeutics and Zytokine

Dimepranol-4-acetate amido benzoate, thymopentin, α -interferon, β -interferon, γ -interferon, filgrastim, interleukin, azathioprine, ciclosporin

Local Anaesthetics

internal:

Butanilicaine, mepivacaine, bupivacaine, etidocaine, lidocaine, articaine, prilocaine,

external, in addition:

Propipocaine, oxybuprocaine, tetracaine, benzocaine

Migraine Agent

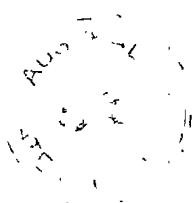
Proxibarbal, lisuride, methysergide, dihydroergotamine, clonidine, ergotamine, pizotifen

Anaesthetic Agent

Methohexital, propofol, etomidate, ketamine, alfentanil, thiopental, droperidol, fentanyl

Parathyroid Gland Hormones, Calcium Metabolism Regulators

Dihydrotachysterol, calcitonin, clodron acid etidron acid



Opthalmics

atropine, cycloclrin, cyclopentolate, homatropine, tropicamide, scopolamine, poledrin, edoxudine, tromantadine, aciclovir, acetazolamide, diclofenamide, carteolol, timolol, metipranolol, betaxolol, pindolol, befunolol, bupranolol, levobunolol, carbachol, pilocarpine, clonidine, neostigmine, idouridin.

Psycho-Drugs

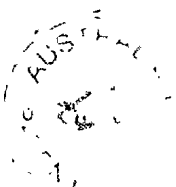
Benzodiazepines (lorazepam, diazepam), clomethiazol

Tyroid Gland Therapeutics

1-thyroxin, carbimazole, thiamazole, propylthiouracil

Serums, Immunoglobulins, Vaccines

- a) Immunoglobulins in general, and specifically such as hepatitis types, German measles, cytomegaly, rabies, FSME, chickenpox/shingles, tetanus, rhesus factors
- b) Immunosera such as botulism-antitoxin, diphtheria, gas gangrene, snake poison, scorpion poison
- c) Vaccines such as influenza, tuberculosis, cholera, diphtheria, hepatitis types, FSME, German measles, haemophilus influenzae, measles, neisseria, mumps, poliomyelitis, tetanus, rabies, typhoid



Sex hormones and their inhibiting agents

Anabolics, androgens, anti-androgens, gestagens, estrogens, anti-estrogens (tamoxifen, etc.)

Cystostatics and Metastasis Inhibitors

- a) Alkylants such as nimustine, melphalane, carmustine, lomustine, cyclophosphamide, ifosfamide, trofosfamide, chlorambucil, busulfan, treosulfan, prednimustine, thiotepa
- b) Antimetabolites such as cytarabine, fluorouracil, methotrexate, mercaptopurine, tioguanine
- c) Alkaloids such as vinblastine, vincristine, vindesine
- d) Antibiotics such as aclarubicin, bleomycin, dactinomycin, daunorubicin, doxorubicin, epirubicin, idarubicin, mitomycin, plicamycin
- e) Complexes of secondary group elements (e.g. Ti, Zr, V, Nb, Ta, Mo, W, Pt) such as carbo-platinum, ~~cis-platinum~~ and metallocene compounds such as titanocendichloride
- f) Amsacrine, dacarbazine, estramustine, etoposide, hydroxycarbamide, mitoxanthrone, procarbazine, temiposide
- g) Alkyl amido phospholipids (described in J.M. Zeidler, F. Emling, W. Zimmermann and H.J. Roth, Pharmacy Archives, 324 (1991), 687)
- h) Etherlipids such as hexadecylphosphocholine, ilmofosin and analogs, described in R. Zeisig, D. Arndt and H. Brachwitz, Pharmacy 45 (1990), 809-818.

The invention is explained in greater detail by the following examples.



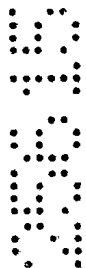
Example II

- 10.0 g cera alba (bleached wax)
2.5 g poloxamer 188 (polyoxyethylene-polyoxypropylene-block-copolymer)
5 0.1 g dicetylphosphate
87.4 g water for injection purposes

Cera alba and dicetylphosphate were heated to 70°C and mixed with a solution of poloxamer 188, in water for injection purposes which was likewise heated to 70°C. The mixture was predispersed at 70°C with the
10 help of an Ultra Turrax. The resulting preliminary dispersion subsequently put through an APV Gaulin high-pressure homogeniser which had been temperature adjusted to 70°C (5 cycles with 500 bar). A SIN-dispersion was attained with a mean diameter of 216 nm. The polydispersity index, serving
15 as measure for the width of the particle size distribution, was 0.143 (PCS-photon correlation spectroscopy). All particles were smaller than 60 µm (measured with a Sympatek laser diffractometer).

Example 2

- 10.0 g cetulpalmitate
2.5 g poloxamer 188
20 87.5 g water for injection purposes



The production was done as described in example 1. The mean diameter was 215 nm and the polydispersity index was 0.131 (PCS-data). All particles were smaller than 4.2 μm (laser diffractometer.
~~diffraction meter).~~

Example 3:

10.0 g	cetylpalmitate
2.5 g	lipoid S 75 (soyalecithin with 75% of phosphatidylcholin)
0.1 g	dicetylphosphate
87.4 g	water for injection purposes

The production was done as described in example 1. However, lipoid S 75 was dispersed in the heated lipid phase. The mean diameter was 183 nm, and the polydispersity index was 0.1333 (PCS-data). All particles were smaller than 8.6 μm (laser diffraction meter).



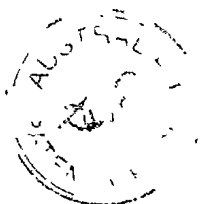
Example 4:

10.5 g	glycerintrilaurate (Dynasan ^(R) 112)
2.5 g	poloxamer 188
87.5 g	water for injection purposes

The production was done as described in example 1. The mean diameter was 199 nm and the polydispersity index was 0.180 (PCS-data). All particles were smaller than 7.2 μm (laser diffraction meter).

Example 5:

10.0 g	cetylpalmitate
2.5 g	poloxamer 188
0.5 g	dicetylphosphate
87.0 g	water for injection purposes



The production was done as described under example 1. The characteristic data before and after the autoclaving substantiates the applicability of the sterilization method.

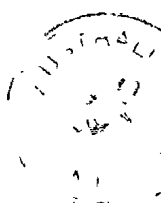
	mean diameter	polydispersity index	all particles smaller than
before sterilization	215 nm	0.131	4.2 μm
after sterilization	214 nm	0.109	3.0 μm

Example 6:

As a model drug, 0.25g of tetracaine base were incorporated in preparation No. 5.

The production was done as described in example 1. The mean diameter was 218 nm and the polydispersity index was 0.186 (PCS-data). All particles were smaller than 10.2 μm (laser diffractometer.
~~diffraction meter~~).

incorporation rate
The drug load was 92.8%.



Example 7:

As a model drug, tetracaine base was incorporated in the following preparation:

10.0 g	glycerin trilaurate (Dynasan 112)
5.0 g	lipoid S 75
	tetracaine base of 0.1 g, 0.5 g, 1.0 g or 2.0 g
to 100.0 g	water for injection purposes

The production was done as described in example 1. However the high-pressure homogenization was carried out at 1500 bar (three cycles). The following values were achieved as mean diameter (PCS-data).

<u>Drug Content</u> <u>(related to lipid phase)</u>	<u>PCS-diameter</u> <u>(nm)</u>
1 %	103
5 %	102
10 %	101
20 %	125

Example 8:

The preparations, as mentioned under example 7, were autoclaved (A 121) according to DAB9.

<u>Drug Content</u> <u>(related to lipid phase)</u>	<u>PCS-diameter</u> <u>before autoclaving</u>	<u>PCS-diameter</u> <u>after autoclaving</u>
1%	103 nm	101 nm
5%	102 nm	102 nm
10%	101 nm	95 nm

When active substances are used which are sensitive to hydrolysis, the particles can also be lyophilized or dried by spraying.

Example 9:

10.0 g	glycerintrilaurate (Dynasan 112)
5.0 g	lipoid S 75
0.5 g	tetracaine base
84.5 ml	watery glucose solution (30% m/V)

The production was done as described under example 1. However, the high-pressure homogenization was carried out at 1500×10^5 pa (1500 bar) (three cycles). As mean diameter (PCS-data), the following values were obtained before and after lyophilization:

	<u>Mean</u> <u>diameter</u>	<u>Polydispersity index</u>
before lyophilization	90 nm	0.277
after lyophilization	481 nm	0.289



As another drug, the active substance hexadecylphosphocholin (HPC) was incorporated in a model preparation.

Example 10:

10.0 g	glycerintrilaurate (Dynasan 112)
5.0 g	poloxamer 188
0.1 g	hexadecylphosphocholin
84.9 g	water for injection purposes

The production was done as described in example 1. The attained SLN-dispersion had a mean PCS diameter of 178 nm. The polydispersity index was 0.1653. All particles were smaller than 3.6 μm (^{diffractometer} ~~laser diffraction meter~~). By varying the tenside content or the tenside components it was possible to produce SLN-dispersions with a HPC-content of 0.1 to 50 mg/g.

By using viscosity increasing substances, it is possible to produce tenside-free SLN-dispersions.

Example 11:

10.0 g	glycerintrilaurate (Dynasan 112)
0.5 g	tylose MH 300
89.5 g	water for injection purposes

The production was done as described in example 1. However, the high-pressure homogenization was carried out at 500×10^5 pa (500 bar) (three cycles). The PCS-diameter of the main population was 879 nm with a polydispersity index of 0.367.

By varying the processing conditions it is possible to produce SLN-dispersions with a mean PCS-diameter below 100 nm.



Example 12:

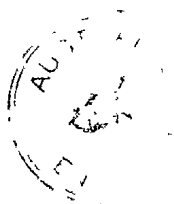
10.0 g	glycerintrilaurate (Dynasan 112)
5.0 g	lipoid S 75
85.0 g	water for injection purposes

The production was done as described under example 1. However, the high-pressure homogenization was carried out at 1500×10^5 pa (1550 bar) (three cycles).

The PCS-diameter of the main population was 88 nm (~~attained~~^{obtained} through polydispersity analysis by means of Fourier's transformation of the ~~attained~~^{obtained} correlation function).

The invention also includes the procedure to produce the described drug carrier as well as its use for administering active substances.

Seen on the whole, the solid lipid nanospheres combine the advantages of polymer nanoparticles (solid core, controllable liberation over a longer period of time, possibility of incorporating hydrophilic ~~medicine~~^{drug}) with the advantages of parenteral fatty emulsions (relatively fast degradation, low or no toxicity, producibility on an industrial scale by methods established for the emulsion products, no difficulties with sterilization by autoclaving) by avoiding the disadvantages of nanoparticles (too slow degradation in vivo or toxic degradation products, lack of scaling-up possibility in the production) and the disadvantages of fatty emulsions (e.g. very quick metabolization, very fast liberation of the medicine).



THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:-

1. A process for the manufacture of a drug carrier which comprises tenside-containing or tenside-free particles of lipid or lipid-like (lipoid) material or mixtures thereof and having a diameter range of 10nm to 10µm,
5 whereby the particles have an average diameter of between 40 and 1000 nm and are solid at room temperature characterised in that the particles when in a melted or softened state are homogenised under high pressure in a dispersion medium being water, aqueous solution or a liquid miscible with water, or the particles when in a solid state are dispersed under high
10 pressure in the dispersion medium, whereby the particles are finely dispersed.
2. The process as in claim 1, characterised in that the particles have an average diameter of 100 to 500 nm.
3. The process as in claim 2 characterised in that the particles have an
15 average diameter of 40 to 80nm.
4. The process as in claim 1, 2 or 3 characterised in that the proportion of particles in relation to the total preparation is 0.1 to 30% by weight.
5. The process as in claim 4, characterised in that the proportion of the particles in relation to the total preparation is 1 to 10% by weight.
- 20 6. The process as in one of the claims 1 to 5, characterised in that the lipid particle material comprises monoglyceride, diglyceride, triglyceride, fatty alcohols and the esters or ethers thereof, waxes and lipid peptides or mixtures thereof.
7. The process as in claim 6, characterised in that the triglyceride
25 comprises glycerine trilaurate, glycerine myristate, glycerine palmitate, glycerine stearate and glycerine behenate; the fatty alcohol comprises cetyl and stearyl alcohol; and the wax comprises cetyl palmitate and bleached beeswax.
8. The process as in one of the claims 1 to 7, characterised in that the
30 drug carrier further includes one or more dispersion-stabilising substances, whereby the dispersion-stabilising substances are included in a quantity of 0.1 to 20% by weight in relation to the total preparation.
9. The process as in claim 8 wherein the dispersion-stabilising substances are included in a quantity of 0.5 to 5% by weight.
- 35 10. The process as in claim 8 or 9 characterised in that the dispersion stabilising substances comprise compounds selected from the group



consisting of poloxamers, poloxamins, ethoxylated monoglycerides and diglycerides, ethoxylated lipids and lipoids, ethoxylated fatty alcohols and alkyl phenols, ethoxylated fatty acid esters, polyglycerine ethers and esters, lecithins, esters and ethers of sugars or sugar alcohols with fatty acids or fatty alcohols, phospholipid and sphingolipids, sterols and the esters and ethers thereof, and mixtures thereof.

11. The process as in claim 8, 9 or 10 characterised in that the dispersion-stabilising substances comprise egg-lecithin, soya-lecithin or hydrogenated lecithin, mixtures thereof, or mixtures of one or both lecithins with one or more phospholipid components, cholesterol, cholesterol palmitate, stigmaterin or other sterols.

12. The process as in one of the preceding claims characterised in that the drug carrier further includes charge-enhancing sterically stabilising compounds in a quantity of 0.01 to 10% by weight in relation to the total preparation.

13. The process as in claim 12 wherein the charge enhancing sterically stabilising compounds are in a quantity of 0.05 to 2% by weight.

14. The process as in claim 13 or 14, characterised in that the charge-enhancing sterically stabilising compounds comprise dicetyl phosphate, phosphatidylglycerol, saturated or unsaturated fatty acids, sodium cholate, sodium glycholate, sodium taurocholate or mixtures thereof, antiflocculants or amino acids.

15. The process as in claim 8, characterised in that the drug carrier further comprises one or more viscosity-increasing substances, whereby the viscosity-increasing substances in a quantity of 0.1 to 10% by weight in relation to the total preparation.

16. The process as in claim 15, wherein the one or more viscosity increasing substances in a quantity of 0.5 to 15% by weight.

17. The process as in claim 15 or 16, characterised in that the viscosity-increasing substances comprise cellulose ethers and esters, polyvinyl derivatives, alginates, polyacrylates, xanthanes and pectins.

18. The process as in claim 15, 16 or 17 characterised in that the drug carrier further comprises sugar or sugar alcohols.

19. The process as in claim 18 wherein the sugar is glucose.

20. The process as in one of the claims 15 to 19 characterised in that the drug carrier further comprises ^{charged}~~charged~~ compounds.



21. The process as in one of the preceding claims, characterised in that the particles are dispersed in distilled water, in an aqueous solution with additives of electrolytes, monosaccharides and disaccharides, polyols or mixtures thereof or a liquid miscible with water, whereby the additives
5 comprise sodium chloride, mannose, glucose, fructose, xylose, trehalose, mannitol, sorbitol, xylitol and glycerol in a quantity of 0.1 to 50% by weight in relation to the total preparation.
22. The process as in claim 21 wherein the further additives are in a quantity of 1 to 30% by weight.
- 10 23. The process as in one of the preceding claims, characterised in that the particles are lyophilised or spray-dried.
24. The process as in claim 1, characterised in that the drug carrier is manufactured without the use of halogenated organic solvents.
25. The process as in one of the preceding claims, characterised in that
15 the drug carrier further includes one or more active substances.
26. The process as in claim 25 wherein the one or more active substances are pharmaceutically active substances.
27. The process as in claim 25 or 26, characterised in that the one or
20 more active substances are dissolved or dispersed in the particles, adsorbed on the surface of the particles or dispersed in the particles as an aqueous solution.
28. The process as in claim 25 or 26 characterised in that the drug carrier contains one or more active substances and is suitable for intravenous administration, intramuscular administration, intra-articular
25 administration, intracavitary administration, subcutaneous administration, intradermal administration, enteral administration, pulmonary application and topical and ophthalmological application.
29. A drug carrier consisting of tenside-free particles of lipid or lipid-like (lipoid) material or mixtures thereof and having a diameter of 10nm to 10µm,
30 manufactured by means of a high-pressure homogenisation process in accordance with one of the claims 1 to 28, whereby the majority of the particles have an average diameter of between 40 and 1000nm and are solid at room temperature.
30. The drug carrier as in claim 29 when used for the manufacture of
35 drugs which are suitable for intravenous administration, intramuscular administration, intra-articular administration, intracavitary administration,

subcutaneous administration, intradermal administration, enteral administration, pulmonary application and topical and ophthalmological application.

DATED this 12th day of July 1996

MEDAC GESELLSCHAFT FUR
KLINISCHE SPEZIALPRAPARATE
MBH

Patent Attorneys for the Applicant:

F.B. RICE & CO.

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ABSTRACT

The invention relates to a drug carrier which comprises particles of lipid or lipid-like (lipoid) material or mixtures thereof which have a diameter of 10 nm to 10 μ m and which are solid at room temperature. On account of its solid core, the drug carrier allows a controllable liberation of active substances over a longer period of time and the incorporation of hydrophilous medicinal agents into the solid core. Furthermore, the drug carrier makes a relatively quick degrading possible at which no toxic by-products are produced.



INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 92/02132

A. CLASSIFICATION OF SUBJECT MATTER

Int. Cl. 5 A61K9/16; A61K9/51

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)

Int. Cl. 5 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)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP, A, 0 167 825 (DR. RENTSCHLER ARZNEIMITTEL GMBH & CO) 15 January 1986	1-14, 24-27
Y	see page 1, line 1 - line 4 see page 4, line 6 - line 10 see page 4, line 17- page 5, line 23 see page 16 - page 17; examples 1,2 see page 18 - page 19; example 4 see page 20; example 9 see claims	15-19
X	EP, A, 0 418 153 (MEDGENIX GROUP SA) 20 March 1991	1-5, 20-23
Y	see page 2, line 1 - line 44 see page 3, line 6 - line 45 see pages 8,9 see claims 1,8,9,11	18 9"

☐ 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 document but published on or after the international filing date

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search
24 November 1992 (24.11.92)

Date of mailing of the international search report
07 December 1992 (07.12.92)

Name and mailing address of the ISA/
European Patent Office

Authorized officer

Facsimile No.

Telephone No.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/EP 92/02132

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP, A, 0 375 520 (CENTRE INTERNATIONAL DE RECHERCHES DERMATOLOGIQUES CIRD) 27 June 1990 see page 2, line 28 - line 32 see page 3, line 41 - line 46 see page 11; example 8 see page 12; example 11 ----	1-3, 6-9
Y	EP, A, 0 438 359 (RHONE POULENC RORER SA) 24 July 1991 see page 2, line 30 - page 3, line 51 ----	15-17, 19
Y	JOURNAL OF PHARMACEUTICAL SCIENCES Vol. 55, No. 4, April 1966, pages 376-380 DRAPER E.V. ET AL'SOME WAX FORMULATIONS OF SULFAETHYLTHIADIAZOLE PRODUCED BY AQUEOUS DISPERSION FOR PROLONGED RELEASE MEDICATION' see page 377 - page 378 -----	15-17

INTERNATIONALER RECHERCHENBERICHT

Internationales Aktenzeichen

PCT/EP 92/02132

I. KLASSEFIZIKATION DES ANMELDUNGSGEGENSTANDS (bei mehreren Klassifikationssymbolen sind alle anzugeben)⁶

Nach der Internationalen Patentklassifikation (IPC) oder nach der nationalen Klassifikation und der IPC
 Int.Kl. 5 A61K9/16; A61K9/51

II. RECHERCHIERTE SACHGEBIETE

Recherchierter Mindestprüfstoff⁷

Klassifikationssystem	Klassifikationssymbole
Int.Kl. 5	A61K

Recherchierte nicht zum Mindestprüfstoff gehörende Veröffentlichungen, soweit diese unter die recherchierten Sachgebiete fallen⁸

III. EINSCHLAGIGE VERÖFFENTLICHUNGEN⁹

Art. ⁹	Kennzeichnung der Veröffentlichung ¹¹ , soweit erforderlich unter Angabe der maßgeblichen Teile ¹²	Betr. Anspruch Nr. ¹³
X	EP,A,0 167 825 (DR. RENTSCHLER ARZNEIMITTEL GMBH & CO) 15. Januar 1986	1-14, 24-27
Y	siehe Seite 1, Zeile 1 - Zeile 4 siehe Seite 4, Zeile 6 - Zeile 10 siehe Seite 4, Zeile 17 - Seite 5, Zeile 23 siehe Seite 16 - Seite 17; Beispiele 1,2 siehe Seite 18 - Seite 19; Beispiel 4 siehe Seite 20; Beispiel 9 siehe Ansprüche	15-19
X	EP,A,0 418 153 (MEDGENIX GROUP SA) 20. März 1991	1-5, 20-23 18
Y	siehe Seite 2, Zeile 1 - Zeile 44 siehe Seite 3, Zeile 6 - Zeile 45 siehe Seite 8,9 siehe Ansprüche 1,8,9,11	9 ¹¹

⁹ Besondere Kategorien von angegebenen Veröffentlichungen¹⁰:

- "A" Veröffentlichung, die den allgemeinen Stand der Technik definiert, aber nicht als besonders bedeutsam anzusehen ist
- "E" älteres Dokument, das jedoch erst am oder nach dem internationalen Anmeldedatum veröffentlicht worden ist
- "L" Veröffentlichung, die geeignet ist, einen Prioritätsanspruch zweifelhaft erscheinen zu lassen, oder durch die das Veröffentlichungsdatum einer anderen im Recherchenbericht genannten Veröffentlichung belegt werden soll oder die aus einem anderen besonderen Grund angegeben ist (wie ausgeführt)
- "O" Veröffentlichung, die sich auf eine mündliche Offenbarung, eine Benutzung, eine Ausstellung oder andere Maßnahmen bezieht
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- "X" Veröffentlichung von besonderer Bedeutung; die beanspruchte Erfindung kann nicht als neu oder auf erfinderischer Tätigkeit beruhend betrachtet werden
- "Y" Veröffentlichung von besonderer Bedeutung; die beanspruchte Erfindung kann nicht als auf erfinderischer Tätigkeit beruhend betrachtet werden, wenn die Veröffentlichung mit einer oder mehreren anderen Veröffentlichungen dieser Kategorie in Verbindung gebracht wird und diese Verbindung für einen Fachmann naheliegend ist
- "&" Veröffentlichung, die Mitglied derselben Patentfamilie ist

IV. BESCHEINIGUNG

Datum des Abschlusses der internationalen Recherche

24. NOVEMBER 1992

Absenddatum des internationalen Recherchenberichts

07. 12. 92

Internationale Recherchenbehörde

EUROPÄISCHES PATENTAMT

Unterschrift des bevollmächtigten Bediensteten

BOULOIS D.

III. EINSCHLAGIGE VERÖFFENTLICHUNGEN (Fortsetzung von Blatt 2)

Art *	Kennzeichnung der Veröffentlichung, soweit erforderlich unter Angabe der maßgeblichen Teile	Betr. Anspruch Nr.
X	EP,A,0 375 520 (CENTRE INTERNATIONAL DE RECHERCHES DERMATOLOGIQUES CIRD) 27. Juni 1990 siehe Seite 2, Zeile 28 - Zeile 32 siehe Seite 3, Zeile 41 - Zeile 46 siehe Seite 11; Beispiel 8 siehe Seite 12; Beispiel 11 ---	1-3,6-9
Y	EP,A,0 438 359 (RHONE POULENC RORER SA) 24. Juli 1991 siehe Seite 2, Zeile 30 - Seite 3, Zeile 51 ---	15-17,19
Y	JOURNAL OF PHARMACEUTICAL SCIENCES Bd. 55, Nr. 4, April 1966, Seiten 376 - 380 DRAPER E.V. ET AL 'SOME WAX FORMULATIONS OF SULFAETHYLTHIAZOLE PRODUCED BY AQUEOUS DISPERSION FOR PROLONGED RELEASE MEDICATION' siehe Seite 377 - Seite 378 -----	15-17

**ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO.**

EP 9202132
SA 64480

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information. 24/11/92

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-0167825	15-01-86	DE-A- 3421468	19-12-85
		JP-A- 61056122	20-03-86
		US-A- 4880634	14-11-89

EP-A-0418153	20-03-91	FR-A- 2651680	15-03-91
		CA-A- 2025298	15-03-91
		JP-A- 3169808	23-07-91
		US-A- 5100591	31-03-92

EP-A-0375520	27-06-90	LU-A- 87410	10-07-90
		AU-B- 626619	06-08-92
		AU-A- 4709989	28-06-90
		CA-A- 2006028	20-06-90
		JP-A- 3135913	10-06-91

EP-A-0438359	24-07-91	FR-A- 2657257	26-07-91
		AU-A- 6948191	25-07-91
		CN-A- 1054189	04-09-91
		JP-A- 4212359	03-08-92

ANHANG ZUM INTERNATIONALEN RECHERCHENBERICHT ÜBER DIE INTERNATIONALE PATENTANMELDUNG NR.

EP 9202132
SA 64480

In diesem Anhang sind die Mitglieder der Patentfamilien der im obengenannten internationalen Recherchenbericht angeführten Patentdokumente angegeben.

Die Angaben über die Familienmitglieder entsprechen dem Stand der Datei des Europäischen Patentamts am
Diese Angaben dienen nur zur Unterrichtung und erfolgen ohne Gewähr.

24/11/92

Im Recherchenbericht angeführtes Patentdokument	Datum der Veröffentlichung	Mitglied(er) der Patentfamilie	Datum der Veröffentlichung
EP-A-0167825	15-01-86	DE-A- 3421468	19-12-85
		JP-A- 61056122	20-03-86
		US-A- 4880634	14-11-89
EP-A-0418153	20-03-91	FR-A- 2651680	15-03-91
		CA-A- 2025298	15-03-91
		JP-A- 3169808	23-07-91
		US-A- 5100591	31-03-92
EP-A-0375520	27-06-90	LU-A- 87410	10-07-90
		AU-B- 626619	06-08-92
		AU-A- 4709989	28-06-90
		CA-A- 2006028	20-06-90
		JP-A- 3135913	10-06-91
EP-A-0438359	24-07-91	FR-A- 2657257	26-07-91
		AU-A- 6948191	25-07-91
		CN-A- 1054189	04-09-91
		JP-A- 4212359	03-08-92

EPO FORM P0473

Für nähere Einzelheiten zu diesem Anhang : siehe Amtsblatt des Europäischen Patentamts, Nr.12/82

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 92/02132

A. CLASSIFICATION OF SUBJECT MATTER

Int. Cl. 5 A61K9/16; A61K9/51

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)

Int. Cl. 5 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)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP, A, 0 167 825 (DR. RENTSCHLER ARZNEIMITTEL GMBH & CO) 15 January 1986	1-14, 24-27
Y	see page 1, line 1 - line 4 see page 4, line 6 - line 10 see page 4, line 17- page 5, line 23 see page 16 - page 17; examples 1,2 see page 18 - page 19; example 4 see page 20; example 9 see claims	15-19
X	EP, A, 0 418 153 (MEDGENIX GROUP SA) 20 March 1991	1-5, 20-23
Y	see page 2, line 1 - line 44 see page 3, line 6 - line 45 see pages 8,9 see claims 1,8,9,11	18 9"

☐ 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

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Date of the actual completion of the international search

24 November 1992 (24.11.92)

Date of mailing of the international search report

07 December 1992 (07.12.92)

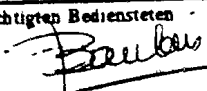
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I. KLASSIFIKATION DES ANMELDUNGSGEGENSTANDS (bei mehreren Klassifikationssymbolen sind alle anzugeben) ⁶		
Nach der Internationalen Patentklassifikation (IPC) oder nach der nationalen Klassifikation und der IPC		
Int.Kl. 5 A61K9/16; A61K9/51		
II. RECHERCHIERTE SACHGEBIETE		
Recherchierter Mindestprüfstoff ⁷		
Klassifikationssystem	Klassifikationssymbole	
Int.Kl. 5	A61K	
Recherchierte nicht zum Mindestprüfstoff gehörende Veröffentlichungen, soweit diese unter die recherchierten Sachgebiete fallen ⁸		
III. EINSCHLAGIGE VERÖFFENTLICHUNGEN ⁹		
Art. ⁹	Kennzeichnung der Veröffentlichung ¹¹ , soweit erforderlich unter Angabe der maßgeblichen Teile ¹²	Betr. Anspruch Nr. ¹³
X	EP,A,0 167 825 (DR. RENTSCHLER ARZNEIMITTEL GMBH & CO) 15. Januar 1986	1-14, 24-27
Y	siehe Seite 1, Zeile 1 - Zeile 4 siehe Seite 4, Zeile 6 - Zeile 10 siehe Seite 4, Zeile 17 - Seite 5, Zeile 23 siehe Seite 16 - Seite 17; Beispiele 1,2 siehe Seite 18 - Seite 19; Beispiel 4 siehe Seite 20; Beispiel 9 siehe Ansprüche	15-19
X	EP,A,0 418 153 (MEDGENIX GROUP SA) 20. März 1991	1-5, 20-23
Y	siehe Seite 2, Zeile 1 - Zeile 44 siehe Seite 3, Zeile 6 - Zeile 45 siehe Seite 8,9 siehe Ansprüche 1,8,9,11	18 9"
-/-		
⁹ Besondere Kategorien von angegebenen Veröffentlichungen ¹⁰ : ^{"A"} Veröffentlichung, die den allgemeinen Stand der Technik definiert, aber nicht als besonders bedeutsam anzusehen ist ^{"E"} Älteres Dokument, das jedoch erst am oder nach dem internationalen Anmeldedatum veröffentlicht worden ist ^{"L"} Veröffentlichung, die geeignet ist, einen Prioritätsanspruch zweifelhaft erscheinen zu lassen, oder durch die das Veröffentlichungsdatum einer anderen im Recherchenbericht genannten Veröffentlichung belegt werden soll oder die aus einem anderen besonderen Grund angegeben ist (wie ausgeführt) ^{"O"} Veröffentlichung, die sich auf eine mündliche Offenbarung, eine Benutzung, eine Ausstellung oder andere Maßnahmen bezieht ^{"P"} Veröffentlichung, die vor dem internationalen Anmeldedatum, aber nach dem beanspruchten Prioritätsdatum veröffentlicht worden ist ^{"T"} Spätere Veröffentlichung, die nach dem internationalen Anmeldedatum oder dem Prioritätsdatum veröffentlicht worden ist und mit der Anmeldung nicht kollidiert, sondern nur zum Verständnis des der Erfindung zugrundeliegenden Prinzips oder der ihr zugrundeliegenden Theorie angegeben ist ^{"X"} Veröffentlichung von besonderer Bedeutung; die beanspruchte Erfindung kann nicht als neu oder auf erfinderischer Tätigkeit beruhend betrachtet werden ^{"Y"} Veröffentlichung von besonderer Bedeutung; die beanspruchte Erfindung kann nicht als auf erfinderischer Tätigkeit beruhend betrachtet werden, wenn die Veröffentlichung mit einer oder mehreren anderen Veröffentlichungen dieser Kategorie in Verbindung gebracht wird und diese Verbindung für einen Fachmann nahelegend ist ^{"&"} Veröffentlichung, die Mitglied derselben Patentfamilie ist		
IV. BESCHEINIGUNG		
Datum des Abschlusses der internationalen Recherche	Absendedatum des internationalen Recherchenberichts	
24. NOVEMBER 1992	07. 12. 92	
Internationale Recherchenbehörde	Unterschrift des bevollmächtigten Bediensteten	
EUROPAISCHES PATENTAMT	BOULOIS D. 	

INTERNATIONAL SEARCH REPORT

International application No.

PCT/EP 92/02132

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP, A, 0 375 520 (CENTRE INTERNATIONAL DE RECHERCHES DERMATOLOGIQUES CIRD) 27 June 1990 see page 2, line 28 - line 32 see page 3, line 41 - line 46 see page 11; example 8 see page 12; example 11 ---	1-3, 6-9
Y	EP, A, 0 438 359 (RHONE POULENC RORER SA) 24 July 1991 see page 2, line 30 - page 3, line 51 ---	15-17, 19
Y	JOURNAL OF PHARMACEUTICAL SCIENCES Vol. 55, No. 4, April 1966, pages 376-380 DRAPER E.V. ET AL 'SOME WAX FORMULATIONS OF SULFAETHYLTHIAZOLE PRODUCED BY AQUEOUS DISPERSION FOR PROLONGED RELEASE MEDICATION' see page 377 - page 378 -----	15-17

III. EINSCHLAGIGE VERÖFFENTLICHUNGEN (Fortsetzung von Blatt 2)

Art *	Kennzeichnung der Veröffentlichung, soweit erforderlich unter Angabe der maßgeblichen Teile	Betr. Anspruch Nr.
X	EP,A,0 375 520 (CENTRE INTERNATIONAL DE RECHERCHES DERMATOLOGIQUES CIRD) 27. Juni 1990 siehe Seite 2, Zeile 28 - Zeile 32 siehe Seite 3, Zeile 41 - Zeile 46 siehe Seite 11; Beispiel 8 siehe Seite 12; Beispiel 11 ---	1-3,6-9
Y	EP,A,0 438 359 (RHONE POULENC RORER SA) 24. Juli 1991 siehe Seite 2, Zeile 30 - Seite 3, Zeile 51 ---	15-17,19
Y	JOURNAL OF PHARMACEUTICAL SCIENCES Bd. 55, Nr. 4, April 1966, Seiten 376 - 380 DRAPER E.V. ET AL 'SOME WAX FORMULATIONS OF SULFAETHYLTHIAZOLE PRODUCED BY AQUEOUS DISPERSION FOR PROLONGED RELEASE MEDICATION' siehe Seite 377 - Seite 378 -----	15-17