Use of nanodispersions in pharmaceutical end formulations

The present invention relates to the use of nanodispersions in pharmaceutical end formulations, to pharmaceutical end formulations comprising said nanodispersions and to the different pharmaceutical uses of these end formulations.

Pharmaceutical end formulations are understood here to mean formulations which comprise, in addition to the basic substances responsible for forming the pharmaceutical formulation, other functional active agents. These are added to the pharmaceutical base formulations and can be used for the therapeutic treatment of the nervous system, endocrine system, cardiovascular system, respiratory tract, gastro-intestinal tract, kidneys and efferent urinary tracts, locomotor apparatus, immunological system, skin and mucosae and for the treatment of infectious diseases.

In order for these substances to have an effect at the desired site, they must be transported to the respective site. To optimise their availability at the site of action, many active agents are applied by means of so-called carrier and transport vehicles (carrier systems), for example mixed micelles, liposomes or nanoemulsions (nanoparticles). Examples of such active agents are amphotericin (NeXstar, Sequus, TLC), daunorubicin (NeXstar), doxorubicin (Sequus), inactivated hepatitis A viruses (Berna), or econazol (Cilag). Applying these active agents by means of said carrier systems results in therapeutic advantages such as fewer side-effects or better vaccinal effect.

Surprisingly, it has now been found that so-called nanodispersions of suitable composition can enhance the effectivity of medicinal agents in pharmaceutical end formulations.

Accordingly, this invention relates to the use of a nanodispersion, which comprises

(a) a membrane-forming molecule,

(b) a coemulsifier and

(c) a lipophilic component,

in pharmaceutical end formulations, the nanodispersion being obtainable by

(α) mixing the components (a), (b) and (c) until a homogeneous clear liquid is obtained (so-called nanodispersion prephase), and

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(β) adding the liquid obtained in step (α) to the water phase of the pharmaceutical end formulations, steps (α) and (β) being carried out without any additional supply of energy.

Step (α) is usually carried out at room temperature, where necessary with heating and under normal pressure conditions. Mixing is carried out using standard stirring apparatus, for example propeller, angled paddle or magnetic agitators, and without using any special mechanical stirring aids.

Components (a), (b) and (c) (= step (α)) are mixed in anhydrous medium, i.e. it is not necessary to add any water.

Step (β) is carried out by adding the liquid obtained in step (α), the nanodispersion prephase, to the water phase of the pharmaceutical end formulations. The particular choice of components (a), (b) and (c) results directly in ultrafine, monodisperse nanodispersions. In this case it is possible to forego homogenisation via nozzle, rotor-stator or ultrasound homogenisers, which is usually carried out to convert coarsely disperse or at least heterodisperse systems to fine monodisperse systems. Step (β) is thus characterised by the absence of high shear or cavitation forces.

Step (β) is usually carried out at room temperature, which is the range of the respective oil/water phase inversion temperature (PIT).

The nanodispersions characterised by the process steps (α) and (β) contain particles having an average diameter of <50 nm, typically of less than 30 nm. The distribution is monodisperse and obeys a Gaussian distribution.

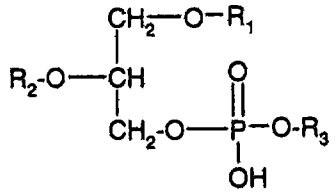
It is preferred to use a nanodispersion, which contains,

(a) as membrane-forming molecules, substances which are suitable for forming so-called bilayers,

(b) as coemulsifiers, substances which preferably form O/W structures and,

(c) as lipophilic component, a lipophilic agent customarily used for pharmaceutical preparations.

The nanodispersion preferably contains as component (a) a phospholipid, a hydrated or partially hydrated phospholipid, a lysophospholipid, a ceramide, or mixtures of these compounds,

(1) 

wherein

R_1 is C_{10}-C_{20}acyl;

R_2 is hydrogen or C_{10}-C_{20}acyl

R_3 is hydrogen, 2-trimethylamino-1-ethyl, 2-amino-1-ethyl; C_1-C_5alkyl which is unsubstituted or substituted by one or several carboxy, hydroxy or amino groups; the inositol or glyceryl group;

or salts of these compounds.

C_{10}-C_{20}Acyl is preferably straight-chain C_{10}-C_{20}alkanoyl containing an even number of carbon atoms and straight-chain C_{10}-C_{20}alkenoyl containing a double bond and an even number of carbon atoms.

Straight-chain C_{10}-C_{20}alkanoyl containing an even number of carbon atoms is, for example, n-dodecanoyl, n-tetradecanoyl, n-hexadecanoyl or n-octadecanoyl.

Straight-chain C_{10}-C_{20}alkenoyl containing a double bond and an even number of carbon atoms is, for example, 6-cis- or 6-trans-, 9-cis- or 9-trans-dodecenoyl, -tetradecenoyl, -hexadecenoyl, -octadecenoyl or -eicosenoyl, preferably 9-cis-octa-decenoyl (oleoyl), and also 9,12-cis-octadecadienoyl or 9,12,15-cis-octadecatrienoyl.

A phospholipid of formula (1), wherein R_3 is 2-trimethylamino-1-ethyl, is referred to by the trivial name lecithin, and a phospholipid of formula (1), wherein R_3 is 2-amino-1-ethyl, by the trivial name cephalin. Suitable are, for example, naturally occurring cephalin or lecithin, e.g. cephalin or lecithin from soybeans or chicken eggs with different or identical acyl groups, or mixtures thereof.

The phospholipid of formula (1) may also be of synthetic origin. The expression "synthetic phospholipid" is used to define phospholipids having uniform composition with respect to R_1 and R_2. Such synthetic phospholipids are preferably the lecithins and cephalins defined above, wherein the acyl groups R_1 and R_2 have a defined structure and which are derived from a defined fatty acid having a degree of purity greater than about 95%. R_1 and R_2 may be identical or different and unsaturated or saturated. Preferably, R_1 is saturated, for example n-hexadecanoyl, and R_2 is unsaturated, for example 9-cis-octadecenoyl (oleoyl).

The expression "naturally occurring" phospholipid defines a phospholipid that does not have a uniform composition with respect to R_1 and R_2. Such natural phospholipids are likewise lecithins and cephalins, wherein the acyl groups R_1 and R_2 are derived from naturally occurring fatty acid mixtures.

The requirement "substantially pure" phospholipid of formula (1) defines a degree of purity of more than 90 % by weight, preferably of more than 95 % by weight of the phospholipid of formula (1), which can be demonstrated by means of suitable determination methods, for example by paper chromatography, thin-layer chromatography, by HPLC or by means of enzymatic colour testing.

In a phospholipid of formula (1), R_3 defined as C_1-C_4alkyl is, for example, methyl or ethyl. Methyl is preferred.

R_3 defined as C_1-C_5alkyl substituted by one or several carboxy, hydroxy or amino groups is, for example, 2-hydroxyethyl, 2,3-dihydroxy-n-propyl, carboxymethyl, 1- or 2-carboxyethyl, dicarboxymethyl, 2-carboxy-2-hydroxyethyl or 3-carboxy-2,3-dihydroxy-n-propyl, 3-amino-3-carboxy-n-propyl or 2-amino-2-carboxy-n-propyl, preferably 2-amino-2-carboxyethyl.

Phospholipids of formula (1) containing these groups can be present in salt form, for example as sodium or potassium salt.

Phospholipids of formula (1), wherein R_3 is the inositol or glyceryl group, are known by the names phosphatidylinositol and phosphatidylglycerol.

The acyl radicals in the phospholipids of formula (1) are also customarily known by the

names given in brackets:
9-cis-dodecenoyl (lauroleoyl), 9-cis-tetradecenoyl (myristoleoyl), 9-cis-hexadecenoyl (palmitoleoyl), 6-cis-octadecenoyl (petroseloyl), 6-trans-octadecenoyl (petroselaidoyl), 9-cis-octadecenoyl (oleoyl), 9-trans-octadecenoyl (elaidoyl), 9,12-cis-octadecadienoyl (linoleoyl), 9,12,15-cis-octadecatrienoyl (linolenoyl), 11-cis-octadecenoyl (vaccenoyl), 9-cis-eicosenoyl (gadoleoyl), 5,8,11,14-cis-eicosatetraenoyl (arachidonoyl), n-dodecanoyl (lauroyl), n-tetradecanoyl (myristoyl), n-hexadecanoyl (palmitoyl), n-octadecanoyl (stearoyl), n-eicosanoyl (arachidoyl), n-docosanoyl (behenoyl), n-tetracosanoyl (lignoceroyl).

A salt of the phospholipid of formula (1) is preferably pharmaceutically acceptable. Salts are defined by the existence of salt-forming groups in the substituent R_3 and by the free hydroxyl group at the phosphorus atom. The formation of internal salts is also possible. Alkali metal salts, especially the sodium salt, are preferred.

In a particularly preferred embodiment of this invention, purified lecithin from soybeans of the quality LIPOID S 100 or S 75, or a lecithin defined in the monograph USP23/NF 18, is used.

Component (a) is preferably used in a concentration of about 0.1 to 30 % by weight, based on the total weight of components (a), (b) and (c).

Component (b) is preferably an emulsifier or emulsifier mixtures forming the preferred O/W structures.

Especially preferred emulsifiers are

- alkali, ammonium and amine salts of fatty acids. Examples of such salts are the lithium, sodium, potassium, ammonium, triethylamine, ethanolamine, diethanolamine or triethanolamine salts. It is preferred to use the sodium, potassium or ammonium (NR1R2R3) salts, wherein R_1, R_1 and R_1 are each independently of one another hydrogen, C_1-C_4alkyl or C_1-C_4hydroxyalkyl.
- saturated and unsaturated alkyl sulfates, such as sodium docecylsulfate and alkanesulfonates such as sodium dodecanesulfonate;
- salts of colic acid, such as sodium cholate, sodium glycocholate and sodium taurocholate;
- invert soaps (quats), such as zetylpyridinium chloride;

- partial fatty acid esters of sorbitan, such as sorbitan monolaurate;
- sugar esters of fatty acids, such as sucrose monolaurate;
- alkylglucosides, such as n-octylglucoside or n-dodecylglucoside;
- alkylmaltosides, such as n-dodecylmaltoside;
- fatty acid partial glycerides, such as lauric acid monoglyceride;
- C_8-C_{18}betaines, C_8-C_{24}alkylamido-C_1-C_4alkylenebetaines and C_8-C_{18}sulfobetaines;
- proteins, such as casein;
- polyglycerol esters of fatty acids;
- propylene glycol esters of fatty acids;
- lactates of fatty acids, such as sodium stearoyllactyl-2-lactate;
- fatty alcohol phosphorates.

Emulsifiers of the polyoxyethylene type are very particularly preferred. Examples of such emulsifiers are:

- polyethoxylated sorbitan fatty acid esters, such as polysorbate 80;
- polyethoxylated fatty alcohols, such as oleth-20;
- polyethoxylated fatty acids, such as polyoxyl 20 stearate;
- polyethoxylated vitamin E derivatives, such as vitamin E polyethylene glycol 1000 succinate;
- polyethoxylated lanoline and lanoline derivatives, such as laneth-20;
- polyethoxylated fatty acid partial glycerides, such as diethylene glycol monostearate;
- polyethoxylated alkylphenols, such as ethylphenolpoly(ethylene glycol ether)11;
- sulfuric acid semiester polyethoxylated fatty alcohols and their salts, such as C_{12}-C_{14}-fatty alcohol ether sulfate-2 EO-sodium salt;
- polyethoxylated fatty amines and fatty acid amides;
- polyethoxylated carbon hydrates
- block polymers of ethylene oxide and propylene oxide, such as poloxamer 188.

Component (b) is present in the nanodispersion used according to this invention in a concentration of about 1 to about 50 % by weight, based on the total weight of the components (a), (b) and (c).

Component (c) is preferably a natural or synthetic or a partially synthetic di- or triglyceride, a mineral oil, silicone oil, wax, fatty alcohol, guerbet alcohol or the ester thereof, a therapeutic oil, a lipophilic pharmaceutical active agent or a mixture of these substances.

Active agents suitable for pharmaceutical application are to be found, inter alia, in Arzneimittelkompendium 1997. Examples of suitable active agents are:
analgesics, antacids/ulcus treatments, antiallergic agents, antianemic drugs, antidepressants, antidiabetic agents, antidiarrheal agents, antidotes/addiction-combating agents/emetics, anti-emetics/antivertiginosa, antiepileptic agents, antihemorrhagic agents, antihypertensives, antihypotonic agents, antiinfectives, anticoagulants, antirheumatic agents/anti-inflammatory agents, appetite depressants, beta blockers, bronchodilators, cholinergic agents, dermatological agents, disinfectants, diagnostic agents, dietetic agents, diuretics, blood flow stimulants, gastroenterological agents, gout remedies, influenza remedies, gynecological agents, antihemorrhoidal agents, hormones, antitussives, hypnotics, immunological agents, intravenous infusions, cardiac remedies, contraceptives, contrast media, adrenocortical steroids, laxatives, liver and gall therapeutic agents, lipid metabolism preparations, local anesthetics, migraine analgesics, mineral metabolism preparations, muscle relaxants, narcotics, neuroleptic agents, odontological agents, ophthalmic agents, otorhinolaryngological agents (ORL), anti-parkinson drugs, psychostimulants, sedatives, spasmolytic agents, tonics/roborants, tranquilisers, anti-tuberculosis drugs, urological agents, preparations for varicose veins, consolidants and zytostatic agents.

Component (c) is present in the nanodispersions used according to this invention in a concentration of preferably 0.1 to 80 % by weight, based on the total weight of components (a), (b) and (c).

The nanodispersion used according to this invention optionally comprises as facultative component (d) a solubiliser, preferably a C_2-C_8alcohol, such as ethanol or propylene glycol.

A nanodispersion containing the components (a), (b), (c) and optionally (d) is distinguished by favourable phase properties of the solubilised functional pharmaceutical agent. Thus if there is opalescence and transparency in incident light, only a very slight turbidity shows that the dispersion is physically still different from the ideal state of a genuine molecular solution. Electron microscopic images show that a population of more than 98 % is present in a

Gaussian distribution as a suspension of particles (nanoparticles) having a particle size of less than about 50 nm, typically of less than about 30 nm. However, these distinctions from a genuine solution can be tolerated because of the particularly good homogeneity properties of the dispersion which can be evidenced, for example, by a surprisingly high storage stability, e.g. no separation after storing for several months at temperatures of up to room temperature (stability to be expected by extrapolation: more than two years).

Laser light scattering measurements and electron microscopic analysis (Cryo-TEM) confirm the very small size and excellent homogeneity of the nanoparticles present in the nanodispersion.

Another advantage of the nanodispersions used according to this invention is that they are easy to prepare.

The nanodispersions characterised by claim 1 are used according to this invention for pharmaceutic end formulations.

This invention also relates to the so-called nanodispersion prephase characterised in step (α), which is obtainable by mixing the components

(a) membrane-forming molecules,
(b) coemulsifier,
(c) lipophilic component and, optionally,
(d) a C_2-C_8alcohol, preferably propylene glycol and, more preferably, ethanol

until a homogeneous clear liquid is obtained, mixing being carried out in anhydrous medium.

In accordance with this invention, the nanodispersion prephase or the nanodispersion is used directly for pharmaceutical end formulations.

The pharmaceutical end formulations are preferably liquid, semisolid or solid preparations.

Examples of liquid pharmaceutical end formulations are injectable solutions, infusion solutions, drops, sprays, aerosols, emulsions, lotions, suspensions, drinking solutions, gargles and inhalants.

Examples of semisolid pharmaceutical end formulations are ointments, creams (O/W emulsions), rich creams (W/O emulsions), gels, lotions, foams, pastes, suspensions, ovula, plasters, including transdermal systems.

Examples of solid pharmaceutical end formulations are tablets, coated tablets, capsules, granules, effervescent granules, effervescent tablets, lozenges, sucking and chewing tablets, suppositories, implants, lyophilisates, adsorbates or powders.

This invention also relates to these end formulations.

The end formulations contain the nanodispersion in a concentration of 0.01 to 100 by weight, preferably of 0.05 to 20 by weight and, more preferably, of 0.1 to 10 % by weight.

To prepare liquid and semisolid pharmaceutical end products (Examples 20 to 29), the nanodispersions are incorporated into the aqueous component of the end product. It is also possible to add instead of the nanodispersion the corresponding nanodispersion prephase to the water phase of the pharmaceutical end formulation. The nanodispersion prephase is added to the water phase with stirring and preferably at a temperature in the range of the respective oil/water phase inversion temperature (PIT).

Solid pharmaceutical end products, such as tablets (Example 30), effervescent tablets, coated tablets, granules, effervescent granules and plasters, are coated or loaded with nanodispersions by spraying or drenching. In certain cases it is advantageous to admix the dehydrated form of the nanodispersion to the solid mixture. The nanodispersion is usually dehydrated by freeze- or spray-drying in the presence of customary excipients. Capsules, in particular elastic gelatin capsules, can also be loaded with the nanodispersion prephase (Example 31).

Matrix- or membrane-controlled pharmaceutical application systems, such as oros capsules, transdermal systems, injectable microcapsules or implants, are loaded by conventional methods with nanodispersions. Oros capsules can also be loaded with the nanodispersion prephase.

In addition to the excipients for providing the pharmaceutical dosage form, the pharmaceutical end formulation can also contain other components, for example stabilisers, preservatives such as parabenes, antioxidants, and aromatics, fragrances or colourants.

The pharmaceutical end formulations are preferably used for the therapeutic treatment of the nervous system, endocrine system, cardiovascular system, respiratory tract, gastro-intestinal tract, kidneys and efferent urinary tracts, locomotor apparatus, immunological system, skin and mucosae as well as for the treatment of infectious diseases, tumours and vitamin and mineral deficiency diseases.

The novel pharmaceutical end formulation is preferably applied epicutaneously, buccally, lingually, sublingually, enterally (= perorally), rectally, nasally, pulmonally, per inhalationem, conjunctivally, intravaginally, intraurethrally, intracardially, intraarterially, intravenously, intralumbally, intrathecally, intraarticularly, intracutaneously, subcutaneously, intramuscularly and intraperitoneally.

In the following Examples, percentages are by weight. Unless otherwise stated, amounts of compounds used are based on the pure substance.

Working Examples for nanodispersion prephases

Example 1: Miglyol 812 nanodispersion prephase

soybean lecithin	17.30 %
polysorbate 80	34.00 %
miglyol 812	34.50 %
ethanol	14.20 %

Preparation: Miglyol 812 and polysorbate 80 are mixed. The soybean lecithin is dissolved in ethanol and added to this mixture, resulting in a homogeneous clear liquid.

Example 2: Miglyol 812 nanodispersion prephase

soybean lecithin	17.30 %
oleth-20	34.00 %
miglyol 812	34.50 %
ethanol	14.20 %

Preparation: Miglyol 812 and oleth-20 are mixed, with heating. The soybean lecithin is dissolved in ethanol and added to this mixture, resulting in a homogeneous clear liquid.

Example 3: Miglyol 812 nanodispersion prephase

soybean lecithin	17.30%
laneth-20	34.00 %
miglyol 812	34.50 %
ethanol	14.20 %

Preparation: Miglyol 812 and Laneth-20 are mixed, with heating. The soybean lecithin is dissolved in ethanol and added to this mixture, resulting in a homogeneous clear liquid.

Example 4: Miglyol 812 nanodispersion prephase

soybean lecithin	17.30 %
vitamin E polyethylene glycol succinate (vitamin E TPGS, Eastman)	34.00 %
miglyol 812	34.50 %
ethanol	14.20 %

Preparation: Miglyol 812 and vitamin E polyethylene glycol succinates are mixed, with heating. The soybean lecithin is dissolved in ethanol and added to this mixture, resulting in a homogeneous clear liquid.

Example 5: Vitamin E acetate nanodispersion prephase

soybean lecithin	9.00 %
polysorbate 80	34.00 %
vitamin E acetate	36.60 %
miglyol 812	13.00 %
ethanol	7.40 %

Preparation: Miglyol 812, vitamin E acetate and polysorbate 80 are mixed. The soybean lecithin is dissolved in ethanol and added to this mixture, resulting in a homogeneous clear liquid.

Example 6: Vitamin A palmitate nanodispersion prephase

soybean lecithin	17.30 %
polysorbate 80	34.00 %
vitamin A palmitate (1.7×10^6 IU/g)	4.50 %
miglyol 812	30.00 %
ethanol	14.20 %

Preparation: Vitamin A palmitate, miglyol 812 and polysorbate 80 are mixed. The soybean lecithin is dissolved in ethanol and added to this mixture, resulting in a homogeneous clear liquid.

Example 7: Tridecyl salicylate nanodispersion prephase

soybean lecithin	11.00 %
polysorbate 80	26.00 %
tridecyl salicylate	40.50 %
miglyol 812	13.50 %
ethanol	9.00 %

Preparation: Tridecyl salicylate, miglyol 812 and polysorbate 80 are mixed. The soybean lecithin is dissolved in ethanol and added to this mixture, resulting in a homogeneous clear liquid.

Working Examples for nanodispersions

Example 8: Miglyol 812 Nanodispersion

soybean lecithin	1.73 %
polysorbate 80	3.40 %
miglyol 812	3.45 %
ethanol	1.42 %
10 mm phosphate buffer, pH 6	ad 100.00 %

Preparation: The water phase (e.g. 90 kg) is placed, with stirring (e.g. magnetic agitator), at 50°C in a vessel. The liquid nanodispersion prephase of Example 1 (e.g. 10 kg) is added to the water phase with stirring (e.g. with a magnetic agitator).

Example 9: Miglyol 812 nanodispersion

soybean lecithin	1.73 %
oleth-20	3.40 %
miglyol 812	3.45 %
ethanol	1.42 %
10 mm phosphate buffer, pH 6	ad 100.00 %

The nanodispersion is prepared in analogy to the procedure of Example 8.

Example 10: Miglyol 812 nanodispersion

soybean lecithin	1.73 %
laneth-20	3.40 %
miglyol 812	3.45 %
ethanol	1.42 %
10 mm phosphate buffer, pH 6	ad 100.00 %

The nanodispersion is prepared in analogy to the procedure of Example 8.

Example 11: Miglyol 812 nanodispersion

soybean lecithin	1.73 %
vitamin E polyethylene glycol succinate (vitamin E TPGS, Eastman)	3.40 %
miglyol 812	3.45 %
ethanol	1.42 %
10 mm phosphate buffer, pH 6	ad 100.00 %

The nanodispersion is prepared in analogy to the procedure of Example 8.

Example 12: Dexpanthenol nanodispersion

dexpanthenol	5.00 %
soybean lecithin	1.73 %
polysorbate 80	3.40 %
miglyol 812	3.45 %
ethanol	1.42 %
10 mm phosphate buffer, pH 6	ad 100.00 %

Preparation: The water phase comprising dexpanthenol (e.g. 90 kg) is placed, with stirring (e.g. magnetic agitator), at 50°C in a vessel. The liquid nanodispersion prephase of Example 1 (e.g. 10 kg) is added to the water phase with stirring (e.g. magnetic agitator).

Example 13: Dexpanthenol nanodispersion

dexpanthenol	5.00 %
soybean lecithin	1.73 %
polysorbate 80	3.40 %
miglyol 812	3.45 %
ethanol	1.42 %
10 mm phosphate buffer, pH 7.4	ad 100.00 %

The nanodispersion is prepared in analogy to the procedure of Example 12.

Example 14: Vitamin E acetate nanodispersion

vitamin E acetate	2.00 %
soybean lecithin	0.49 %
polysorbate 80	1.86 %
miglyol 812	0.71 %
ethanol	0.63 %
10 mm phosphate buffer, pH 6	ad 100.00 %

Preparation: The water phase (e.g. 94.54 kg) is placed, with stirring (e.g. magnetic agitator), at 50°C in a vessel. The liquid nanodispersion prephase of Example 5 (e.g. 5.46 kg) is added to the water phase with stirring (e.g. magnetic agitator).

Example 15: Vitamin E acetate nanodispersion

vitamin E acetate	2.00 %
soybean lecithin	0.49 %
polysorbate 80	1.86 %
miglyol 812	0.71 %
ethanol	0.63 %
10 mm phosphate buffer, pH 7.4	ad 100.00 %

The nanodispersion is prepared in analogy to the procedure of Example 14.

Example 16: Vitamin A palmitate nanodispersion

vitamin A palmitate (1.7×10^6 IU/g)	0.45 %
soybean lecithin	1.73 %
miglyol 812	3.00 %
polysorbate 80	3.40 %
ethanol	1.42 %
10 mm phosphate buffer, pH 6	ad 100.00 %

The nanodispersion is prepared in analogy to the procedure of Example 8.

Example 17: Vitamin A palmitate nanodispersion

vitamin A palmitate (1.7×10^6 IU/g)	0.45 %
soybean lecithin	1.73 %
miglyol 812	3.00 %
polysorbate 80	3.40 %
ethanol	1.42 %
10 mm phosphate buffer, pH 7.4	ad 100.00 %

The nanodispersion is prepared in analogy to the procedure of Example 8.

Example 18: Solcoseryl nanodispersion

solcoseryl	1.00 %
soybean lecithin	1.73 %
polysorbate 80	3.40 %
miglyol 812	3.45 %
ethanol	1.42 %
10 mm phosphate buffer, pH 6	ad 100.00 %

Preparation: The water phase comprising solcoseryl (e.g. 90 kg) is placed, with stirring (e.g. magnetic agitator), at 50°C in a vessel. The liquid nanodispersion prephase of Example 1 (e.g. 10 kg) is added to the water phase with stirring (e.g. magnetic agitator).

Example 19: Tridecyl salicylate nanodispersion

tridecyl salicylate	4.05 %
soybean lecithin	1.10 %
polysorbate 80	2.60 %
miglyol 812	1.35 %
ethanol	0.90 %
10 mm phosphate buffer, pH 6	ad 100.00 %

Preparation: The water phase (e.g. 90 kg) is placed, with stirring (e.g. magnetic agitator), at 50°C in a vessel. The liquid nanodispersion prephase of Example 7 (e.g. 10 kg) is added to the water phase with stirring (e.g. magnetic agitator).

The particle sizes and particle size distributions of nanodispersions are compiled in the following Table 1.

Table 1			
Nanodispersion	Particle diameter[1] [nm]	Standard deviation [nm]	Particle size distribution
migylol 812 nanodispersion Example 8	13.8	4.1	Gauss
dexpanthenol nanodispersion Example 12	19.7	5.4	Gauss
vitamin E acetate nanodispersion Example 14	12.2	5.5	Gauss
vitamin A palmitate nanodispersion Example 16	10.1	3.9	Gauss
solcoseryl nanodispersion Example 18	7.3	3.4	Gauss
tridecyl salicylate nanodispersion Example 19	16.3	6.6	Gauss

As the following Tables show, nanodispersions also have excellent storage stability:

[1] The particle diameters and particle size distributions are determined via laser light scattering (Nicomp 370 Submicron Particle Sizer, number weighting)

Dexpanthenol nanodispersion (Example 12)

Table 2

Storage conditions		pH	Diameter[2] [nm]	Standard deviation [nm]	Dexpanthenol[3] content [%]
Duration [months]	Temperature [°C]				
0		6.1	19.7	5.4	5.37
3	7	6.1	19.0	6.7	5.36
	25	6.1	22.2	7.7	5.32
	40	6.3	36.6	14.2	5.23
6	7	6.1	20.8	7.3	5.30
	25	6.2	24.1	9.2	5.26
	40	6.4	35.4	17.7	5.20

[2] The particle diameters and particle size distributions are determined via laser light scattering (Nicomp 370 Submicron Particle Sizer, volume weighting)

[3] The dexpanthenol content is determined via HPLC

Vitamin E acetate nanodispersion (Example 14)

Table 3

Storage conditions		pH	Diameter[4] [nm]	Standard deviation [%]	Vitamin E acetate[5] content [%]
Duration [months]	Temperature [°C]				
0		6.1	12.2	5.5	2.04
3	7	6.1	16.1	6.6	2.02
	25	6.1	17.5	7.0	2.04
	40	6.0	15.4	6.8	2.01
6	7	6.1	17.0	6.9	2.04
	25	6.0	17.6	7.2	2.03
	40	6.0	20.8	7.9	2.02

Working Examples for pharmaceutical end formulations with nanodispersions or nanodispersion prephases

Example 20: Dexpanthenol 5 % controlled dosage non-aerosol spray

Nanodispersion according to Example 12 100.00 %

The preparation has good anti-inflammatory action.

Example 21: Dexpenthanol vitamin E acetate lotion

cera emulsificans cetomacrogolis	3.0 %
oleylium oleinicum	6.0 %
propylene glycolum	3.0 %
nanodispersion of Example 12	10.0 %
nanodispersion of Example 14	10.0 %
aqua purificata	ad 100.0 %

[4] The particle diameters and the particle size distributions are determined via laser light scattering

[5] The vitamin E acetate content is determined via HPLC

The preparation has good anti-inflammatory action.

Example 22: Dexpanthenol 2.5 % eye drops

mannitol	4.70 %
nanodispersion of Example 13	50.00 %
10 mm phosphate buffer, pH 7.4	ad 100.00 %

The preparation has good anti-inflammatory action.

Example 23: Vitamin A palmitate 0.1 % cream

cetyl alcohol	10.00 %
hydrogenated groundnut oil	20.00 %
polysorbate 60	5.00 %
propylene glycol	20.00 %
phenoxyethanol	0.50 %
nanodispersion of Example 16	23.00 %
aqua purificata	ad 100.00 %

The preparation has good vitamin A action.

Example 24: Vitamin A palmitate 0.1 % aerosol

sodium EDTA	0.05 %
mannitol	4.70 %
nanodispersion of Example 17	23.00 %
10 mm phosphate buffer, pH 7.4	ad 100.00 %

The preparation has good vitamin A action.

Example 25: Tridecyl salicylate 1.0 % ointment

citric acid	0.75 %
ammonia solution	0.09 %
medium-chain triglyceride	5.00 %
unguentum alcoholum lanae aquosum DAB 9	40.00 %
nanodispersion of Example 19	25.00 %
aqua purificata	ad 100.00 %

The preparation has good keratinolytic action.

Example 26: Solcoseryl 0.5 % hydrogel

sodium carboxymethylcellulose 450 cP	3.50 %
nanodispersion of Example 18	50.00 %
aqua purificata	ad 100.00 %

The preparation is pleasantly cooling and has good antiphlogistic action.

Example 27: Solcoseryl 1.0 % controlled dosage non-aerosol spray

Nanodispersion of Example 18	100.00 %

The preparation has good anti-inflammatory action.

Example 28: vitamin E acetate drink ampoules

citric acid	0.40 %
glucose	7.50 %
aroma	0.50 %
nanodispersion of Example 14	50.00 %
aqua purificata	ad 100.00 %

The preparation has good antioxidative action.

Example 29: Vitamin E acetate injectable solution

mannitol	4.70 %
nanodispersion of Example 15	75.00 %
10 mm phosphate buffer, pH 7.4	ad 100.00 %

The preparation has good antioxidative action.

Example 30: Vitamin E acetate tablets

hydroxypropylmethylcellulose (methocel E4M CR grade)	15.00 %
magnesium stearate	0.70 %
vitamin E acetate[6]	1.00 %
lactose	ad 100.00 %

The preparation has good antioxidative action.

Example 31: Vitamin E acetate elastic gelatin capsules

Elastic gelatin capsules are filled with the nanodispersion prephase of Example 5.

The preparation has good antioxidative action.

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[6] Vitamin E acetate is incorporated during granulation in the form of the nanodispersion, i.e. the nanodispersion of Example 14 is used as granulating liquid.

What is claimed is

1. Use of a nanodispersion, which comprises



(a) a membrane-forming molecule,

(b) a coemulsifier and

(c) a lipophilic component,

in pharmaceutical end formulations, the nanodispersion being obtainable by

(α) mixing the components (a), (b) and (c) until a homogeneous clear liquid is obtained (so-called nanodispersion prephase), and

(β) adding the liquid obtained in step (α) to the water phase of the pharmaceutical end formulations, steps (α) and (β) being carried out without any additional supply of energy.

2. Use according to claim 1, which is characterised in that step (α) is carried out in anhydrous medium.

3. Use according to either claim 1 or claim 2, which is characterised in that step (β) is carried out without homogenisation.

4. Use according to any one of claims 1 to 3, which is characterised in that the particles in the nanodispersion have an average diameter of <50 nm.

5. Use according to any one of claims 1 to 4, which is characterised in that the nanodispersion comprises,

(a) as membrane-forming molecules, substances which are suitable for forming bilayers,

(b) as coemulsifiers, substances which preferably form O/W structures and,

(c) as lipophilic component, a lipophilic active agent.

6. Use according to any one of claims 1 to 5, which is characterised in that the nanodispersion comprises as component

(a) a phospholipid, a hydrated or partially hydrated phospholipid, a lysophospholipid, a ceramide or mixtures thereof.

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7. Use according to claim 6, which is characterised in that the component (a) is present in the nanodispersion in a concentration of 0.1 to 30 % by weight, based on the total weight of the components (a), (b) and (c).

8. Use according to any one of claims 1 to 7, which is characterised in that the nanodispersion comprises as component

(b) an emulsifier of the polyoxethylene type, saturated and unsaturated C_8-C_{18}alkylsulfates, the alkali metal, ammonium or amine salts of C_8-C_{20}fatty acids, C_8-C_{20}alkanesulfonates, fatty alcohol phosphorates, the salts of colic acid, invert soaps (quats); partial fatty acid esters of sorbitan, sugar esters of fatty acids, fatty acid partial glycerides, alkylmaltosides, alkylglucosides, C_8-C_{18}betaines, C_8-C_{18}sulfobetaines or C_8-C_{24}alkylamido-C_1-C_4alkylenebetaines, proteins, polyglycerol esters of fatty acids, propylene glycol esters of fatty acids, lactates of fatty acids or a mixture of these substances.

9. Use according to claim 8, which is characterised in that the nanodispersion comprises as component

(b) at least one emulsifier of the polyoxyethlene type.

10. Use according to claim 9, which is characterised in that the nanodispersion comprises as component (b)

polyethoxylated sorbitan fatty acid esters, polyethoxylated fatty alcohols, polyethoxylated fatty acids, polyethoxylated vitamin E derivatives, polyethoxylated lanolin and the derivatives thereof, polyethoxylated fatty acid partial glycerides, polyethoxylated alkylphenols, sulfuric acid semiesters, polyethoxylated fatty alcohols and the salts thereof, polyethoxylated fatty amines and fatty acid amides, polyethoxylated carbohydrates, block polymers of ethylene oxide and propylene oxide.

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11. Use according to any one of claims 1 to 10, which is characterised in that component (b) is present in the nanodispersion used according to this invention in a concentration of 1 to 50 % by weight, based on the total weight of the components (a), (b) and (c).

12. Use according to any one of claims 1 to 11, which is characterised in that the nanodispersion comprises as component

(c) a natural or synthetic or a partially synthetic di- or triglyceride, mineral oil, silicone oil, wax, fatty alcohol, guerbet alcohol or the ester thereof, a lipophilic functional pharmaceutical active agent or a mixture of these substances.

13. Use according to any one of claims 1 to 12, which is characterised in that component (c) is present in the nanodispersion used according to this invention in a concentration of 0.1 to 80 % by weight, based on the total weight of the components (a), (b) and (c).

14. Use according to any one of claims 1 to 13, which is characterised in that the nanodispersion comprises as component

(d) a C_2-C_8alcohol.

15. Use according to any one of claims 1 to 14, which is characterised in that the pharmaceutical end formulation is a liquid, semisolid or solid preparation.

16. A pharmaceutical liquid end formulation in the form of an injectable solution, infusion solution, drops, spray, aerosol, emulsion, lotion, suspension, drinking solution, gargle or inhalant, which comprises a nanodispersion as defined in claim 1.

17. A pharmaceutical semisolid end formulation in the form of an ointment, cream (O/W emulsions), rich cream (W/O emulsions), gel, lotion, foam, paste, suspension, ovula or plaster, which comprises a nanodispersion as defined in claim 1.

18. A pharmaceutical solid end formulation in the form of a tablet, coated tablet, capsule, granules, effervescent granules, effervescent tablet, lozenge, sucking and chewing tablet, suppositories, implant, lyophilisate, adsorbate or powder, which comprises a nanodispersion as defined in claim 1.

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19. A matrix- or membrane-controlled pharmaceutical application system in the form of an oros capsule, transdermal system, injectable microcapsule, which comprises a nanodispersion as defined in claim 1.

20. A pharmaceutical end formulation according to either claim 16, claim 17 or claim 19, wherein the nanodispersion is present in the aqueous phase.

21. A pharmaceutical end formulation according to either claim 16, claim 17, claim 19 or claim 20, wherein the nanodispersion is present in the aqueous phase in a concentration of 0.01 to 100 % by weight.

22. A pharmaceutical end formulation according to either claim 16 or 19, wherein the nanodispersion is present per se.

23. A pharmaceutical end formulation according to claim 18, wherein the nanodispersion prephase is present per se.

24. A pharmaceutical end formulation according to claim 18, wherein the nanodispersion is present in dehydrated form.

25. Use of the pharmaceutical end formulation according to any one of claims 16 to 23 for the therapeutic treatment of the nervous system, endocrine system, cardiovascular system, respiratory tract, gastro-intestinal tract, kidneys and efferent urinary tracts, locomotor apparatus, immunological system, skin and mucosae as well as for the treatment of infectious diseases, tumours and vitamin/mineral deficiency diseases.

26. A nanodispersion prephase, which is obtainable by mixing the components

(a) membrane-forming molecule,
(b) coemulsifier and
(c) lipophilic component

until a homogeneous clear liquid is obtained, mixing being carried out in anhydrous medium.

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27. A nanodispersion prephase according to claim 26, which is characterised in that mixing is carried out without any additional supply of energy.

28. A nanodispersion, which comprises

(a) a membrane-forming molecule,

(b) a coemulsifier and

(c) a lipophilic component,

which is obtainable by

(α) mixing the components (a), (b) and (c) until a homogeneous clear liquid is obtained, and

(β) adding the liquid obtained in step (α) to the water phase, steps (α) and (β) being carried out without additional supply of energy.