

(12) STANDARD PATENT
(19) AUSTRALIAN PATENT OFFICE

(11) Application No. **AU 2007271828 B2**

- (54) Title
Improvements relating to anti-parasitic compositions
- (51) International Patent Classification(s)
A61K 9/16 (2006.01) **A61K 31/496** (2006.01)
- (21) Application No: **2007271828** (22) Date of Filing: **2007.06.29**
- (87) WIPO No: **WO08/006713**
- (30) Priority Data
- (31) Number (32) Date (33) Country
0613925.7 **2006.07.13** **GB**
- (43) Publication Date: **2008.01.17**
(44) Accepted Journal Date: **2010.12.02**
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- (56) Related Art
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(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
17 January 2008 (17.01.2008)

PCT

(10) International Publication Number
WO 2008/006713 A3

(51) International Patent Classification:
A61K 9/16 (2006.01) A61K 31/496 (2006.01)

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(21) International Application Number:
PCT/EP2007/056561

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(22) International Filing Date: 29 June 2007 (29.06.2007)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
0613925.7 13 July 2006 (13.07.2006) GB

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

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(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

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Published:

- with international search report
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

(88) Date of publication of the international search report:
31 July 2008

(54) Title: IMPROVEMENTS RELATING TO ANTI-PARASITIC COMPOSITIONS

(57) Abstract: The present invention relates to nanodisperse antiparasitics and provides a composition comprising at least one water insoluble anti-parasitic drug and a water-soluble carrier material, wherein the water-insoluble anti-parasitic drug (preferably an Artemisinin-type drug or a quinine type drug) is dispersed through the carrier material in nano-disperse form having a peak diameter of the nano-disperse form below 1000nm. The invention further provides an aqueous dispersion of a water insoluble anti-parasitic drug and a water-soluble carrier material, wherein the anti-parasitic drug is in nano-disperse form having a peak diameter of the nano-disperse form below 1000nm, the invention further subsists in a process for preparing an anti-parasitic composition comprising a water insoluble anti-parasitic agent and a water-soluble carrier, which comprises the steps of either: a) providing an emulsion comprising a solution of the anti-parasitic agent in a water-immiscible solvent for the same, and an aqueous solution of the carrier, or providing a mixture comprising at least one non-aqueous solvent optional water a water-soluble carrier material soluble in the mixture and a water-insoluble anti-parasitic agent soluble in the mixture, and, b) drying the emulsion (preferably by spray drying) to remove water and the water-immiscible solvent to obtain a substantially solvent-free nano-dispersion of the anti-parasitic agent in the carrier.

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IMPROVEMENTS RELATING TO ANTI-PARASITIC COMPOSITIONS**Field of the Invention**

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The present invention relates improvements relating to anti-parasitic compositions.

10 In particular it relates to pharmaceutically active compositions and precursors therefor which contains a substance active against malaria parasites and which in particular has a high activity against multi-resistant lines of malaria parasites, particularly **Plasmodium falciparum**.

15 The present invention further relates to a pharmaceutically acceptable form of artemisinin and/or a derivative of artemisinin, for example arteether, artemether, artemisin, dihydroartemisinin or artesunate, whether alone or in combination with another anti-malarial agent.

20

Background of the Invention

25 The present invention is believed to be generally applicable to anti-parasitic compositions but will be described with particular reference to malaria parasites.

30 Malaria is a vector-borne infectious disease that is widespread in tropical and subtropical regions. It infects between 300 and 500 million people every year and causes between one and three million deaths annually, mostly among

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young children in Sub-Saharan Africa. The disease is caused by protozoan of the genus *Plasmodium*. The most serious forms of the disease are caused by *P. falciparum* and *P. vivax* but other related species *P. ovale*, *P. malariae* and *P. knowlesi* can infect humans. This group of human-pathogenic *Plasmodium* species is usually referred to as the *malaria parasites*. Many areas of the world now have widespread strains of chloroquine-resistant *P. falciparum*.

10 Effective agents for the treatment and prophylaxis of malaria have been known for many years however there has been a long standing problem that these have a poor water solubility. A well known solution to this problem has been to dissolve the anti-malarial agent in alcohol and consume the solution. Thus quinine could be dissolved in gin (by the English) and artemisinin used to make absinthe (by the French). While these were popular treatments, they were not without side-effects due to the levels of alcohol used and could not be used by abstainers from alcohol.

20 Artemisinin (qinghaosu) is obtained from the leaves of the shrub *Artemisia annua* and is a naturally occurring sesquiterpene lactone with an endo peroxide group. *Artemisia* has been used by Chinese herbalists for more than a thousand years in the treatment of many illnesses, including malaria. Its mechanism of action is not fully understood. It is also believed to be effective in the treatment of other parasitic infections including those caused by worms and flukes.

30 Artemisinin preparations are currently among the substances which are believed to act most rapidly against malaria

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parasites. In particular, they show a high activity against
multiresistant lines of *Plasmodium falciparum*. Also, when
administered to humans, only a few side effects and no
significant toxicity have been observed, although
5 neurotoxicity has occurred in animals.

However, physical properties such as poor water solubility
(in the case of artemisinin, artemether, arteether,
dihydroartemisinin), poor bioavailability (in the case of
10 artemisinin, artemether, arteether), or poor stability (in
the case of artesunate) often limit their effectiveness,
application, and increase their cost either by having to
increase dosages or by using special packaging. Artemisin is
therefore mostly presented in a tablet form. For example
15 U.S. Pat. Nos. 6,326,023; 6,307,068; 6,306,896; 5,834,491;
5,677,331; 5,637,594; 5,486,535; 5,278,173; 5,270,037;
5,219,865; 5,021,426; 5,011,951 are only directed to
compositions which are to be packaged as solids for oral
dosing.

20 Artemisinin is typically used in treatment of malaria rather
than in prophylaxis. Malarial patients in the advanced
stages of the disease may be unable to swallow tablets.
Therefore it is desirable to have anti-malarial drugs
25 available in liquid form to provide an injectable medication
or allow rectal administration. Liquid forms of medication
also allow for a continuous variation in dosage and this is
especially useful in the treatment of children, where dosage
may be calculated on the basis of body weight.

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Attempts have been made to improve the solubility of less soluble Artemisinin-type drugs so as allow liquid forms, but these can cause side-effects at the injection site or the formulation may introduce undesirable carrier materials
5 (such as DMSO). US 7084132 describes many of these problems and offers a solution in the form of admixing the drugs with cyclodextrins.

It is therefore desirable to provide artemisinin-type drugs
10 in a soluble form. Advantageously, these should form physiologically acceptable solutions. It is also advantageous that the drugs should exhibit high bioavailability.

15 Quinine and its stereoisomer quinidine, are rapidly acting schizontocides that target the erythrocytic asexual stages of all malaria parasites. Previously chloroquine was used instead of quinine, but it has now become the first choice of treatment due malarial resistance of chloroquine.

20 Application of an anti-malarial formulation must be specific to administration in hot, humid tropical regions native to the malarial parasites. Thus, chemical stability under drastic environmental conditions is desirable. It is
25 therefore a further advantage that they should be storage stable.

The activity of artemisinin and its derivatives is short-lived when compared to other anti-malarial drugs. With
30 significant decreases in effectiveness after one to two hours, artemisinin and its derivatives are administered in

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combination with long half-life anti-malarial drugs, such as lumefantrine, mefloquine, or amodiaquine, etc. to treat uncomplicated *falciparum* malaria.

5 Lumefantrine has a half-life of about 3 to 6 days. Such a treatment is called ACT (artemisinin-based combination therapy). Examples include artemether-lumefantrine, artesunate-mefloquine, artesunate-amodiaquine, and artesunate-sulfadoxine/ pyrimethamine. Trials have shown
10 that ACT is more than 90% effective, with a recovery from malaria after three days, especially for the chloroquine-resistant *P. falciparum*. Advantageously, artemisinin should be presented in a form which makes it suitable for combination treatment.

15

Our co-pending international patent application PCT/GB03/03226 describes the formation of solid, porous beads comprising a three dimensional open-cell lattice of a water-soluble polymeric material. These are typically
20 'templated' materials formed by the removal of both water and a non-aqueous dispersed phase from a high internal phase emulsion (HIPE) which has a polymer dissolved in the aqueous phase. The beads are formed by dropping the HIPE emulsion into a low temperature fluid such as liquid nitrogen, then
25 freeze-drying the particles formed to remove the bulk of the aqueous phase and the dispersed phase. This leaves behind the polymer in the form of a 'skeletal' structure. The beads dissolve rapidly in water and have the remarkable property that a water-insoluble component dispersed in the dispersed
30 phase of the emulsion prior to freezing and drying can also

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be dispersed in water on solution of the polymer skeleton of the beads.

5 WO 2005/011636 discloses a non-emulsion based spray drying process for forming 'solid amorphous dispersions' of drugs in polymers. In this method a polymer and a low-solubility drug are dissolved in a solvent and spray-dried to form dispersions in which the drug is mostly present in an amorphous form rather than in a crystalline form.

10

Our co-pending applications GB 0501835 and GB 0613925 (filed 13th July 2006) describe how materials which will form a nano-dispersion in water can be prepared, preferably by a spray-drying process. In the first of these applications the water insoluble materials is dissolved in the solvent-phase of an emulsion. In the second, the water-insoluble materials are dissolved in a mixed solvent system and co-exist in the same phase as a water-soluble structuring agent. In both cases the liquid is dried above ambient temperature (above 15 20 Celsius), such as by spray drying, to produce particles of the structuring agent, as a carrier, with the water-insoluble materials dispersed therein. When these particles are placed in water they dissolve, forming a nano-dispersion of the water-insoluble material with particles typically 20 below 300nm. This scale is similar to that of virus particles, and the water-insoluble material behaves as though it were in solution.

25

In the present application the term 'ambient temperature' means 20 degrees Celsius and all percentages are percentages by weight unless otherwise specified.

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Our GB 0501835 application showed that fluorescer materials prepared by the method disclosed exhibited better performance than those prepared by a known freeze-drying method.

Our GB 0613925 application makes it clear that a Triclosan™ nano-dispersion has the additional benefit that weight for weight it is more effective than is normally expected of Triclosan™ even at very low concentrations.

Brief Description of the Invention

We have now determined that both the emulsion-based and the single-phase method can be used to produce a water-soluble form of anti-parasitic drugs, particularly relatively insoluble artemisinin-type and quinine-type anti-malarial drugs.

Accordingly, a first aspect of the present invention provides a composition comprising at least one water insoluble anti-parasitic drug wherein the water-insoluble anti-parasitic drug is in nano-disperse form having a peak diameter of the nano-disperse form below 1000nm.

A further aspect of the present invention provides an anti-parasitic drug preparation comprising at least one water insoluble anti-parasitic drug and a water-soluble carrier material, wherein the water-insoluble anti-parasitic drug is dispersed through the carrier material in nano-disperse form

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having a peak diameter of the nano-disperse form below 1000nm.

The preferred method of particle sizing for the dispersed products of the present invention employs a dynamic light scattering instrument (Nano S, manufactured by Malvern Instruments UK). Specifically, the Malvern Instruments Nano S uses a red (633nm) 4mW Helium-Neon laser to illuminate a standard optical quality UV curvette containing a suspension of material. The particle sizes quoted in this application are those obtained with that apparatus using the standard protocol. Particle sizes in solid products are the particle sizes inferred from the measurement of the particle size obtained by solution of the solid in water and measurement of the particle size. Preferably, the peak diameter of the water-insoluble anti-parasitic drug is below 800nm. More preferably the peak diameter of the water-insoluble anti-parasitic drug is below 500nm. In a particularly preferred embodiment of the invention the peak diameter of the water-insoluble anti-parasitic drug is below 200nm, most preferably below 100nm.

It is believed that reduction of the particle size in the eventual nano-dispersion has significant advantages in improving the availability of the otherwise water-insoluble material. This is believed to be particularly advantageous where an improved bio-availability is sought, or, in similar applications where high local concentrations of the material are to be avoided. Moreover it is believed that nano-dispersions with a small particle size are more stable than those with a larger particle size.

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Preferred water-insoluble anti-parasitic drugs are water-insoluble anti-malarial drugs.

5 In the context of the present invention, "water insoluble" as applied to the antiparasitic agent means that its solubility in water is less than 10g/L.

Preferably, the water insoluble anti-parasitic agent has
10 solubility in water at ambient temperature (20 Celsius) less than 5g/L preferably of less than 1g/L, especially preferably less than 150mg/L, even more preferably less than 100mg/L. This solubility level provides the intended interpretation of what is meant by water-insoluble in the
15 present specification.

Preferred water-insoluble anti-parasitic drugs include peroxides, lactones, peroxy-lactones, quinines, quinolines and quinidines.

20 Preferred water-insoluble anti-malarial drugs are peroxy-bridged compounds, preferably Artemisinin-type drugs (including Artemisinin and derivatives thereof) or quinine type drugs (including quinine and derivatives thereof).

25 Preferred Artemisinin-type drugs are selected from the group consisting of artemisinin (soluble at 84mg/L), artemether, arteether, dihydroartemisinin and mixtures thereof. Artemisinin itself is a particularly preferred water
30 insoluble anti-parasitic drug for use in the present invention.

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Preferred quinine type drugs are quinine and quinidine.

5 Compositions according to the present invention can comprise a combination of anti-parasitic drugs. Preferred combinations include a water-insoluble Artemisinin-type drug and at least one of lumefantrine, mefloquine, amodiaquine, sulfadoxine and pyrimethamine.

10 Preferred carrier materials are selected from the group consisting of water-soluble inorganic materials, surfactants, polymers and mixtures thereof.

15 A further aspect of the present invention provides an aqueous dispersion of a water insoluble anti-parasitic drug and a water-soluble carrier material, wherein the anti-parasitic drug is in nano-disperse form having a peak diameter of the nano-disperse form below 1000nm, preferably below 800nm, more preferably below 500nm, and especially
20 below 200nm, most especially below 100nm. The anti-parasitics discussed above being preferred in the aqueous form.

25 A particularly preferred aspect of the invention is that in which the particle size is below 100nm. Particles sizes as low as 25nm were obtained in the examples given below. The preferred particle distributions are such that the sizes are in the range 20-800 nm with a range of 20-200 being particularly preferred.

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A further aspect of the present invention provides a process for preparing an anti-parasitic composition comprising a water insoluble anti-parasitic agent and a water-soluble carrier, which comprises the steps of:

5

a) forming an emulsion comprising:

10 i) a solution of the anti-parasitic agent in a water-immiscible solvent for the same, and

ii) an aqueous solution of the carrier, and,

15 b) drying the emulsion to remove water and the water-immiscible solvent to obtain a substantially solvent-free nano-dispersion of the anti-parasitic agent in the carrier

20 For convenience, this class of method is referred to herein as the "emulsion" method.

A further aspect of the present invention provides a process for preparing an anti-parasitic composition comprising a
25 water insoluble anti-parasitic agent and a water-soluble carrier which comprises the steps of:

a) providing a mixture comprising:

30 i) at least one non-aqueous solvent

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- ii) optionally, water
 - iii) a water-soluble carrier material soluble in the mixture of (i) and (ii) and
 - 5 iv) a water-insoluble anti-parasitic agent which is soluble in the mixture of (i) and (ii), and,
- b) drying the solution to remove water and the water miscible solvent to obtain a substantially solvent-free
- 10 nano-dispersion of the anti-parasitic agent in the carrier.

For convenience, this class of method is referred to herein

15 as the "single-phase" method.

In the context of the present invention substantially solvent free means that the free solvent content of the product is less than 15%wt, preferably below 10%wt and more

20 preferably below 5%wt.

In the context of the present invention it is essential that both the carrier material and the anti-parasitic drug are essentially fully dissolved in their respective solvents

25 prior to the drying step. It is not within the ambit of the present specification to teach the drying of slurries. For the avoidance of any doubt, it is therefore the case that the solids content of the emulsion or the mixture is such that over 90%wt, preferably over 95%, and more preferably

30 over 98% of the soluble materials present is in solution prior to the drying step.

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In relation to the methods mentioned above, the preferred anti-parasitic drugs and the preferred carrier materials are as described above and as elaborated on in further detail
5 below. Similarly the preferred physical characteristics of the material are as described above.

The 'single phase' method where both the anti-parasitic agent and the carrier material are dissolved in a phase
10 comprising at least one other non-aqueous solvent (and optional water) is preferred. This is believed to be more efficacious in obtaining a smaller particle size for the nano-disperse anti-parasitic agent. Preferably, the drying step simultaneously removes both the water and other
15 solvents and, more preferably, drying is accomplished by spray drying at above ambient temperature.

The products obtainable by the process aspects of the present invention are suitable for use in the preparation of
20 medicaments for treatment or prophylaxis of parasitic diseases and particularly, where the anti-parasitic agent is a water-insoluble anti-malarial agent, the preparation of medicaments for use in the treatment or prophylaxis of malaria.

25

A further aspect of the present invention provides a method for the preparation of a medicament for use in the treatment of parasitic infections which comprises the step of preparing a composition according to the present invention.

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According to another aspect the present invention provides a composition comprising at least one water-insoluble anti-malarial drug and a water-soluble carrier material, wherein the water-insoluble anti-malarial drug is dispersed through
5 the carrier material in nano-disperse form having a z-average particle diameter of the nano-disperse form within the composition of 20-800nm.

Detailed Description of the Invention

Various preferred features and embodiments of the present invention are described in further detail below.

5

Anti-Parasitic Agents

As noted above the preferred water-insoluble anti-parasitic drugs are water-insoluble anti-malarial drugs selected from the group consisting of artemisinin, artemether, arteether, dihydroartemisinin and mixtures thereof and quinine, quinidine and mixtures thereof. These can be present as the sole pharmaceutically active ingredient in compositions according to the present invention or be together with other anti-parasitic drugs to provide a so-called 'combination therapy'. Suitable agents for combination therapy include lumefantrine, mefloquine, amodiaquine, sulfadoxine and pyrimethamine.

20 Water-Dispersible Product Form

The present invention provides a method for obtaining a water-dispersible form of an otherwise water-insoluble material. This is prepared by forming a not wholly aqueous intermediate emulsion or solution in which both a water-soluble carrier material and the water insoluble anti-parasitic are dissolved. On removal of solvents the insoluble anti-parasitic material is left dispersed through the water-soluble carrier material. Suitable carrier materials are described in further detail below.

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- 15 -

The most preferred method for drying of the intermediate emulsion or solution is spray drying. This is particularly effective at removing both the aqueous and non-aqueous volatile components to leave the carrier and the 'payload'
5 material behind in a powder form. The drying step is described in further detail below.

The structure of the material obtained after the drying step is not well understood. It is believed that the resulting
10 dry materials are not encapsulates, as discrete macroscopic bodies of the water-insoluble materials are not present in the dry product. Neither are the dry materials 'dry emulsions' as little or none of the volatile solvent comprising the 'oil' phase of the emulsion remains after the
15 drying step. On addition of water to the dry product the emulsion is not reformed, as it would be with a 'dry emulsion'. It is also believed that the compositions are not so-called solid solutions, as with the present invention the ratios of components present can be varied without loss of
20 the benefits. Also from Xray and DSC studies, it is believed that the compositions of the invention are not solid solutions, but comprise nano-scale, phase-separated mixtures.

25 Preferably, the compositions produced after the drying step will comprise the anti-parasitic agent and the carrier in a weight ratio of from 1:500 to 1:1 (as anti-parasitic agent:carrier), 1:100 to 1:1 being preferred. Typical levels of around 10-30%wt water-insoluble anti-parasitic agent and
30 90-70%wt carrier can be obtained by spray drying.

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'Emulsion' Preparation Method

In one preferred method according to the invention the solvent for the water-insoluble anti-parasitic material is not miscible with water. On admixture with water it
5 therefore can form an emulsion.

Preferably, the non-aqueous phase comprises from about 10% to about 95% v/v of the emulsion, more preferably from about
10 20% to about 68% v/v.

The emulsions are typically prepared under conditions which are well known to those skilled in the art, for example, by using a magnetic stirring bar, a homogeniser, or a
15 rotational mechanical stirrer. The emulsions need not be particularly stable, provided that they do not undergo extensive phase separation prior to drying.

Homogenisation using a high-shear mixing device is a particularly preferred way to make an emulsion in which the
20 aqueous phase is the continuous phase. It is believed that this avoidance of coarse emulsion and reduction of the droplet size of the dispersed phase of the emulsion, results in an improved dispersion of the 'payload' material in the
25 dry product.

In a preferred method according to the invention a water-continuous emulsion is prepared with an average dispersed-phase droplet size (using the Malvern peak intensity) of
30 between 500nm and 5000nm. We have found that an 'Ultra-Turrux' T25 type laboratory homogenizer (or equivalent)

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gives a suitable emulsion when operated for more than a minute at above 10,000 rpm.

There is a directional relation between the emulsion droplet size and the size of the particles of the 'payload' material, which can be detected after dispersion of the materials of the invention in aqueous solution. We have determined that an increase in the speed of homogenization for precursor emulsions can decrease final particle size after re-dissolution.

It is believed that the re-dissolved particle size can be reduced by nearly one half when the homogenization speed increased from 13,500 rpm to 21,500 rpm. The homogenization time is also believed to play a role in controlling re-dissolved particle size. The particle size again decreases with increase in the homogenization time, and the particle size distribution become broader at the same time.

Sonication is also a particularly preferred way of reducing the droplet size for emulsion systems. We have found that a Hert Systems Sonicator XL operated at level 10 for two minutes is suitable.

It is believed that ratios of components which decrease the relative concentration of the anti-parasitic to the solvents and/or the carrier give a smaller particle size.

'Single Phase' Preparation Method

In an alternative method according to the present invention both the carrier and the anti-parasitic agent are soluble in

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a non-aqueous solvent or a mixture of such a solvent with water. . Both here and elsewhere in the specification the non-aqueous solvent can be a mixture of non-aqueous solvents.

5

In this case the feedstock of the drying step can be a single phase material in which both the water-soluble carrier and the water-insoluble anti-parasitic agent are dissolved. It is also possible for this feedstock to be an emulsion, provided that both the carrier and the agent are dissolved in the same phase.

10

The 'single-phase' method is generally believed to give a better nano-dispersion with a smaller particle size than the emulsion method.

15

It is believed that ratios of components which decrease the relative concentration of the anti-parasitic to the solvents and/or the carrier give a smaller particle size.

20

Drying

Spray drying, the most preferred method of drying the emulsion, is well known to those versed in the art. In the case of the present invention some care must be taken due to the presence of a volatile non-aqueous solvent in the emulsion being dried. In order to reduce the risk of explosion when a flammable solvent is being used, an inert gas, for example nitrogen, can be employed as the drying medium in a so-called closed spray-drying system. The solvent can be recovered and re-used.

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We have found that the 'Buchi' B-290 type laboratory spray drying apparatus is suitable.

5 It is preferable that the drying temperature should be at or above 100 Celsius, preferably above 120 Celsius and most preferably above 140 Celsius. Elevated drying temperatures have been found to give smaller particles in the re-

10

Carrier Material

The carrier material is water soluble, which includes the formation of structured aqueous phases as well as true ionic
15 solution of molecularly mono-disperse species. The carrier material preferably comprises an inorganic material, surfactant, a polymer or may be a mixture of two or more of these.

20 It is envisaged that other non-polymeric, organic, water-soluble materials such as sugars can be used as the carrier. However the carrier materials specifically mentioned herein are preferred.

Suitable carrier materials (referred to herein as 'water
25 soluble carrier materials') include preferred water-soluble polymers, preferred water-soluble surfactants and preferred water-soluble inorganic materials.

Preferred polymeric carrier materials

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- 20 -

Examples of suitable water-soluble polymeric carrier materials include:

- 5 (a) natural polymers (for example naturally occurring gums such as guar gum, alginate, locust bean gum or a polysaccharide such as dextran;
- 10 (b) cellulose derivatives for example xanthan gum, xyloglucan, cellulose acetate, methylcellulose, methyl-ethylcellulose, hydroxy-ethylcellulose, hydroxy-ethylmethyl-cellulose, hydroxy-propylcellulose, hydroxy-propylmethylcellulose, hydroxy-propylbutylcellulose, ethylhydroxy-ethylcellulose, carboxy-methylcellulose and its salts (eg the sodium salt - SMC), or carboxy-methylhydroxyethylcellulose and its salts (for example the sodium salt);
- 15 (c) homopolymers of or copolymers prepared from two or more monomers selected from: vinyl alcohol, acrylic acid, methacrylic acid, acrylamide, methacrylamide, acrylamide methylpropane sulphonates, aminoalkylacrylates, aminoalkyl-methacrylates, hydroxyethylacrylate, hydroxyethylmethacrylate, vinyl pyrrolidone, vinyl imidazole, vinyl amines, vinyl
- 20 pyridine, ethyleneglycol and other alkylene glycols, ethylene oxide and other alkylene oxides, ethyleneimine, styrenesulphonates, ethyleneglycolacrylates and ethyleneglycol methacrylate
- 25 (d) cyclodextrins, for example *beta*-cyclodextrin
- 30

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(e) mixtures thereof

When the polymeric material is a copolymer it may be a statistical copolymer (heretofore also known as a random
5 copolymer), a block copolymer, a graft copolymer or a hyperbranched copolymer. Co-monomers other than those listed above may also be included in addition to those listed if their presence does not destroy the water soluble or water dispersible nature of the resulting polymeric
10 material.

Examples of suitable and preferred homopolymers include poly-vinylalcohol, poly-acrylic acid, poly-methacrylic acid, poly-acrylamides (such as poly-N-isopropylacrylamide), poly-
15 methacrylamide; poly-acrylamines, poly-methyl-acrylamines, (such as polydimethylaminoethylmethacrylate and poly-N-morpholinoethylmethacrylate), polyvinylpyrrolidone, polystyrenesulphonate, polyvinylimidazole, polyvinylpyridine, poly-2-ethyl-oxazoline poly-ethyleneimine and ethoxylated
20 derivatives thereof.

Polyethylene glycol (PEG), polyvinylpyrrolidone (PVP), poly(2-ethyl-2-oxazoline), polyvinyl alcohol (PVA) hydroxypropyl cellulose and hydroxypropyl-methyl cellulose (HPMC) and alginates are preferred polymeric carrier
25 materials.

Preferred surfactant carrier materials

Where the carrier material is a surfactant, the surfactant
30 may be non-ionic, anionic, cationic, amphoteric or zwitterionic.

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Examples of suitable non-ionic surfactants include ethoxylated triglycerides; fatty alcohol ethoxylates; alkylphenol ethoxylates; fatty acid ethoxylates; fatty amide
5 ethoxylates; fatty amine ethoxylates; sorbitan alkanates; ethylated sorbitan alkanates; alkyl ethoxylates; Pluronic[™]; alkyl polyglucosides; stearyl ethoxylates; alkyl polyglycosides.

10 Examples of suitable anionic surfactants include alkylether sulfates; alkylether carboxylates; alkylbenzene sulfonates; alkylether phosphates; dialkyl sulfosuccinates; sarcosinates; alkyl sulfonates; soaps; alkyl sulfates; alkyl
15 carboxylates; alkyl phosphates; paraffin sulfonates; secondary n-alkane sulfonates; alpha-olefin sulfonates; isethionate sulfonates.

Examples of suitable cationic surfactants include fatty amine salts; fatty diamine salts; quaternary ammonium
20 compounds; phosphonium surfactants; sulfonium surfactants; sulfonxonium surfactants.

Examples of suitable zwitterionic surfactants include N-alkyl derivatives of amino acids (such as glycine, betaine,
25 aminopropionic acid); imidazoline surfactants; amine oxides; amidobetaines.

Mixtures of surfactants may be used. In such mixtures there may be individual components which are liquid, provided that
30 the carrier material overall, is a solid.

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Alkoxylated nonionic's (especially the PEG/PPG Pluronic™ materials), phenol-ethoxylates (especially TRITON™ materials), alkyl sulphonates (especially SDS), ester surfactants (preferably sorbitan esters of the Span™ and Tween™ types) and cationics (especially cetyltrimethylammonium bromide - CTAB) are particularly preferred as surfactant carrier materials.

Preferred inorganic carrier materials

10

The carrier material can also be an water-soluble inorganic material which is neither a surfactant nor a polymer. Simple organic salts have been found suitable, particularly in admixture with polymeric and/or surfactant carrier materials as described above. Suitable salts include carbonate, bicarbonates, halides, sulphates, nitrates and acetates, particularly soluble salts of sodium, potassium and magnesium. Preferred materials include, sodium carbonate, sodium bicarbonate and sodium sulphate. These materials have the advantage that they are cheap and physiologically acceptable. They are also relatively inert as well as compatible with many materials found in pharmaceutical products.

25

Mixtures of carrier materials are advantageous. Preferred mixtures include combinations of surfactants and polymers. Which include at least one of:

a) Polyethylene glycol (PEG), polyvinylpyrrolidone (PVP), hydroxypropyl cellulose and hydroxypropyl-methyl

30

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cellulose (HPMC) , alginates and, at least one of;

- b) Alkoxyated nonionic's (especially the PEG/PPG Pluronic™ materials), phenol-ethoxylates (especially TRITON™ materials), alkyl sulphonates (especially SDS), ester surfactants (preferably sorbitan esters of the Span™ and Tween™ types) and cationics (especially cetyltrimethylammonium bromide - CTAB)
- 10 The carrier material can also be a water-soluble small organic material which is neither a surfactant , a polymer nor an inorganic carrier material. Simple organic sugars have been found to be suitable, particularly in admixture with a polymeric and/or surfactant carrier material as
- 15 described above. Suitable small organic materials include mannitol, polydextrose, xylitol and inulin etc.

Non-aqueous solvent

- 20 The compositions of the invention comprise a volatile, second non-aqueous solvent. This may either be miscible with the other solvents in pre-mix before drying or, together with those solvents may form an emulsion.
- 25 In one alternative form of the invention a single, non-aqueous solvent is employed in which can form a single phase with water in the presence of the anti-parasitic agent, and the carrier. Preferred solvents for these embodiments are polar, protic or aprotic solvents. Generally preferred
- 30 solvents have a dipole moment greater than 1 and a dielectric constant greater than 4.5.

- 25 -

Particularly preferred solvents are selected from the group consisting of haloforms (preferably dichloromethane, chloroform), lower (C1-C10) alcohols (preferably methanol, ethanol, isopropanol, isobutanol), organic acids (preferably formic acid, acetic acid), amides (preferably formamide, N,N-dimethylformamide), nitriles (preferably aceto-nitrile), esters (preferably ethyl acetate) aldehydes and ketones (preferably methyl ethyl ketone, acetone), and other water miscible species comprising hetroatom bond with a suitably large dipole (preferably tetrahydrofuran, dialkylsulphoxide).

Haloforms, lower alcohols, ketones and dialkylsulphoxides are the most preferred solvents.

In another alternative form of the invention the non-aqueous solvent is not miscible with water and forms an emulsion.

The non-aqueous phase of the emulsion is preferably selected from one or more from the following group of volatile organic solvents:

- alkanes, preferably heptane, n-hexane, isooctane, dodecane, decane;
- cyclic hydrocarbons, preferably toluene, xylene, cyclohexane;
- halogenated alkanes , preferably dichloromethane, dichoroethane, trichloromethane (chloroform), fluoro-

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trichloromethane and tetrachloroethane;

- esters preferably ethyl acetate;
- 5 • ketones preferably 2-butanone;
- ethers preferably diethyl ether;
- volatile cyclic silicones preferably either linear or
10 cyclomethicones containing from 4 to 6 silicon units.
Suitable examples include DC245 and DC345, both of
which are available from Dow Corning Inc.

Preferred solvents include dichloromethane, chloroform,
15 ethanol, acetone and dimethyl sulphoxide.

Preferred non-aqueous solvents, whether miscible or not have
a boiling point of less than 150 Celsius and, more
preferably, have a boiling point of less than 100 Celsius,
20 so as to facilitate drying, particularly spray-drying under
practical conditions and without use of specialised
equipment. Preferably they are non-flammable, or have a
flash point above the temperatures encountered in the method
of the invention.

25

Preferably, the non-aqueous solvent comprises from about 10
% to about 95% v/v of any emulsion formed, more preferably
from about 20% to about 80 % v/v. In the single phase method
the level of solvent is preferably 20-100%v/v.

30

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Particularly preferred solvents are alcohols, particularly ethanol and halogenated solvents, more preferably chlorine-containing solvents, most preferably solvents selected from (di- or tri- chloromethane).

5

Optional Cosurfactant

In addition to the non-aqueous solvent an optional co-surfactant may be employed in the composition prior to the drying step. We have determined that the addition of a relatively small quantity of a volatile cosurfactant reduced the particle diameter of the material produced. This can have a significant impact on particle volume. For example, reduction from 297nm to 252nm corresponds to a particle size reduction of approximately 40%. Thus, the addition of a small quantity of co-surfactant offers a simple and inexpensive method for reducing the particle size of materials according to the present invention without changing the final product formulation.

20

Preferred co-surfactants are short chain alcohols or amine with a boiling point of <220°C.

Preferred co-surfactants are linear alcohols. Preferred co-surfactants are primary alcohols and amines. Particularly preferred co-surfactants are selected from the group consisting of the 3-6 carbon alcohols. Suitable alcohol co-surfactants include n-propanol, n-butanol, n-pentanol, n-hexanol, hexylamine and mixtures thereof.

30

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Preferably the co-surfactant is present in a quantity (by volume) less than the solvent preferably the volume ratio between the solvent and the co-surfactant falls in the range 100:40 to 100:2, more preferably 100:30 to 100:5.

5

Preferred Spray-Drying Feedstocks

Typical spray drying feedstocks comprise:

- 10 a) a surfactant,
- b) at least one lower alcohol,
- c) more than 0.1% of at least one water-insoluble anti-
15 parasitic agent dissolved in the feedstock,
- d) a polymer, and,
- e) optional water

20

Preferred spray-drying feedstocks comprise:

- a) at least one non-aqueous solvent selected from
dichloromethane, chloroform, ethanol, acetone, and
25 mixtures thereof,
- b) a surfactant selected from PEG co-polymer nonionic's
(especially the PEG/PPG Pluronic™ materials), alkyl
sulphonates (especially SDS), ester surfactants
30 (preferably sorbitan esters of the Span™ and Tween™
types) and cationics (especially cetyltrimethylammonium

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bromide - CTAB) and mixtures thereof,

- 5 c) more than 0.1% of at least one water-insoluble anti-parasitic agent (preferably an anti-malarial agent, more preferably Artemisinin or quinine),
- d) a polymer selected from Polyethylene glycol (PEG), Polyvinyl alcohol (PVA), polyvinyl-pyrrolidone (PVP), hydroxypropyl cellulose and hydroxypropyl-methyl
10 cellulose (HPMC) , alginates and mixtures thereof, and
- e) optionally water.

15 The drying feed-stocks used in the present invention are either emulsions or solutions which preferably do not contain solid matter and in particular preferably do not contain any undissolved anti-parasitic agent.

20 It is particularly preferable that the level of the anti-parasitic agent in the composition should be such that the loading in the dried composition is below 40%wt, and more preferably below 30%wt. Such compositions have the advantages of a small particle size and high effectiveness as discussed above.

25

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Water-Dispersed Form

On admixture of the water-soluble carrier material with water, the carrier dissolves and the water-insoluble anti-parasitic agent is dispersed through the water in sufficiently fine form that it behaves like a soluble material in many respects. The particle size of the water-insoluble materials in the dry product is preferably such that, on solution in water the water-insoluble materials have a particle size of less than 1 micron as determined by the Malvern method described herein. It is believed that there is no significant reduction of particle size for the anti-parasitic agent on dispersion of the solid form in water.

By applying the present invention significant levels of 'water-insoluble' materials can be brought into a state which is largely equivalent to true solution. When the dry product is dissolved in water it is possible to achieve optically clear solutions comprising more than 0.1%, preferably more than 0,5% and more preferably more than 1% of the water-insoluble material.

It is envisaged that the solution form will be a form suitable for administration to a patient either 'as is' or following further dilution. In the alternative, the solution form of embodiments of the invention may be combined with other active materials to yield a medicament suitable for use in combination therapy.

30

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In order that the present invention may be further understood and carried forth into practice it is further described below with reference to non-limiting examples.

5

Examples:

For each sample (unless stated otherwise), about 10 mg powder was re-dispersed into 10 ml distilled water at room
10 temperature (21.5 °C) to give a 1mg/ml nano-dispersion for particle size measurements.

A method of particle sizing for the dispersed products of the present invention used in the following examples employs
15 a dynamic light scattering instrument (Nano S, manufactured by Malvern Instruments UK). Specifically, the Malvern Instruments Nano S uses a red (633nm) 4mW Helium-Neon laser to illuminate a standard optical quality UV curvette containing a suspension of material.

20

For convenience the results in the first twelve examples are summarised in the table below:

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Ex.	Solvent	Carrier	Method	Particle size
1	Ethanol, Water	PEG, HPMC	Single phase (100C spray)	695
2	Ethanol, Water	Pluronic, HPMC	Single phase (100C spray)	770
3	Ethanol, Water	Pluronic, PVP	Single phase (100C spray)	705
4	Ethanol, Water	Cyclodextrin, HPMC	Single phase (100C spray)	667
5	Ethanol, Water	PEG, HPMC	Single phase (150C spray)	56
6	Ethanol, Water	Pluronic, HPMC	Single phase (150C spray)	42
7	Ethanol, Water	Lipoid, HPMC	Single phase (150C spray)	211
8	Ethanol, Water	Pluronic, HPMC, CTAB	Single phase (150C spray)	25
9	Ethanol, Water	Pluronic, HPMC, SDS	Single phase (150C spray)	39
10	Ethanol, Water	Pluronic, HPMC, CTAB, SDS	Single phase (150C spray)	331
11	Ethanol	Pluronic, Span, Klucel	Single phase (150C spray)	180-182
12	Ethanol	Pluronic, Span, Klucel	Single phase (150C spray)	183-207

Example 1:

5 0.10 g artemisinin (99 %, supplied by Hunan Keyuan Biology Product Co. Ltd, China) and 0.05 g polyethylene glycol (PEG, Mw 3,000, Fluka) were both dissolved into 50 ml ethanol. 0.85 g Hydroxypropyl methylcellulose (HPMC, 5cps, Aldrich) was added into the ethanol solution with intensive stirring

10 using a magnetic bar to form a uniform HPMC/EtOH suspension. 50 ml distilled water was then added into the suspension, and a clear solution was obtained. The solution was then spray dried (BUCHI Mini-290) at 100 °C with liquid feed rate 2.5 ml/min. A white powder with 10 wt% (theoretical)

15 artemisinin was obtained and collected in a sample vial for further characterization.

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The particle size of the redispersed material (d,nm) was 695+/-15.

5 **Example 2:**

0.10 g artemisinin and 0.10 g pluronic F-68 (BASF, USP) were both dissolved into 50 ml ethanol. 0.80 g HPMC was added into the ethanol solution with intensive stirring using a magnetic bar to form a uniform HPMC/EtOH suspension. 50 ml
10 distilled water was then added into the suspension, and a clear solution was obtained. The solution was then spray dried at 100 °C with liquid feed rate 2.5 ml/min. A white powder with 10 wt% (theoretical) artemisinin was obtained and collected in a sample vial for further characterization.

15

The particle size of the redispersed material (d,nm) was 770+/-27.

Example 3:

20 0.10 g artemisinin and 0.10 g pluronic F-68 were both dissolved into 50 ml ethanol. 0.80 g polyvinylpyrrolidone (PVP k30, Aldrich) was added into the ethanol solution following 50 ml distilled water, and a clear solution was obtained. The solution was then spray dried at 100 °C with
25 liquid feed rate 2.5 ml/min. A white powder with 10 wt% (theoretical) artemisinin was obtained and collected in a sample vial for further characterization.

The particle size of the redispersed material (d,nm) was
30 705+/-64.

Example 4:

0.20 g artemisinin was dissolved into 50 ml ethanol. 0.40 g HPMC and 0.40 g beta-cyclodextrin (Aldrich) were both dispersed into the ethanol solution with stirring using a magnetic bar to form a uniform HPMC/EtOH suspension. 50 ml distilled water was then added into the suspension, and a clear solution was obtained. The solution was then spray dried at 100 °C with liquid feed rate 2.5 ml/min. A white powder with 20 wt% (theoretical) artemisinin was obtained and collected in a sample vial for further characterization.

The particle size of the redispersed material (d,nm) was 667+/-35.

Example 5:

0.10 g Artemisinin and 0.05 g PEG (Mw 6,000, Fluka) were both dissolved into 50 ml ethanol. 0.85 g HPMC (5 cps, Aldrich) was added into the ethanol solution with intensive stirring using a magnetic bar in order to form a uniform HPMC/EtOH suspension. 50 ml Distilled water was then added into the suspension, and a clear solution was obtained. The solution was then spray dried at 150 °C with liquid feed rate 2.5 ml/min. A white powder with 10 wt% (theoretical) artemisinin was obtained and collected in a sample vial for further characterization.

The particle size of the redispersed material (d,nm) was 56+/-3.

Example 6:

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0.10 g Artemisinin and 0.10 g Pluronic F-127 (Aldrich) were both dissolved into 50 ml ethanol. 0.80 g HPMC (5 cps, Aldrich) was added into the ethanol solution with intensive stirring using a magnetic bar to form a uniform HPMC/EtOH suspension. 50 ml distilled water was then added into the suspension, and a clear solution was obtained. The solution was then spray dried at 150 °C with liquid feed rate 2.5 ml/min. A white powder with 10 wt% (theoretical) artemisinin was obtained and collected in a sample vial for further characterization.

The particle size of the redispersed material (d,nm) was 42+/-14.

15 **Example 7:**

0.10 g Artemisinin and 0.10 g lipoid S75 (Lipoid GmbH) were both dissolved into 50 ml ethanol. 0.80 g HPMC (5 cps, Aldrich) was added into the ethanol solution with intensive stirring using a magnetic bar to form a uniform HPMC/EtOH suspension. 50 ml Distilled water was then added into the suspension, and a clear solution was obtained. The solution was then spray dried at 150 °C with liquid feed rate 2.5 ml/min. A white powder with 10 wt% (theoretical) artemisinin was obtained and collected in a sample vial for further characterization.

The particle size of the redispersed material (d,nm) was 211+/-5.

30 **Example 8:**

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0.10 g Artemisinin and 0.09 g Pluronic F-127 were both dissolved into 50 ml ethanol. 0.80 g HPMC (5 cps, Aldrich) and 0.01 g Cetrimide (Cetyltrimethylammonium Bromide, Aldrich) were added into the ethanol solution with intensive stirring using a magnetic bar to form a uniform HPMC/EtOH suspension. 50 ml Distilled water was then added into the suspension, and a clear solution was obtained. The solution was then spray dried at 150 °C with liquid feed rate 2.5 ml/min. A white powder with 10 wt% (theoretical) artemisinin was obtained and collected in a sample vial for further characterization.

The particle size of the redispersed material (d,nm) was 25+/-2.

15

Example 9:

0.10 g Artemisinin and 0.09 g Pluronic F-127 were both dissolved into 50 ml ethanol. 0.80 g HPMC (5 cps, Aldrich) and 0.01 g SDS (Aldrich) were added into the ethanol solution with intensive stirring using a magnetic bar to form a uniform HPMC/EtOH suspension. 50 ml Distilled water was then added into the suspension, and a clear solution was obtained. The solution was then spray dried at 150°C with liquid feed rate 2.5 ml/min. A white powder with 10 wt% (theoretical) artemisinin was obtained and collected in a sample vial for further characterization.

25

The particle size of the redispersed material (d,nm) was 39+/-9.

30

Example 10:

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0.10 g Artemisinin and 0.09 g Pluronic F-127 were both dissolved into 50 ml ethanol. 0.80 g HPMC (5 cps, Aldrich), 0.005 g Cetrimide, and 0.005 g SDS were all added into the ethanol solution with intensive stirring using a magnetic
5 bar to form a uniform HPMC/EtOH suspension. 50 ml Distilled water was then added into the suspension, and a clear solution was obtained. The solution was then spray dried at 150 °C with liquid feed rate 2.5 ml/min. A white powder with 10 wt% (theoretical) artemisinin was obtained and collected
10 in a sample vial for further characterization.

The particle size of the redispersed material (d,nm) was 331+/-9.

15 **Example 11:**

0.20 g Artemisinin, 0.05 g Pluronic F68, 0.05 g Span 80 (Aldrich), and 0.70 g Klucel EF (Hydroxypropyl cellulose, Mw 80,000, Hercules Ltd) were all dissolved into 70 ml ethanol. The solution was then spray dried at 150 °C with liquid feed
20 rate 2.5 ml/min. A white powder with 20 wt% (theoretical) artemisinin was obtained and collected in a sample vial for further characterization.

The particle size of the redispersed material (d,nm) was measured at 182+/-4 when dispersed at 1mg/ml and 180+/-2 when dispersed at 2 mg/ml.

Example 12:

0.30 g Artemisinin, 0.08 g Pluronic F68, 0.07 g Span 80 (Aldrich), and 0.55 g Klucel EF were all dissolved into 70
30 ml ethanol. The solution was then spray dried at 150 °C with

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liquid feed rate 2.5 ml/min. A white powder with 30 wt% (theoretical) artemisinin was obtained and collected in a sample vial for further characterization.

- 5 The particle size of the redispersed material (d,nm) was measured at 183+/-2 when dispersed at 1mg/ml and 207+/-13 when dispersed at 2 mg/ml.

Example 13:

- 10 0.1015 g Artemisinin was prepared with EtOH in 100 ml volumetric flask as a standard solution. Six aliquots equivalent to 0, 0.50, 1.00, 1.50, 2.00, and 3.00 ml of standard solution were pipetted into six 50 ml volumetric flasks, respectively. The solutions were then diluted up to
15 5.00 ml with ethanol, using a pipette, and mixed with 20 ml of 0.2 wt% NaOH solutions, respectively. These mixtures were then warmed in a water bath at 50 °C for 40 min to obtain a new chemical named Q292, which has UV absorption at 292 nm. After being cooled to room temperature in water, these
20 mixtures were acidified by adding 0.08 M acetic acid to make up the volumes, and a new chemical named Q260 with UV absorption at 260 nm was obtained. This follows the method of G Qian, Y Yang, Q Ren, (*Determination of Artemisinin in Artemisia annua L. by Reversed Phase HPLC*, J. Liquid
25 Chromatography & Related Technologies, 28, 2005). The solutions were then analysed by UV to obtain a calibration curve. An example with a theoretical level of 15% was analysed with the method to identify the artemisinin content in solid powder. The analysis found that there was 13.88 wt%
30 artemisinin in the powder.

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Example 14-17:

A solution of the excipients and active (for example 14), was made by dissolving 0.1g of Quinine, 0.62g Klucel (Hercules incorporated), 0.03g of Span 80 (Sigma Aldrich), 0.2g of Tween 80 (Croda) and 0.05g of Cremophor ELP (No. 35) (BASF Chem. Trade), (see table below) in 80ml of ethanol and 40ml of water. The solution placed was on a magnetic stirrer for 5-10 minutes to ensure all of the excipients and active were completely dispersed.

10

The solution was spray dried on a Buchi B290 Mini spray-drier with a pump rate of 10% and inlet temperature of 140°C. In all cases a white powder was obtained.

The total powder content in each formulation was 1g dissolved in 50ml of ethanol and 20ml deionised water.

15

Extra ethanol was added if the solution was cloudy, until it turned clear and all the excipients were dissolved.

Example	Drying Temp	Quinine	Klucel	HPMC	Span 80	Span 83	Tween 20	Tween 80	Cremophor ELP	Particle size	Water solubility
14	140	0.1	0.62	-	0.03	-	-	0.2	0.05	64nm	Good/clearish
15	140	0.1	0.63	-	-	0.02	0.15	-	0.1	213nm	Good/clear
16	140	0.15	0.2	0.37	-	0.03	0.25	-	0.05	225nm	Good/clearish
17	140	0.15	0.27	0.3	-	0.03	0.25	-	0.05	134nm	Good/clearish

20

- 40 -

Dissolution tests were carried out on examples 14 and 15. The dissolution vessel was filled with a 1L of pre-warmed deionised water placed in a pre-warmed water bath set at 37°C. Each powder was added to the vessel containing the 1L
 5 of water with constant stirring as follows: example 14 2000mg (equivalent to 200mg quinine) powder, and example 16 approximately 2707mg (equivalent to 271mg quinine).

Aliquots of 2.5 -5ml were collected using a pipette at set
 10 time intervals of 1, 5, 10 and 20minutes. In each test a further aliquot was collected at 30 minutes because not all the powder dissolved and the speed of the overhead stirring paddle was increased to 140rpm to speed up the dissolution. One final aliquot was then collect to be used as the
 15 equilibrium concentration at the end of the test.

The tables below show the % Dissolution Vs Time:

Example 14

Time (mins)	% Dissolved	Time (mins)	% Dissolution
1	60.8	1	48.6
5	81.7	5	65.4
10	84.7	10	67.7
20	86.8	20	69.4
30	87.3	30	69.8
115	124.3	115	99.5

20

Example 16:

Time (mins)	% Dissolved	Time (mins)	% Dissolution
1	59.9	1	55.8
5	83.9	5	78.2
10	94	10	87.5

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20	106.9	20	99.5
30	110.2	30	102.6

Example 18a-f:5 **18a**

0.2 g artemisinin and 0.05 g Span 80 were both dissolved into 20 ml Chloroform. 0.05 g Pluronic F68, 0.65 g Klucel EF and 0.05 g sodium alginate were all dissolved into 80 ml distilled water. The oil phase was added dropwise into the aqueous phase with overhead stirring at 600 rpm for 2 min. The coarse emulsion was further treated with a homogenizer (Yellowline DI25 Basic) at 13,500 rpm for 5 min. The fine emulsion was then spray dried at 150 °C with a Buchi Mini spray dryer B-290, and the emulsion droplet size was measured with a Malvern Nano-S. 10 mg dry powder was then dispersed into 10 ml distilled water and the nanoparticle size was measured with the Malvern Nano-S.

18b

Using the same formulation as example 18a, the coarse emulsion was further treated with a homogenizer at 20,500 rpm for 10 min. The fine emulsion was then spray dried at 150 °C with a Buchi Mini spray dryer B-290, and the emulsion droplet size was measured with the Malvern Nano-S. 10 mg dry powder was then dispersed into 10 ml distilled water and the nanoparticle size was measured with the Malvern Nano-S.

18c

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Using the same formulation as example 18a, the coarse emulsion was further treated with a homogenizer at 24,000 rpm for 5 min. The fine emulsion was then spray dried at 150 °C with a Buchi Mini spray dryer B-290, and the emulsion droplet size was measured with the Malvern Nano-S. 10 mg dry powder was then dispersed into 10 ml distilled water and the nanoparticle size was measured with the Malvern Nano-S.

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18d

Using the same formulation as example 18a, the coarse emulsion was further treated with a homogenizer at 24,000 rpm for 10 min. The fine emulsion was then spray dried at 5 150 °C with a Buchi Mini spray dryer B-290, and the emulsion droplet size was measured with the Malvern Nano-S. 10 mg dry powder was then dispersed into 10ml distilled water and the nanoparticle size was measured with the Malvern Nano-S.

10 **18e**

Using the same formulation as example 18a, the coarse emulsion was further treated with an ultrasonic probe (Sonicator ®, Ultrasonic Processor XL) for 1 min. The fine emulsion was then spray dried at 150 °C with a Buchi Mini 15 spray dryer B-290, and the emulsion droplet size was measured with the Malvern Nano-S. 10 mg dry powder was then dispersed into 10 ml distilled water and the nanoparticle size was measured with the Malvern Nano-S.

20 **18f**

Using the same formulation as example 18a, the coarse emulsion was further treated with an ultrasonic probe at for 3 min. The fine emulsion was then spray dried at 150 °C with a Buchi Mini spray dryer B-290, and the emulsion droplet 25 size was measured with the Malvern Nano-S. 10 mg dry powder was then dispersed into 10 ml distilled water and the nanoparticle size was measured with the Malvern Nano-S.

Further concerning these experiments is given in the 30 following table

Examples	18a	18b	18c	18d	18e	18f
Emulsion Droplet size, nm	3217	2928	2454	2293	1730	900
Artemisinin Nanoparticle size, nm	636	467	311	273	146	101

Throughout this specification and the claims which follow, unless the context requires otherwise, the word "comprise", and variations such as "comprises" or "comprising", will be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integers or steps.

The reference in this specification to any prior publication (or information derived from it), or to any matter which is known, is not, and should not be taken as, an acknowledgement or admission or any form of suggestion that that prior publication (or information derived from it) or known matter forms part of the common general knowledge in the field of endeavour to which this specification relates.

2007271828 01 Nov 2010

The Claims defining the invention are as follows:

1. A composition comprising at least one water-insoluble anti-malarial drug and a water-soluble carrier material, wherein the water-insoluble anti-malarial drug is dispersed through the carrier material in nano-disperse form having a z-average particle diameter of the nano-disperse form within the composition of 20-800nm.
2. A composition according to claim 1 wherein the z-average diameter of the water-insoluble anti-malarial drug is below 500nm.
3. A composition according to claim 2 wherein the z-average diameter of the water-insoluble anti-malarial drug is below 200nm.
4. A composition according to claim 3 wherein the z-average diameter of the water-insoluble anti-malarial drug is below 100nm.
5. A composition according to any one of the preceding claims wherein the anti-malarial drug has a water solubility of less than 5g/L
6. A composition according to claim 5 wherein the anti-malarial drug has a water solubility of less than 1g/L
7. A composition according to claim 6 wherein the anti-malarial drug has a water solubility of less than 150mg/L.

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8. A composition according to any one of the preceding claims wherein the anti-malarial drug includes a peroxide, lactone, peroxy-lactone, quinine, quinoline and/or quinidine.
- 5
9. A composition according to claim 8 wherein the anti-malarial drug is an Artemisinin-type drug or a quinine-type drug.
- 10
10. A composition according to claim 9, wherein the anti-malarial drug is selected from the group comprising artemisinin, artemether, arteether, dihydroartemisinin and mixtures thereof.
- 15
11. A composition according to claim 9 wherein the anti-malarial drug is selected from the group comprising quinine and quinidine.
- 20
12. An aqueous dispersion of a water-insoluble anti-malarial drug and a water-soluble carrier material, wherein the anti-malarial drug is in nano-disperse form having a z-average particle diameter of 20-800nm.
- 25
13. An aqueous dispersion according to claim 12, obtainable by combining water and the composition of any one of claims 1-11.
- 30
14. A process for preparing a composition according to any one of claims 1 to 11 which comprises the steps of:

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- a) providing an emulsion comprising:
 - i) a solution of the anti-malarial drug in a water-immiscible solvent for the same, and
 - ii) an aqueous solution of the carrier material,
- 5 and,
- b) drying the emulsion to remove water and the water-immiscible solvent to obtain a substantially solvent-free nano-dispersion of the anti-malarial
- 10 drug in the carrier material.

15. A process for preparing a composition according to any one of claims 1 to 11 which comprises the steps of:

- 15 a) providing a mixture comprising:
 - i) at least one water-miscible, non-aqueous solvent
 - ii) optionally, water
 - iii) a water-soluble carrier material soluble in the mixture of (i) and (ii) and
 - 20 iv) a water-insoluble anti-malarial drug which is soluble in the mixture of (i) and (ii) , and,
- b) drying the solution to remove water and the water-miscible solvent to obtain a substantially solvent-free nano-dispersion of the anti-malarial drug in
- 25 the carrier material.

16. A process according to claim 14 or 15 wherein the drying process includes spray drying.

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17. A process according to claim 16 wherein the spray drying process is conducted at a temperature of above 120 Celsius.
- 5 18. A process according to claim 14 or 15 or a composition according to any one of claims 1 to 11 or an aqueous dispersion according to claims 12 or 13 in which the carrier material includes a polymer and/or a surfactant.
- 10 19. A process, composition or dispersion according to claim 18 wherein the carrier material includes at least one of polyethylene glycol, polyvinylpyrrolidone, poly (2-ethyl-2-oxazoline) , polyvinyl alcohol, hydroxypropyl cellulose and hydroxypropyl-methyl cellulose and
15 alginate.
20. A process, composition or dispersion according to claim 18 wherein the carrier material includes at least one
20 of alkoxylated non-ionic surfactant, ether sulphate surfactant, cationic surfactant or ester surfactant.
21. A process according to any one of claims 15-20 wherein the non-aqueous solvent includes at least one of
25 dichloromethane, chloroform, ethanol, acetone and dimethyl sulphoxide.
22. A process for the preparation of a medicament for use in the treatment or prophylaxis of malaria which
30 comprises the step of preparing a composition according to any one of claims 1-11.

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23. A composition according to claim 1 substantially as
hereinbefore described with reference to the examples.

24. A process according to claim 14 or 15 substantially as
5 hereinbefore described with reference to the examples.