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(54) Title: Nanosusupension formulation comprising a polydimethylsiloxane hydrophobic phase

(57) Abstract: A nanosuspension formulation comprising particles of at least one functional ingredient dispersed in a hydrophobic phase comprising a polydimethylsiloxane that can be used, e.g., in the pharmaceutical, cosmetics and food industry, in agriculture as well as for technical applications, and a method for producing said nanosuspension formulation are provided. The nanosuspension formulation of the invention can be highly concentrated, can be prepared also with poorly soluble functional ingredients and allows a gradual release of the functional ingredient into an aqueous environment which is accelerated compared to the dissolution of the functional ingredient when added as bulk material to the aqueous medium.

Nanosuspension formulation comprising a polydimethylsiloxane hydrophobic phase

The invention relates to a nanosuspension formulation comprising particles of at least one functional ingredient dispersed in a hydrophobic phase comprising a polydimethylsiloxane for application, *e.g.*, in the pharmaceutical, cosmetics and food industry, in agriculture as well as for technical applications, and to a method for producing said nanosuspensions.

About 40% of all pharmaceutically active substance currently in development or clinical clinical testing are poorly soluble in aqueous media, *i.e.* belong to biopharmaceutics classification system class II (BSC II) or class IV (BSC IV). These compounds have a very low bioavailability after oral administration making it difficult to reach adequate therapeutic levels in the blood. Parenteral, e.g. intravenous, application of an adequate amount of poorly soluble compounds often would require injection volumes which were too large to actually be administered. Traditional approaches for solving this problem comprise the increase of solubility by complexing, *e.g.* in the form of cyclodextrin inclusion complexes (Uekama K. Design and evaluation of cyclodextrin-based drug formulation. Chem Pharm Bull. Vol. 52(8), p. 900-915, 2004), and the use of injectable solvent mixtures, *e.g.* water ethanol mixtures, or organic solvents (*e.g.* polyethylene glycol) which often result in painful injections. The number of pharmaceutical products on the market which actually use these formulation approaches is low indicating that they are applicable to only a limited number of compounds.

As the number of poorly soluble pharmaceutically active substances is growing constantly there is a high need for providing alternative formulations which improve their bioavailability. An estimated 60% of the pharmaceutically active substances coming directly from synthesis are poorly soluble (Merisko-Liversidge E. Nanocrystals: Resolving pharmaceutical formulation issues associated with poorly water-soluble compounds. Particles; 2002; Orlando, Marcel Dekker), many of them not only in aqueous media but also in the few organic solvents, the toxicity of which is sufficiently low to allow for parenteral administration, e.g. ethanol or propylene glycol; thus often excluding a formulation based on solvent mixtures.

The traditional formulation approaches described above are relatively compound-specific and not applicable in any case. A formulation approach universally applicable for all poorly soluble compounds is therefore desirable. Such a universal approach is micronization which has been used for oral administration of pharmaceutically active substances for many years. The principle of micronization is the surface area enlargement of the particles of the compound resulting in an increased rate of dissolution according to the Noyes-Whitney-equation. However, the solubility of many new pharma-

ceutical active substances is so low that the surface area enlargement by micronization does not increase the rate of dissolution sufficiently. As a consequence an even smaller particle size was aimed for by moving from micronization to nanonization. Thus decreasing the particle size to below 1 µm does not only mean a further enlargement of the surface area of the particles but additionally increases the saturation concentration resulting in an even higher rate of dissolution according to the Noyes-Whitney-equation. In general it is preferred to use nanoparticles being as small as possible to achieve a maximum improvement of oral bioavailability or a very fast rate of dissolution in den blood after intravenous application.

Several methods for transferring micronized substance crystals dispersed in a liquid into the nanometer range, i.e. for producing nanocrystals, are known. One of these methods is wet ball milling. Depending on the hardness of the milling material, it requires milling times ranging from hours to days and typically yields particle sizes below 400 nm. However, one disadvantage of this technology is a potential contamination of the product with dust abraded from the balls (Buchmann S, Fischli W, Thiel FP, Alex R. Aqueous microsuspension, an alternative intravenous formulation for animal studies. 42nd Annual Congress of the International Association for Pharmaceutical Technology. p.124, 1996). In particular the very long milling times required for obtaining particle sizes of about 100 nm are associated with a stronger contamination of the product with abraded dust.

Alternative methods avoiding such contamination are high pressure homogenization (HPH) technologies comprising piston-gap homogenization and the microfluidizer technology of jet stream homogenizers described in US 6,018,080. These technologies are capable of generating suspensions of nanoparticles by forcing the particles dispersed in a liquid through a tiny homogenization gap or by frontal collision of two liquid streams. The effects caused by these treatments, such as particle collision, shear forces and cavitation, lead to comminution of the particles in the liquid.

Using non-aqueous suspension media may improve the stability of the suspended compound, *e.g.* by avoiding hydrolysis. However, manufacture of stable nanosuspensions of poorly soluble compounds, in particular of poorly soluble pharmaceutically active agents, in a non-aqueous medium by high pressure homogenization is very challenging. The majority of organic liquids are unsuitable for this application because many of them (i) readily dissolve BSC II and BSC IV compounds, (ii) are volatile and flammable or (iii) are either toxic or not pharmaceutically acceptable. Options for suitable non-aqueous liquids are therefore very limited. For example, there is one variant of the so called nanopure technology for producing suspensions in liquid PEG or oils (Bushrab FN, Müller RH. Nanocrystals of poorly soluble drugs for oral administration, New Drugs 5, p. 20-22, 2003).

The inventors have unexpectedly found that polydimethylsiloxane is suitable as vehicle for producing nanosuspension formulations of poorly soluble compounds including poorly soluble pharmaceutically active agents by high pressure homogenization. This inert hydrophobic polymer, also known as PDMS, dimethicone or E900, is not resorbed in the gastrointestinal tract and has been used as excipient for pharmaceutical and cosmetic applications without significant side effects.

The present invention thus provides a nanosuspension formulation comprising particles of at least one functional ingredient dispersed in a hydrophobic phase comprising a polydimethylsiloxane wherein at least 90% by weight of the particles have a particle size in the range of about 5 nm to about 2000 nm.

The present invention also provides a method for producing a nanosuspension formulation according to the invention, comprising:

(a) providing a hydrophobic phase comprising a polydimethylsiloxane,

(b) contacting the hydrophobic phase of (a) with at least one particulate functional ingredient,

(c) subdividing the particulate functional ingredient and dispersing the particulate functional ingredient throughout the hydrophobic phase by high pressure homogenization.

When the nanosuspension formulation according to the invention is brought into contact with or dispersed in an aqueous environment, e.g. a body fluid such as gastric juice, the functional ingredient(s) is/are gradually released into the aqueous environment. The release is accelerated compared to the dissolution of the functional ingredient when added as bulk material to the aqueous medium.

The functional ingredient release from the nanosuspension formulation according to the invention was observed to be near zero-order. In many instances, there are clear pharmacological benefits to having constant release of pharmaceutical ingredients.

Two release mechanisms from a nanosuspension droplet that consists of a polydimethylsiloxane liquid phase and a uniformly dispersed number of very slightly soluble functional ingredient particles were considered: Although being almost insoluble in the polydimethylsiloxane, a small amount of the functional ingredient becomes dissolved in the polydimethylsiloxane liquid phase. When the nanosuspension droplet is dipped in release media the dissolved functional ingredient is eluted into the outer sink of the surrounding medium. Moreover, the functional ingredient particles may accumulate at the interfacial surface between the droplet and the surrounding aqueous medium where they become eluted by the aqueous medium. In both instances, release occurs

exclusively via the interfacial surface between the droplet and the surrounding aqueous medium. Release will be near zero-order because the droplet surface has a fixed area.

This behaviour is in contrast to aqueous nanosuspensions of the same functional ingredients. When the nanocrystals dissolve their particle size decreases and, consequently, the particle surface decreases quadratically.

At least 90% by weight of the functional ingredient particles, preferably essentially all of the functional ingredient particles, dispersed in the hydrophobic phase have a particle size in the range of about 5 nm to about 2000 nm, for example in the range of about 300 nm to about 1500 nm. The percentage of particles having a particle size within a certain range can be taken from the cumulative particle size distribution as determined, e.g., by Photon Correlation Spectroscopy (PCS). In most instances, the particle size distribution can also be determined by identifying the smallest particle and the largest particle of a representative sample by optical microscopy. Particle size is considered the diameter of a particle or, when the diameter of a particle is non-uniform in different spatial directions, the maximum particle diameter.

Typically, the hydrophobic phase (irrespective of the functional ingredient particles) comprises at least 50 % by weight of polydimethylsiloxane, preferably at least 70 % by weight. In certain embodiments, the hydrophobic phase consists essentially of polydimethylsiloxane or polydimethylsiloxane and one or more surfactants as described below.

Polydimethylsiloxane is a silicon-based polymer comprising repeating $[SiO(CH_3)_2]$ units, wherein the chain length, *i.e.* the number of $[SiO(CH_3)_2]$ units, determines the viscosity of the polymer. Polydimethylsiloxanes useful for the present invention typically have viscosities at 25°C from about 5 mm^2s^{-1} to about 1000 mm^2s^{-1}, for example from about 5 mm^2s^{-1} to about 100 mm^2s^{-1}, from about 5 mm^2s^{-1} to about 50 mm^2s^{-1}, from about 5 mm^2s^{-1} to about 30 mm^2s^{-1}, or have a viscosity of about 20 mm^2s^{-1}.

For nanosuspensions for pharmaceutical use, preferably compendial grade polydimethylsiloxanes are employed which are pharmaceutically acceptable and often designated with the non-proprietary names “dimethicone” or “dimeticone”.

Crystalline, solid particles with an average particle size of about 5 nm to about 2000 nm are described as nanocrystals. As used herein, this term in particular refers to nanocrystals of the functional ingredient of a nanosuspension. The functional ingredient in the nanosuspension formulation of the invention may be any poorly soluble compound of interest, for example pharmaceutically active agents, cosmetically active agents, food additives, dyes or pigments.

Thus the nanosuspension formulations of the present invention are applicable to compounds used in pharmaceuticals, cosmetics, food products; or can be used in technical applications as varnishes or coatings. In a particularly preferred embodiment, the invention relates to a nanosuspension of a pharmaceutically active agent (drug). Pharmaceutically active agents are biologically active agents and include those which exert a local physiological effect, as well as those which exert a systemic effect, after oral or parenteral administration. The invention is particularly useful for water-insoluble or poorly water-soluble (or ''hydrophobic'' or "lipophilic") compounds. Compounds are considered water-insoluble or poorly water-soluble if their solubility in water at 25°C is less than 1 g/100 ml, especially less than 0.1 g/100 ml.

The invention also includes the use of the nanosuspension for pharmaceutical and cosmetic application, preferably in the form of tablets and capsules, creams, ointments or powders for reconstitution before use or for the production of such pharmaceutical and cosmetic preparations.

Examples of suitable pharmaceutically active agents include, but are not limited to: analgetics and anti-inflammatory drugs such as morphine, codeine, piritramide, fentanyl, levomethadone, tramadol, diclofenac, ibuprofen, dexibuprofen, ketoprofen, dexketoprofen, meloxicam, idometacin, naproxene, piroxicam and COX-2 inhibitors, e.g. rofecoxib and celecoxib;

antiallergics such as pheniramine, dimetindene, terfenadine, astemizole, loratidine, desloratadine, doxylamine, meclozine, fexofenadine and mizolastine;

antibiotics and chemotherapeutics such as rifampicin, ethambutol, thiacetazone, buparvaquone, atovaquone, tarazepid

antiepileptics such as carbamazepine, clonazepam, mesuximide, phenytoin and valproic acid;

antimycotics natamycin, amphotericin B, miconazole, itraconazole, clotrimazole, econazole, fenticonazole, bifonazole, ketoconazole and tolnaftate;

corticoids such as aldosterone, fludrocortisone, betamethasone, dexamethasone, triamcinolone, triamcinolone acetonide, fluocortolone, hydrocortisone, hydrocortisone acetate, prednisolone, prednylidene, cloprednol, budesonide and methylprednisolone;

dermatological agents which are antibiotics, e.g. tetracycline, erythromycin, framycetin, tyrothricin and fusidic acid; which are virostatic agents, e.g. vidarabine; which are corti-

coids, e.g. amcinonide, fluprednidene, alclometasone, clobetasol, halcinonide, fluocinolone, clocortolone, flumetasone, diflucortolone, fludroxycortide, halometasone, desoximetasone, fluocinonide, fluocortin butyl, fluprednidene, prednicarbate and desonide;

hypnotics and sedatives such as cyclobarbital, pentobarbital, methaqualone and benzodiazepines, e.g. flurazepam, midazolam, nitrazepam, lormetazepam, flunitrazepam, triazolam, brotizolam, temazepam and loprazolam;

immunotherapeutics and cytokines such as azathioprine and ciclosporin;

local anaesthetics such as butanilicaine, mepivacaine, bupivacaine, etidocaine, lidocaine, articaine, oxybuprocaine, tetracaine and benzocaine;

anti-migraine drugs such as lisuride, methysergide, dihydroergotamine, ergotamine and triptanes, e.g. zolmitriptan, sumatriptan and rizatriptan;

narcotics such as methohexital, propofol, etomidate, ketamine, thiopental, droperidol and fentanyl

parathyroid hormones, calcium metabolism regulators such as dihydrotachysterol;

ophthalmic agents such as cyclodrine, cyclopentolate, homatropine, tropicamide, pholedrine, edoxudine, aciclovir, acetazolamide, diclofenamide, carteolol, timolol, metipranolol, betaxolol, pindolol, bupranolol, levobununol and carbachol;

psychopharmacological agents such as clomethiazole and benzodiazepines, e.g. lorazepam and diazepam;

sex hormones and inhibitors thereof such as anabolic agents, androgens, anti-androgens, gestagens, oestrogens and anti-oestrogens;

cytostatics and metastasis inhibitors such as alkylating agents, e.g. melphalan, carmustin, lomustin, cyclophosphamide, ifosfamide, trofosfamide, chlorambucil, busulfan, prednimustin and thiotepa; antimetabolites, e.g. fluorouracil, methotrexate, mercaptopurine and thioguanine; alkaloids, e.g. vinblastine, vincristine and vindesine; antibiotics, e.g. dactinomycin; taxol and related or analogous compounds; dacarbazine, estramustin and etoposide.

Pharmaceutical active agents of particular interest are oxaliplatin, paclitaxel, taxane, ketoconazole, itraconazole, ibuprofen, naproxene, omeprazole, pantoprazole, loratadine, desloratadine, loperamide and daglutril.

The pharmaceutically active agent may be present as its N-oxide, i.e. one or several nitrogen atoms of the pharmaceutically active agent are oxidized; as its pharmaceutically acceptable acid or base addition salt; or in any stereoisomerically isomeric form.

Pharmaceutically acceptable acid addition salts can be formed by treatment of the base form of the pharmaceutically active agent with appropriate organic or inorganic acids. Active agents containing an acidic proton may be converted into their non-toxic metal or amine addition salt forms by treatment with appropriate organic and inorganic bases. Pharmaceutically acceptable acid addition salts as herein also comprises the hydrates and solvent addition forms of the active agent, e.g. hydrates, alcoholates and the like.

The term "stereochemically isomeric forms" defines all possible stereoisomeric forms which the active ingredients may possess. In particular, stereogenic centers may have the R- or S-configuration and double bonds may have the E- or Z-configuration.

The term “pharmaceutically acceptable” as used herein means that a respective compound is substantially non-toxic to the subject to which it is administered at doses as they are normally administered.

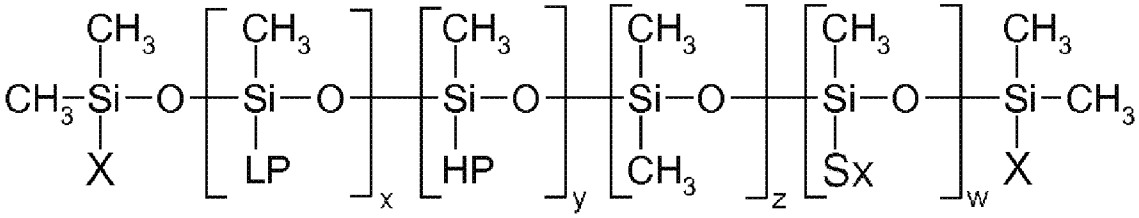
The nanosuspension formulations according to the invention may comprise at least one surfactant. The surfactant can stabilize the nanosuspensions and avoid the functional ingredient particles from uncontrolled aggregation and flocculation. Useful surfactants have to be soluble or dispersible in the polydimethylsiloxane.

It is expedient that surfactants in nanosuspension formulations for administration to animal or human subjects are pharmaceutically acceptable surfactants. A single surfactant as well as combinations of surfactants may be used. Accordingly, a nanosuspension formulation of the invention may comprise a combination of two or more pharmaceutically acceptable surfactants.

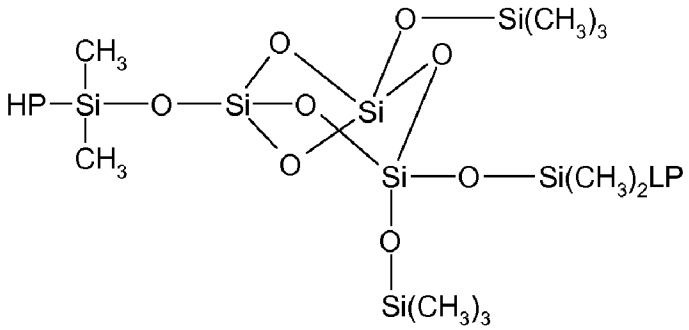
Typically, the amount of the at least one surfactant in the nanosuspension formulation of the invention lies in the range from about 0.1% to about 10%, in particular in the range from about 0.25 to about 5% and more particularly in the range from about 0.5 to about 2% by weight of the surfactant, based on the total weight of the nanosuspension formulation.

In one embodiment, said surfactant is a silicone based surfactant. A silicone based surfactant is meant to be a compound having a polydimethylsiloxane backbone and at least one hydrophilic moiety, such as a polyether chain or polyglycerol chain, as a pendant group and/or as terminal group.

Silicone based surfactants may have any of the following generic formulae:



(I)



(II)

wherein
X is independently selected from the group consisting of LP, HP and $-CH_3$;
LP is a lipophilic radical,
HP is a hydrophilic radical,
Sx is a siloxylalkyl radical,
x is 0 to 5000 (preferably 0 to 200), y is 0 to 5000 (preferably 0 to 200), z is 1 to 5000 (preferably 3 to 200), and w is 0 to 5000 (preferably 0 to 200), with the proviso that the organosiloxane contains at least one hydrophilic radical.

The Formula (I) is a stoichiometric formula meant to indicate the type and number of the repeating units which constitute the surfactant molecule, *i.e.* said formula does not define the order of units given in square brackets.

The hydrophilic radicals (HP) can be polyether side chains, for example polyethylene oxide chains, polypropylene oxide chains, polyether chains containing moieties derived from both ethylene oxide and propylene oxide, or polyglycerol chains, or mixtures of these chains.

In certain embodiments, HP is $-C_cH_{2c}-(OC_2H_4)_a-(OC_3H_6)_b-(OC_4H_8)_d-R^1$; where R^1 is hydrogen, hydroxy, linear or branched C_1-C_{12}-alkyl, linear or branched C_1-C_6-alkoxy, linear or branched C_1-C_{12}-acyloxy, $-NHCH_2CH_2COOM$, $-NHCO(CH_2)_d-COOM$, C_1-C_{30}-carb-oxyacyl, $-NHCO(CH_2)_d-OH$ or $-NH_3Y$; M is hydrogen, sodium, potassium, lithium, ammonium or an organic ammonium; Y is a monovalent organic or inorganic anion such as chloro, bromo, sulfate or carboxylate; a is a number from 0 to 100; b is a number from 0 to 50; c is a number from 0 to 5; and d is a number from 0 to 10, and the sum of a+b+d is 2 to 100.

In other embodiments, HP comprises a polyglycerol chain, such as $-R^2-O[CH_2-CH(OH)CH_2O]_nH$, where R^2 is C_2-C_6 alkylene and n is an integer from 1 to 20.

The lipophilic radicals (LP) may be selected from C_6-C_{30}-alkyl and phenyl.

The siloxylalkyl radicals (Sx) may be $-C_nH_{2n}[(CH_3)_2SiO]_mSi(CH_3)_3$, wherein n is 1-6 and m is 0-25.

A non exhaustive list of silicone based surfactants suitable for use in the invention is given in the following:

PEG/PPG dimethicones & silicone polyethers, Bis-PEG/PPG -14/14 dimethicone, Bis-PEG/PPG -20/20 dimethicone, Bis-PEG/PPG -16/16 PEG/PPG -16/16dimethicone, Bis-PEG-15 methyl ether dimethicone, Bis(PPG-7 undeceneth-21) dimethicone, Cetyl PEG/PPG -15/15 butyl ether dimethicone, Cetyl PEG/PPG - 7/3 dimethicone, Cetyl PEG/PPG -10/1 dimethicone, Dimethicone copolyol, Dimethicone PEG-8 adipate, Dimethicone PEG-7 avocadoate, Dimethicone PEG-8 avocadoate, Dimethicone PEG-8 beeswax, Dimethicone PEG-n esters, Dimethicone/PEG-10 crosspolymer, Dimethicone/PEG-15 crosspolymer, Dimethicone/PEG-7 phosphate, Dimethicone/PEG-n phosphates, Dimethicone PEG/PPG-7/4 phosphate, Dimethicone PEG/PPG-12/4 phosphate, Dimethicone PEG-7 undecylenate, Laurylmethicone copolyol PEG-10 dimethicone crosspolymer, PEG-12 dimethicone crosspolymer, PEG-10 lauryl dimethicone crosspolymer, PEG-15 lauryl dimethicone crosspolymer, PEG-6 methyl ether dimethicone, PEG-n methyl ether dimethicones, PEG-32 methyl ether dimethicone, PEG/PPG - 20/22 butyl ether dimethicone, PEG/PPG - 22/22 butyl ether dimethicone, PEG/PPG - 23/23 butyl ether dimethicone, PEG/PPG - 24/18 butyl ether dimethicone, PEG/PPG - 27/9 butyl ether dimethicone, PEG/PPG -3/10 dimethicone, PEG/PPG - 5/3 trisiloxane, PEG/PPG -n/m dimethicones PEG/PPG -30/10 dimethicone, Potassium dimethicone, PEG-7 phosphate PPG-12 butyl ether dimethicone, PPG-12 dimethicone, PPG-27 dimethicone, TEA-dimethicone PEG-7 phosphate, Caprylyl dimethicone ethoxy glucoside, Dimethicone ethoxy glucoside, Dimethicone/polyglycerin-3 crosspoly-

mer, PEG-9 dimethicone, PEG-9 methyl ether dimethicone, PEG-9 polydimethylsiloxyethyl dimethicone, PEG-10 dimethicone, Polydimethylsiloxy PEG/PPG - 24/19 butyl ether silsesquioxane, Polydimethylsiloxy PPG-13 butyl ether silsesquioxane, Polyglyceryl-3 disiloxane dimethicone, Polyglyceryl-3 polydimethylsiloxyethyl dimethicone, Sodium carboxydecyl PEG-8 dimethicone, C_6-C_8Alkyl C_3-C_6alkyl glucoside dimethicone, PEG-9 dimethicone, PEG-9 methyl ether dimethicone, PEG-10 dimethicone, lauryl PEG-9 polydimethylsiloxyethyl dimethicone

Preferred silicone based surfactants are selected from the group consisting of PEG-9 dimethicone, PEG-9 methyl ether dimethicone, PEG-10 dimethicone, PEG-9 polydimethylsiloxyethyl dimethicone, lauryl PEG-9 polydimethylsiloxyethyl dimethicone, polyglyceryl-3 disiloxane dimethicone, and polyglyceryl-3 dimethylsiloxyethyl dimethicone.

A preferred silicone based surfactant is a compound of formula (I), wherein X is $-CH_3$; Sx is $-C_2H_4[(CH_3)_2SiO]_mSi(CH_3)_3$ where m is 3-9; HP is $-C_3H_6O[CH_2-CH(OH)CH_2O]_nH$ with n being 1-5; z:w:x:y is [1-1.4]:[0.02-0.04]:[0]:[0.02-0.04]. The compound is available under the designation Polyglycerol-3 polydimethylsiloxyethyl dimethicone and is sold by Shin-Etsu under reference number KF6104. It has a viscosity of 4,000 mm^2/s at 25°C.

A further preferred silicone based surfactant is a compound of formula (I), wherein X is $-CH_3$; Sx is $-O(CH_3)_2SiO-Si(CH_3)_3$; HP is $-C_3H_6O[CH_2-CH(OH)CH_2O]_nH$ with n being 1-5; z:w:x:y is [1-1.4]:[0.02-0.04]:[0]:[0.02-0.04]. The compound is available under the designation Polyglyceryl-3 disiloxane dimethicone and is sold by Shin-Etsu under reference number KF6100. It has a viscosity of 40,000 mm^2/s at 25°C.

PEG-9 dimethicone has a viscosity of 400 mm^2/s at 25°C and is sold by Shin-Etsu under reference number KF6013.

PEG-9 methyl ether dimethicone has a viscosity of 150 mm^2/s at 25°C and is sold by Shin-Etsu under reference number KF6016.

PEG-10 dimethicone has a viscosity of 600 mm^2/s at 25°C and is sold by Shin-Etsu under reference number KF6017.

PEG-9 polydimethylsiloxyethyl dimethicone has a viscosity of 900 mm^2/s at 25°C and is sold by Shin-Etsu under reference number KF6028.

Lauryl PEG-9 polydimethylsiloxyethyl dimethicone has a viscosity of 700 mm^2/s at 25°C and is sold by Shin-Etsu under reference number KF6038.

In other embodiments, the surfactant that may be comprised by the nanosuspension formulation of the invention is a non-silicone based surfactant. The non-silicone based surfactant may, for example, be a surfactant selected from

sorbitan fatty acid esters,
polyalkoxylated fatty acid esters such as, for example, polyalkoxylated glycerides, polyalkoxylated sorbitan fatty acid esters or fatty acid esters of polyalkylene glycols,
polyalkoxylated ethers of fatty alcohols,
alkylene glycol fatty acid mono ester or
mixtures of two or more thereof.

A fatty acid chain in these compounds ordinarily comprises from 8 to 22 carbon atoms. The polyalkylene oxide blocks comprise on average from 4 to 50 alkylene oxide units, preferably ethylene oxide units, per molecule.

Suitable sorbitan fatty acid esters are sorbitan monolaurate, sorbitan monopalmitate, sorbitan monostearate (Span® 60), sorbitan monooleate (Span® 80), sorbitan tristearate, sorbitan trioleate, sorbitan monostearate, sorbitan monolaurate or sorbitan monooleate.

Examples of suitable polyalkoxylated sorbitan fatty acid esters are polyoxyethylene (20) sorbitan monolaurate, polyoxyethylene (20) sorbitan monopalmitate, polyoxyethylene (20) sorbitan monostearate, polyoxyethylene (20) sorbitan monooleate (Tween® 80), polyoxyethylene (20) sorbitan tristearate (Tween® 65), polyoxyethylene (20) sorbitan trioleate (Tween® 85), polyoxyethylene (4) sorbitan monostearate, polyoxyethylene (4) sorbitan monolaurate or polyoxyethylene (4) sorbitan monooleate.

Suitable polyalkoxylated glycerides are obtained for example by alkoxylation of natural or hydrogenated glycerides or by transesterification of natural or hydrogenated glycerides with polyalkylene glycols. Commercially available examples are polyoxyethylene glycerol ricinoleate 35, polyoxyethylene glycerol trihydroxystearate 40 (Cremophor® RH40, BASF AG), polyoxyethylene glycerol trioleate (Tagat TO), and polyalkoxylated glycerides like those obtainable under the proprietary names Gelucire® and Labrafil® from Gattefosse, e.g. Gelucire® 44/14 (lauroyl macrogol 32 glycerides prepared by transesterification of hydrogenated palm kernel oil with PEG 1500), Gelucire® 50/13 (stearoyl macrogol 32 glycerides, prepared by transesterification of hydrogenated palm oil with PEG 1500) or Labrafil M1944 CS (oleoyl macrogol 6 glycerides prepared by transesterification of apricot kernel oil with PEG 300).

A suitable fatty acid ester of polyalkylene glycols is, for example, PEG 660 hydroxystearic acid (polyglycol ester of 12-hydroxystearic acid (70 mol%) with 30 mol% ethylene glycol).

Suitable polyalkoxylated ethers of fatty alcohols are, for example, PEG (2) stearyl ether (Brij® 72), macrogol 6 cetylstearyl ether or macrogol 25 cetylstearyl ether.

A preferred surfactant is an alkylene glycol fatty acid monoester or a mixture of alkylene glycol fatty acid mono- and diester.

The preferred alkylene glycol fatty acid mono ester is a propylene glycol fatty acid mono ester, such as propylene glycol monolaurate (available under the trade name LAUROGLYCOL® from Gattefossé, France). Commercially available propylene glycol lauric acid mono ester products consist of a mixture of mono- and dilaurate. Two propylene glycol monolaurate products are specified in the European Pharmacopoea (referenced ''type I'' and "type II" respectively). Both types are suitable for carrying out the present invention, with propylene glycol monolaurate ''type I'' being the most preferred. This ''type I'' product having a HLB value of about 4 consists of a mixture having between 45 and up to 70% mono-laurate and between 30 and up to 55% of di-laurate. The ''type II'' product is specified according to Pharm. Eur. as having a minimum of 90% mono-laurate and a maximum of 10% of dilaurate.

Prior to use, the nanosuspension according to the invention may be dispersed in an aqueous medium to form a multiple dispersion.

Thus, the present invention further relates to a multiple dispersion containing:

(a) an external aqueous phase, and
(b) a nanosuspension formulation as described above dispersed in the external aqueous phase.

The multiple dispersion may additionally comprise at least one secondary surfactant which acts as an emulsifier. Said secondary surfactant is suitably selected from the surfactants mentioned above.

The amount of the at least one secondary surfactant in the multiple dispersion of the invention lies typically in the range from about 0.5% to about 20% and ideally from about 1 to about 5% by weight of the secondary surfactant , based on the total weight of the external aqueous phase of the multiple dispersion.

In one embodiment of the invention, the secondary surfactant is a silicone based surfactant as described above. In a particular embodiment, said silicone base surfactant is PEG-9 dimethicone, polyglyceryl-3 disiloxane dimethicone, and polyglyceryl-3 dimethylsiloxyethyl dimethicone.

In another embodiment of the invention, the secondary surfactant is a non-silicone based surfactant as described above. In a particularly preferred embodiment, said secondary surfactant is polyoxyethylene glycerol trioleate . Polyoxyethylene glycerol trioleate is available under the tradename “Tagat TO”.

The multiple dispersion of the present invention may be prepared by providing an aqueous medium optionally comprising at least one secondary surfactant and intimately dispersing the nanosuspension formulation of the present application in said aqueous medium by prolonged high speed rotary homogenization or high pressure homogenization, preferably by high pressure homogenization. Thus a fine emulsion comprising droplets of the hydrophobic phase of the nanosuspension formulation dispersed in the external aqueous phase is formed. In general, the examination of a multiple dispersion of the present invention by light microscopy will show that the functional ingredient nanoparticles accumulate essentially at the at the interface of polydimethylsiloxane hydrophobic phase and external aqueous phase.

In addition, the present invention provides an effective method for a producing nanosuspension formulations as described above using polydimethylsiloxane as dispersion medium. Generation of nanoparticles is achieved by medium to high shear and/or cavitation forces. The resulting nanosuspensions can be applied in a wide range of areas, including pharmacy, cosmetics, food industry, textile industry and other technical fields. In other words, the present invention provides a method for producing nanoparticulate pharmaceutically active agents, cosmetically active agents, food additives, dyes, pigments or other agents having a medium size of less than 1000 nm.

Thus, the present invention provides a method for producing a nanosuspension formulation as described above, comprising:

(a) providing a hydrophobic phase comprising a polydimethylsiloxane,
(b) contacting the hydrophobic phase of (a) with at least one particulate functional ingredient,
(c) subdividing the particulate functional ingredient and dispersing the particulate functional ingredient throughout the hydrophobic phase by high pressure homogenization.

The high pressure homogenization is selected from a group of methods comprising jet stream homogenization and piston-gap homogenization.

The principle of a jet stream homogenizer is based on the frontal collision of two liquid streams at high speed resulting in comminution of particles in the liquid. A piston-gap homogenizer reduces the size of particles dispersed in a liquid by forcing it through a tiny homogenization gap, which is 5-20 µm in size depending on the applied pressure and the viscosity of the dispersion medium (Muller, R. H., Moschwitzer, J. and Bushrab, F. N. (2006). Manufacturing of Nanoparticles by Milling and Homegenization Techniques, in: Gupta, R.B., Kompella, U.B. (eds.), Nanoparticle Technology for Drug Delivery (Taylor & Francis, New York, London), pp. 53-84). The high flow velocity causes cavitation forces to occur; additionally, particle collision and shear forces lead also to a comminution of the particles. Piston-gap homogenizers are used to disperse particles in pure water/surfactant mixtures (US 5,858,410); they are further used to homogenize particles which are dispersed in non-aqueous media or mixtures of water and water-miscible liquids (WO 0103670). The particle sizes which can be obtained by using piston-gap homogenizers are in the range of about 200-600 nm, in case of materials of very high hardness about 700-900 nm (Muller RH, Jacobs C, Kayser O. Nanosuspensions as particulate drug formulations in therapy: Rationale for development and what we can expect for the future. Advanced Drug Delivery Reviews 2001. vol. 47(1), p. 3-19).

The above-described method for producing a nanosuspension formulation may comprise the step of dispersing at least one surfactant in the hydrophobic phase prior to contacting the hydrophobic phase with the particulate functional ingredient. Said at least one surfactant may be any of the above-described surfactants.

Typically, the high pressure homogenization of the above-described method step (c) is performed at a power density of about 10^9 to about 10^{12} W/m^3, for example about 10^{10} W/m^3.

Producing nanosuspensions by high pressure homogenization requires a minimum fluidity of the input suspension. Typically, low concentrated aqueous suspensions (e.g. below 20% functional ingredient) show a flow behaviour identical to the flow behaviour of the outer dispersion phase, i.e. the flow behaviour of a Newtonian fluid. With increasing concentration (e.g. 20-60% functional ingredient), the particles of the disperse phase get in contact to each other, particle to particle interactions occur, and the flow behaviour changes to pseudoplastic, at further increasing concentrations to plastic behaviour exhibiting a flow point. In many cases the flow is thixotropic-pseudoplastic or thixotropic-plastic. This is due to an existing structure which is destroyed when applying the shear force, leading to a reduction in the viscosity, and improved flow ability. After a certain time, the structure re-builds and the original higher viscosity is built up again. In highly concentrated aqueous suspensions (e.g. >60% functional ingredient), there is

only a thin liquid film in between the particles. This liquid film allows that the particles can slide on each other when applying a very low shear force, but is ruptured when higher shear forces are applied. Thus, the particles get in direct contact without lubricant film in between them, the viscosity increase.

The inventors have unexpectedly found that dimethicone acts as excellent lubricant between the particles of functional ingredient reducing the viscosity. Thus, dimethicone suspensions with an high amount of functional ingredient, e.g. with 53.5%, 55.5% or 56,5% nifedipine, show still a Newtonian flow behaviour, characterized by a straight line in a shear rate / shear stress (D/τ) plot. In addition, there are no particle to particle interactions causing time-dependent flow behaviour (i.e. thixotropy), i.e. up and down curves in D/τ plot look virtually identical. Moreover, dimethicone suspensions with even higher amounts of functional ingredient show thixotropic instead of rheopectic flow behaviour; *i.e.* the viscosity of such suspensions is reduced after application of shear stress. These rheological characteristics allow for high pressure homogenization of dimethicone suspensions with concentrations of functional ingredient that are well above the highest processible concentration of aqueous suspensions. Thus, dimethicone nanosuspension formulations with high concentrations of functional ingredient, such as nanosuspension formulations comprising at least 40%, at least 50%, at least 60%, or or at least 70% functional ingredient, relative to the total weight of the nanosuspension formulation, can be prepared, extending their application possibilities.

The accompanying figures and the examples described below are intended to illustrate the present invention without limiting it in any way.

Fig. 1 shows the in vitro release of nifedipine from a nifedipine dimethicone nanosuspension according to the invention.

Fig. 2 shows the in vitro release of nifedipine from an aqueous nifedipine nanosuspension.

Fig. 3a-f show shear rate / shear stress (D/τ) plots of rheometric measurements performed with 53.5% (Fig. 3a), 55.5% (Fig. 3b), 56.5% (Fig. 3c) and 60% (Fig. 3d-f) (w/w) nifedipine dimethicone suspensions. Measurement was performed immediately after filling the sample vial (Fig. 3a-d), or with a delay of 15 min (Fig. 3e) or 30 min (Fig. 3f).

Example 1: Preparation of nanosuspensions

Example1.1

2.0 g (5%) Nifedipin was dispersed in a homogeneous mixture of 0.2 g (0.5%) polyglyceryl-3 polydimethylsiloxyethyl dimethicone (Shin Etsu „KF6104“) and 37.8 g dimethi-

cone (Dow Corning Q7-9120, 20 cSt) by use of mortar and pistil. Using a high pressure homogenizer (Micron LAB 40, APV-Homogenisers, Unna, Germany) 3 cycles at 150 bar, 2 cycles at 500 bar, 3 cycles at 1,000 bar and finally 3 cycles at 1,500 bar were performed successively at room temperature. After each treatment of 3 cycles at a defined pressure, the particle size in the resulting nanosuspension was determined *via* optical microscopy. The microscopic pictures showed an advancing particle size reduction over the cycles leading to particle sizes ranging from 800 to 1,300 nm. A repeated examination of the nanosuspension after 8 weeks showed no significant increase in particle size. The suspension can therefore be regarded as stable.

Example 1.2

2.0 g Nifedipin was dispersed in a homogeneous mixture of 0.8 g KF6104 and 37.2 g dimethicone (Dow Corning Q7-9120) by use of mortar and pistil. High pressure homogenization was performed and the particle size was determined as described in example 1.1. The microscopic pictures showed an advancing particle size reduction over the cycles leading to particle sizes ranging from 800 to 1,300 nm. A repeated examination of the nanosuspension after 12 weeks showed no significant increase in particle size. The suspension can therefore be regarded as stable.

Example 1.3

2.0 g Piroxicam was dispersed in a homogeneous mixture of 0.2 g KF6104 and 37.8 g dimethicone (Dow Corning Q7-9120). High pressure homogenization was performed and the particle size was determined as described in example 1.1. The microscopic pictures showed an advancing particle size reduction over the cycles leading to particle sizes ranging from 800 to 1,300 nm. A repeated examination of the nanosuspension after 12 weeks showed no significant increase in particle size. The suspension can therefore be regarded as stable.

Example 1.4

2.0 g Nifedipine was dispersed in a homogeneous mixture of 0.2 g KF6104 and 37.8 g dimethicone (Dow Corning Q7-9120). Using a high pressure homogenizer (Micron LAB 40, APV-Homogenisers, Unna, Germany) 1 cycle at 150 bar, 1 cycle at 500 bar, 1 cycle at 1,000 bar and finally 7 cycles at 1,500 bar were performed successively. A stable nanosuspension was obtained.

Example 1.5

2.0 g Nifedipine was dispersed in a homogeneous mixture of 0.01 g KF6104 and 37.97 g dimethicone (Dow Corning Q7-9120). Using a high pressure homogenizer (Micron LAB 40, APV-Homogenisers, Unna, Germany) 1 cycle at 150 bar, 1 cycle at 500 bar, 1 cycle at 1,000 bar and finally 10 cycles at 1,500 bar were performed successively. A stable nanosuspension was obtained.

Example 1.6

2.0 g Nifedipine was dispersed in a homogeneous mixture of 4.0 g KF6104 and 32.0 g dimethicone (Dow Corning Q7-9120). Using a high pressure homogenizer (Micron LAB 40, APV-Homogenisers, Unna, Germany) 1 cycle at 150 bar, 1 cycle at 500 bar, 1 cycle at 1,000 bar and finally 10 cycles at 1,500 bar were performed successively. A stable nanosuspension was obtained.

Example 1.7

Nifedipine dimethicone nanosuspensions comprising different surfactants were prepared as follows: 0.2 g PEG-9 dimethicone (Shin Etsu "KF6013"), 0.2 g PEG-9 methyl ether dimethicone (Shin Etsu "KF6016"), 0.2 g PEG-10 dimethicone (Shin Etsu "KF6017"), 0.2 g PEG-9 polydimethylsiloxyethyl dimethicone (Shin Etsu "KF6028"), 0.2 g lauryl PEG-9 polydimethylsiloxyethyl dimethicone (Shin Etsu "KF6038"), 0.2 g polyglyceryl-3 disiloxane dimethicone (Shin Etsu "KF6100") or 0.4 g propylene glycol monolaurate (Gattefossé "Lauroglycol 90") were mixed with an amount dimethicone (Dow Corning Q7-9120) for a final weight of 40 g by stirring for 30 s and subsequently homogenized at room temperature *via* 1 cycle at 1,000 bar using a high pressure homogenizer (Micron LAB 40, APV-Homogenisers, Unna, Germany). 2 g Nifedipine was added and the mixture was homogenized *via* 3 cycles at 150 bar, 2 cycles at 500 bar and 3 cycles at 1,000 bar using said high pressure homogenizer. After storage in a cool and dark place all samples showed sediment and a clear supernatant. The samples were then shaken by hand (three times upward/downward). Each of the surfactants delivered an easily redispersible nifedipine dimethicone nanosuspension.

Example 2: Use of secondary surfactants for emulsifying dimethicone in an aqueous medium

The stability of dimethicone (Dow Corning Q7-9120) in water dispersions containing 1% of a surfactant selected from polyoxyethylene glycerol trioleate (Tagat TO), KF6013, KF6100 and KF6104 was examined as follows: First, water and 1% of the respective surfactant was mixed for 30 s using a dispersing device (Ultra-Turrax, Ika). After adding 3% dimethicone the mixture was treated with the dispersing device for another 30 s or for another 120 s, or alternatively homogenized using a high pressure homogenizer (Micron LAB 40, APV-Homogenisers, Unna, Germany) by performing 1 cycle at 500 bar and 1 cycle at 1000 bar. Subsequently, the droplet size of the resulting dispersions was determined *via* optical microscopy. In general, high pressure homogenization resulted in a smaller droplet size compared to treatment with the dispersing device. Prolonged dispersion also led to the formation of smaller droplets. 1% Tagat TO, 1% KF6100, 1% KF6104 as well as 1% KF6013 delivered stable dimethicone in water dispersions. This indicates that these surfactants are suitable for emulsifying

dimethicone in aqueous media, for example when preparing the multiple dispersions of the present invention.

Example 3: Release of active ingredient from nanosuspensions

The release of nifedipine from a nifedipine dimethicone nanosuspension was compared to the nifedipine release from an aqueous nifedipine nanosuspension.

a) Preparation of nifedipine nanocrystals

Nanocrystals of nifedipine were prepared by ball milling 360 g nifedipine, 1612 g water for injection, 24 g Poloxamer 188 and 4 g SDS (sodium dodecyl sulfate) for 15 cycles. 50% of the resulting crystals had a size below 311 nm, 90% of below 596 nm, 95% of below 740 nm and 99% of below 1153 nm as measured by photon correlation spectroscopy (PCS). The nifedipine nanocrystals were harvested from the nanosuspension by centrifugation (60 min at 7,500 *g*) and divided into portions.

b) Preparation of nifedipine dimethicone nanosuspension

0.8 g KF6104 and 37.2 g dimethicone (Dow Corning Q7-9120) were mixed by stirring for 30 s and subsequently homogenized at room temperature *via* 1 cycle at 1,000 bar using a high pressure homogenizer (Micron LAB 40, APV-Homogenisers, Unna, Germany). A portion of 2 g nifedipine nanocrystals was added and the mixture was homogenized *via* 3 cycles at 150 bar and 2 cycles at 1,000 bar using said high pressure homogenizer.

c) Release studies

An amount of nifedipine dimethicone nanosuspension containing 4 mg nifedipine nanocrystals (prepared as described in b) was dispersed in 1 liter water containing 1% (w/w) Tagat TO at 37°C. As a comparative sample, 4 mg nifedipine nanocrystals (prepared as described in a) were dispersed in 1 liter water containing 1%(w/w) Tagat TO at 37°C. The dispersions were sampled after 0, 2, 5, 10, 15, 30, 60, 120 and 240 min, and the concentration of dissolved nifedipine in the aqueous phase were determined. To assess reproducibility, the experiment was done six times. The mean dissolved nifedipine concentration of the water-dispersed nifedipine dimethicone nanosuspensions or of the comparative samples, respectively, was plotted against the time of sampling.

A constant, delayed and prolonged release of nifedipine was observed in the multiple dispersion of nifedipine dimethicone nanosuspension in water/1% Tagat TO (Fig.1). In contrast, a complete dissolution of nifedipine nanocrystals after only 10 min was observed in the comparative sample (Fig. 2).

Example 4: Flow behavior of concentrated and highly concentrated nifedipine dimethicone suspensions

Nifedipine powder was dispersed in dimethicone using mortal and pestle. The resulting suspension was filled into the sample vial of a shear rheometer (rotational viscometer Rotovisco RV12 from Haake, measuring beaker MV St, rotational body MV III), and the measurement was started immediately. This procedure simulates filling a dimethicone suspension into the sample container of a piston-gap homogenizer and starting to homogenize the suspension. In a piston-gap homogenization the suspension is forced via piston through a small homogenizer gap that corresponds to the gap between outer sample vial and rotating cylinder of the viscometer.

Scale readings (S) were taken while the speed of the rotor (n) was increased manually in 10 steps à 5 seconds from 1 min^{-1} up to 512 min^{-1} and then likewise decreased down to 1 min^{-1}. Shear rate D and shear stress τ were calculated as follows: D = n x 0.0073 τ = S x 5.44 Pa. Results are represented as plots of D vs. τ comprising up curves (n increased from 1 to 512 min^{-1}) and down curves (n decreased down to 1 min^{-1}) in Figures 3a-f.

Dimethicone suspensions comprising 53.5%, 55.5%, 56.5% and 60% (w/w) nifedipine, based on the total weight of the suspension, were prepared and measured immediately after filling the sample vial. Additionally, a set of 60% nifedipine dimethicone suspensions were prepared that were measured with a delay of 15 min or 30 min, respectively, after the filling of the sample vial. All experiments were performed in triplicates.

As shown in Figures 3a-c, the concentrated dimethicone suspensions with 53.5%, 55.5% or 56.5% nifedipine showed essentially Newtonian flow behaviour, characterized by a straight line in the shear rate / shear stress (D/τ) plots. Up and down curves looked virtually the same, indicating the absence of particle to particle interactions which would have caused time-dependent flow behaviour (i.e. thixotropy). Hence, dimethicone acts as viscosity reducing lubricant between the particles, and thus allows processing concentrated suspensions through the small gap of a piston-gap homogenizer. The tested nifedipine concentrations in dimethicone were distinctly higher than the processible concentration in aqueous suspensions that is at about 40% (w/w) nifedipine.

In the D/τ plot of highly concentrated 60% nifedipine dimethicone suspension measured immediately after loading the suspension into the sample vial (Figure 3d), the down curve is above the up curve indicating that after applying shear force (by increasing the rotor speed n) viscosity of the suspension decreased, i.e. a thixotropic behaviour. This was confirmed by experiments where measurement was performed 15 min or 30 min after loading of the sample vial (Figures 3e and f). After a 15 min pause the area between up and down curves was much reduced, indicating a less pronounced

thixotropy of the suspension. After 30 min pause up and down curves looked virtually the same, i.e. the suspension was not thixotropic any more.

The thixotropic behaviour of highly concentrated dimethicone suspensions explains why even suspensions of 80% (w/w) nifedipine in dimethicone were processible with a piston-gap homogenizer.

Example 5: Examination of rheologic properties of highly concentrated nifedipine dimethicone suspensions using a penetrometer

2.5 g KF6104 and 2.5 g dimethicone (Dow Corning Q7-9120) were mixed by stirring for 30 s. 20 g (80%) nifedipine was added and dispersed using mortar and pistil. The resulting paste was either subjected to a resting period of 48 h (non-homogenized sample) or homogenized using a high pressure homogenizer (Micron LAB 40, Unna, Germany) (homogenized sample). Each sample (and vaselinum album for comparison) was analyzed at least 3-times using a cone penetrometer (supplier: Sommer&Runge , Berlin Friedenau; weight of cone 117.2 g; measurement of depth of penetration after 5 s). Results are shown in Table 1 below.

Table 1 Results of rheological analysis of nifedipine dimethicone suspensions using a penetrometer

Measurement no.	80%nipedipine dimethicone suspension		Vaselinum album (for comparison)
	Non-homogenized sample	Homogenized sample	
1	9.95 mm	18.00 mm	21.30 mm
2	9.90 mm	18.00 mm	21.90 mm
3	11.05 mm	18.30 mm	21.50 mm
4	10.65 mm		21.90 mm
5	10.65 mm		
6	10.40 mm		
Average	10.43 mm	18.10 mm	21.65 mm

We claim:

1. A nanosuspension formulation comprising particles of at least one functional ingredient dispersed in a hydrophobic phase comprising a polydimethylsiloxane wherein at least 90% by weight of the particles have a particle size in the range of about 5 nm to about 2000 nm.

2. The nanosuspension formulation according to claim 1, additionally comprising at least one surfactant.

3. The nanosuspension formulation according to claim 2, wherein the surfactant is a silicone based surfactant.

4. The nanosuspension formulation according to claim 3, wherein the silicone based surfactant is a polydimethylsiloxane comprising polyether side chains, or polyglycerol chains, or mixtures of these chains.

5. The nanosuspension formulation according to claim 4, wherein the silicone based surfactant is selected from the group comprising PEG-9 dimethicone, PEG-9 methyl ether dimethicone, PEG-10 dimethicone, PEG-9 polydimethylsiloxyethyl dimethicone, lauryl PEG-9 polydimethylsiloxyethyl dimethicone, polyglyceryl-3 disiloxane dimethicone, and polyglyceryl-3 dimethylsiloxyethyl dimethicone.

6. The nanosuspension formulation according to claim 2, wherein the surfactant is propylene glycol monolaurate

7. The nanosuspension formulation according to any one of claims 2 to 6, wherein the nanosuspension formulation comprises from about 0.1% to about 10% by weight of the surfactant, based on the total weight of the nanosuspension formulation.

8. The nanosuspension formulation according to any one of claims 1 to 7, wherein the polydimethylsiloxane has a viscosity from about 5 mm^2s^{-1} to about 1000 mm^2s^{-1} at 25°C.

9. The nanosuspension formulation according to any one of claims 1 to 8, wherein the hydrophobic phase comprises at least 50% by weight of polydimethylsiloxane.

10. The nanosuspension formulation according to any one of claims 1 to 9, wherein at least 90% by weight of the particles have a particle size in the range of about 500 nm to about 1500 nm.

11. The nanosuspension formulation according to any one of claims 1 to 10, wherein the functional ingredient is selected from pharmaceutically active agents, cosmetically active agents, food additives, dyes or pigments.

12. The nanosuspension formulation according to any one of claims 1 to 11 comprising at least 40% of the functional ingredient, relative to the total weight of the nanosuspension formulation.

13. Multiple dispersion containing:

(a) an external aqueous phase, and
(b) a nanosuspension formulation according to any one of the preceding claims dispersed in the external aqueous phase.

14. The multiple dispersion according to claim 13, additionally comprising at least one secondary surfactant acting as emulsifier.

15. The multiple dispersion according to claim 14, wherein the secondary surfactant is a silicone based surfactant.

16. The multiple dispersion according to claim 15, wherein the silicone based surfactant is a polydimethylsiloxane comprising polyether side chains, for example polyethylene oxide chains, polypropylene oxide chains, polyether chains containing moieties derived from both ethylene oxide and propylene oxide, or polyglycerol chains, or mixtures of these chains.

17. The multiple dispersion according to claim 16, wherein the silicone based surfactant is selected from the group comprising PEG-9 dimethicone, polyglyceryl-3 disiloxane dimethicone, and polyglyceryl-3 dimethylsiloxyethyl dimethicone.

18. The multiple dispersion according to claim 14, wherein the secondary surfactant is polyoxyethylene glycerol trioleate.

19. A method for producing a nanosuspension formulation according to claim 1, comprising:

(a) providing a hydrophobic phase comprising a polydimethylsiloxane,
(b) contacting the hydrophobic phase of (a) with at least one particulate functional ingredient,
(c) subdividing the particulate functional ingredient and dispersing the particulate functional ingredient throughout the hydrophobic phase by high pressure homogenization.

20. The method of claim 19, wherein the high pressure homogenization is selected from jet stream homogenization and piston-gap homogenization.

21. The method of claim 19 or 20, wherein at least one surfactant as defined in claim 3 or 5 is dispersed in the hydrophobic phase prior to contacting the hydrophobic phase with the particulate functional ingredient.

22. The method of any one of claims 19 to 21, wherein the high pressure homogenization is performed at a power density of about 10^9 to about 10^{12} W/m^3.

23. The method of any one of claims 19 to 22, wherein the functional ingredient is used in an amount of at least 40%, relative to the total weight of the nanosuspension formulation.

24. The multiple dispersion according to claim 13, wherein the particles are essentially located at the interface of polydimethylsiloxane hydrophobic phase and external aqueous phase.

25. The nanosuspension formulation according to any one of claims 1 to 12, characterized in that when contacted with an aqueous medium the functional ingredient is released into said aqueous medium at near zero-order.

FIGURE 1

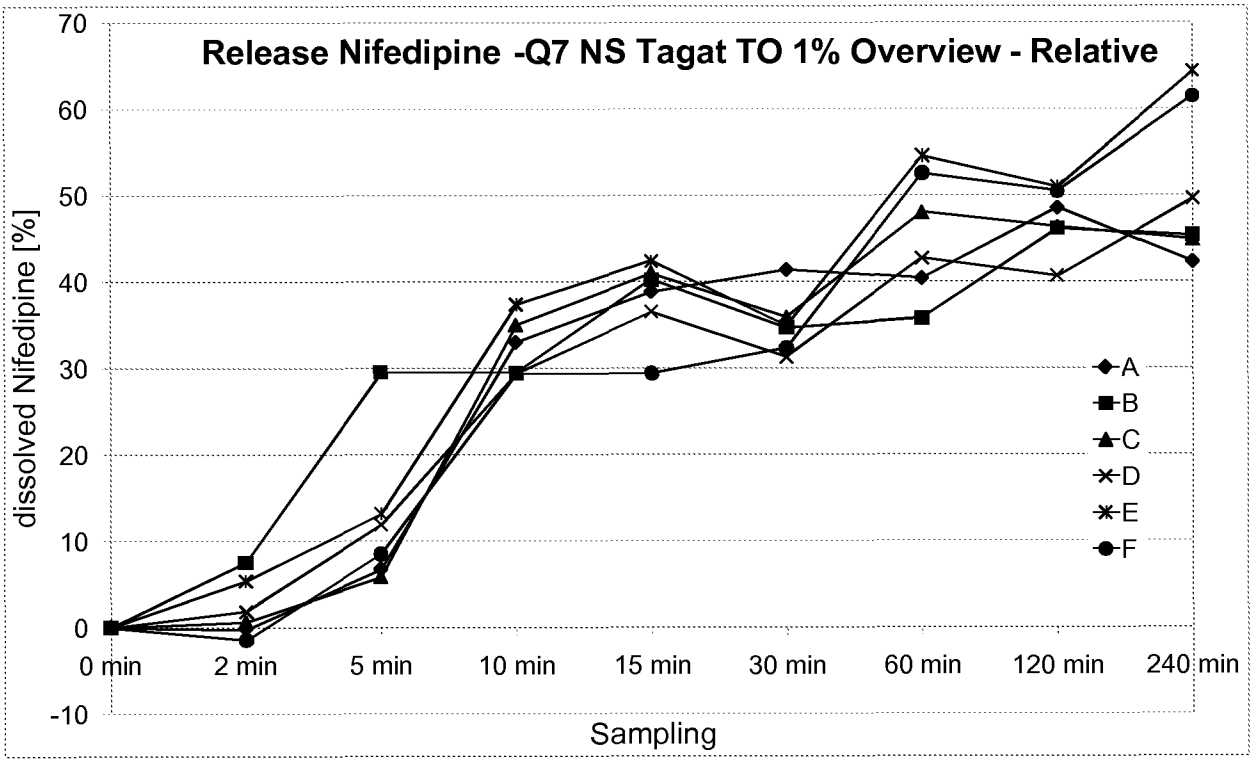


FIGURE 2

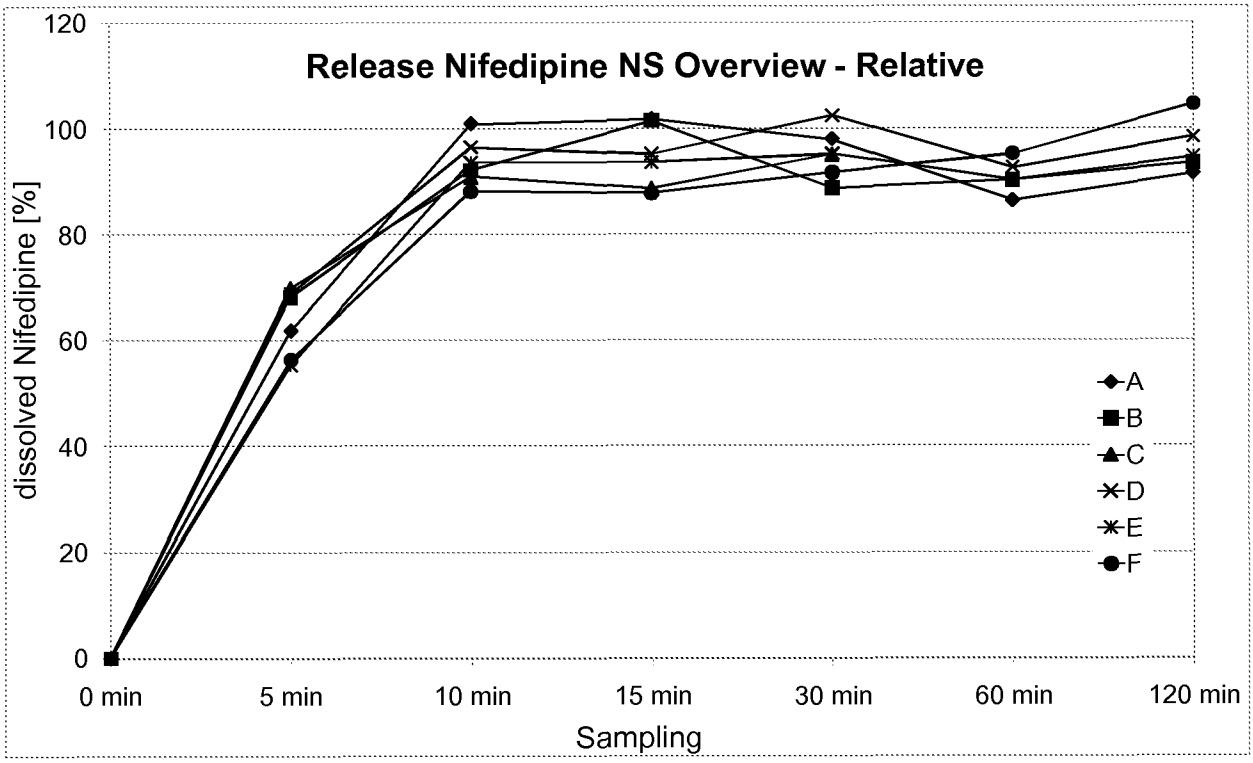
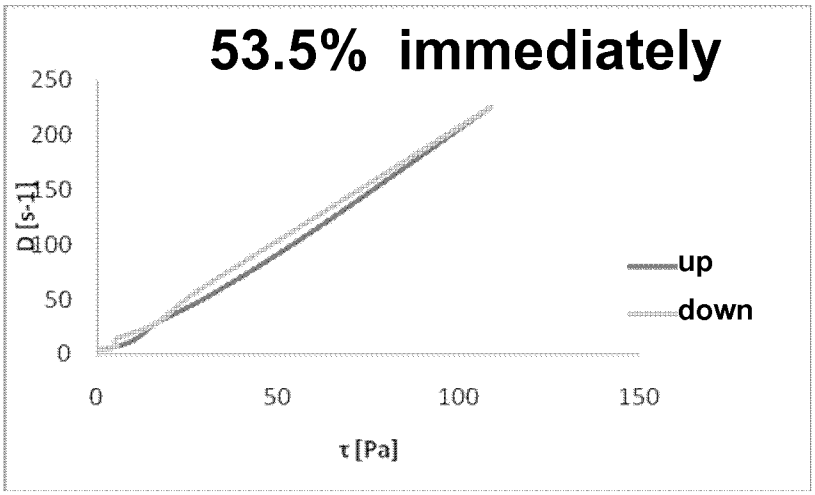
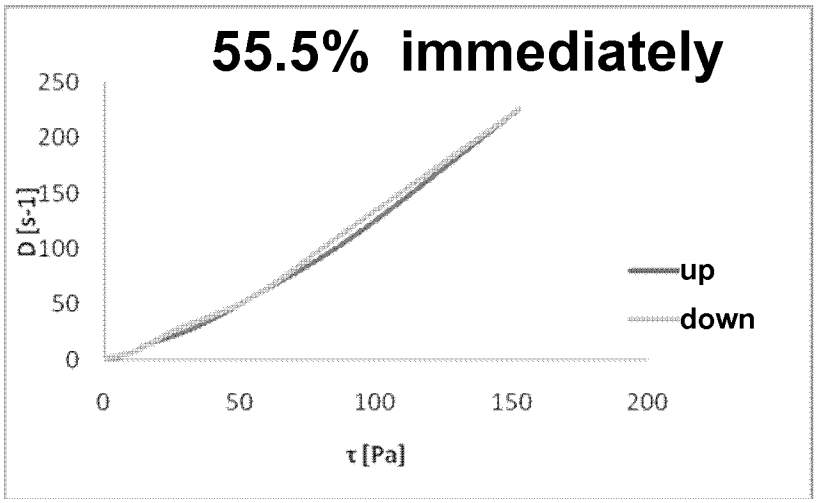


FIGURE 3

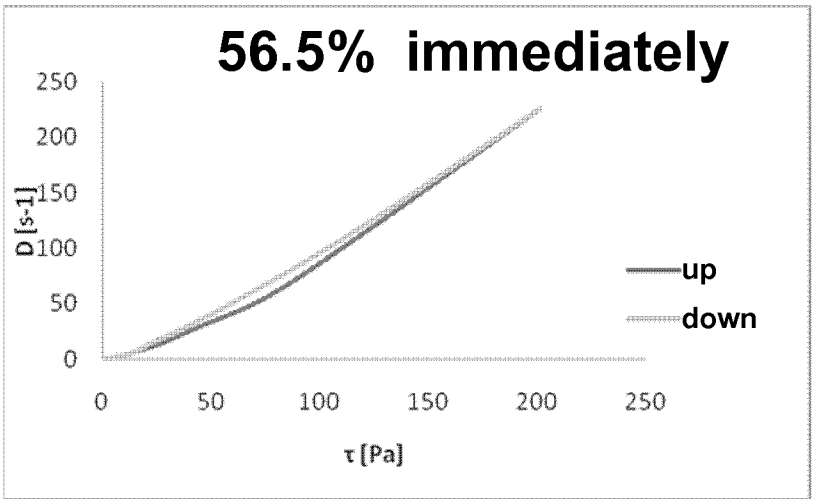
a)


53.5% immediately
250
200
150
100
50
0
D [s-1]
0
50
100
150
τ [Pa]
up
down

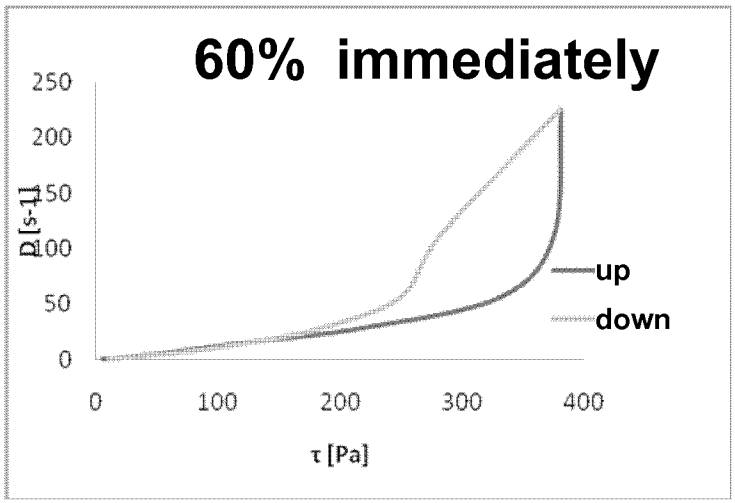
b)


55.5% immediately
250
200
150
100
50
0
D [s-1]
0
50
100
150
200
τ [Pa]
up
down

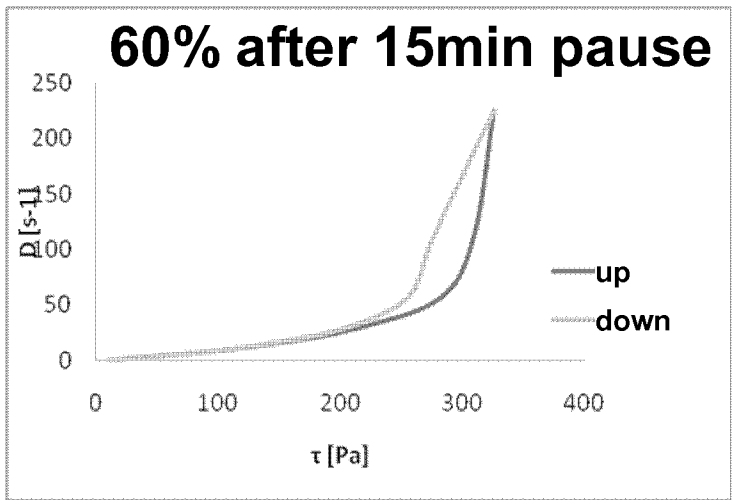
c)


56.5% immediately
250
200
150
100
50
0
D [s-1]
0
50
100
150
200
250
τ [Pa]
up
down

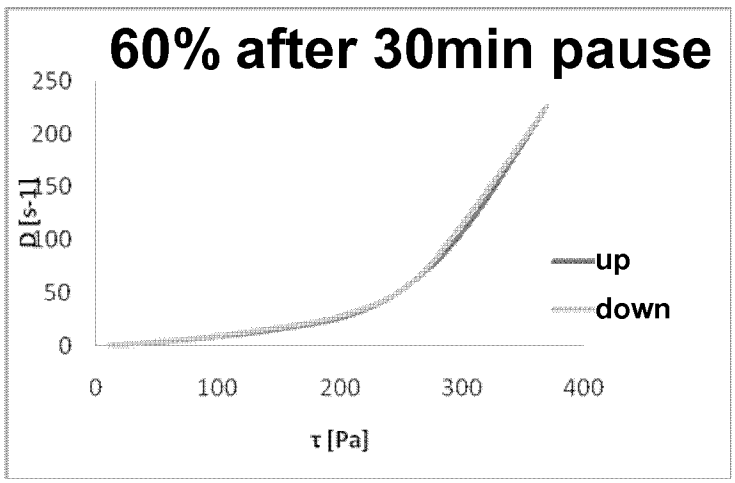
d)


60% immediately
250
200
150
100
50
0
D [s-1]
0
100
200
300
400
τ [Pa]
up
down

e)


60% after 15min pause
250
200
150
100
50
0
D [s-1]
0
100
200
300
400
τ [Pa]
up
down

f)


60% after 30min pause
250
200
150
100
50
0
D [s-1]
0
100
200
300
400
τ [Pa]
up
down